June 18, 2007

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero de Luca
Docket No.	:	SER-125
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Sir:

It is respectfully requested that the above-identified patent application be amended as follows:

In the Specification

Please insert the following new paragraph after the Title of the invention on page 1, line 1:

Cross-Reference to Related Application

This application is the U.S. national stage application of International Patent Application No. PCT/EP2005/056954, filed December 20, 2005, which claims the benefit of U.S. Provisional Patent Application No. 60/638,669, filed December 22, 2004, the disclosures of which are hereby incorporated by reference in their entireties, including all figures, tables and amino acid or nucleic acid sequences.

After page 31: Please insert as new page 32 the attached Abstract of the Disclosure.

In the Claims

1-17 (canceled).

18 (new). A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine, wherein the formulation is to be orally administered following the sequential steps below:

(i) an induction period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the induction period is from 1.7 mg/kg to 3.5 mg/kg;

(ii) a cladribine-free period wherein no cladribine formulation is administered;

(iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine formulation is administered.

19 (new). The method according to claim 18, wherein the induction period lasts up to 4 months, or up to 3 months, or up to 2 months.

20 (new). The method according to claim 19, wherein the induction period lasts up to 2 months.

21 (new). The method according to claim 18, wherein the induction period lasts up to 2 months.

22 (new). The method according to claim 18, wherein the induction period lasts up to 4 months.

23 (new). The method according to claim 19, wherein the induction period lasts up to 4 months.

24 (new). The method according to claim 18, wherein the total dose of cladribine reached at the end of the induction period is 1.7 mg/kg.

25 (new). The method according to claim 18, wherein the total dose of cladribine reached at the end of the induction period is 3.5 mg/kg.

26 (new). The method according to claim 18, wherein the cladribine-free period lasts up to 10 months, or up to 9 months, or up to 8 months.

27 (new). The method according to claim 18, wherein the cladribine-free (iv) period lasts up to 10 months.

28 (new). The method according to claim 18, wherein the maintenance period lasts up to 4 months, or up to 3 months or up to 2 months.

29 (new). The method according to claim 18, wherein the total dose of cladribine reached at the end of the maintenance period is 1.7 mg/kg.

30 (new). The method according to claim 18, wherein the formulation is to be orally administered following the sequential steps below:

(i) an induction period wherein said cladribine formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from 1.7 mg/kg to 3.5 mg/kg;

(ii) a cladribine-free period wherein no cladribine formulation is administered;

(iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period is

lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine formulation is administered;

wherein the induction period lasts up to 4 months, or up to 3 months or up to 2 months; the cladribine-free period (ii) lasts up to 10 months, or up to 8 months or up to 10 months; the maintenance period (iii) lasts up to 2 months; the cladribine-free period (iv) lasts up to 10 months; the total dose of cladribine reached at the end of the maintenance period is 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

31 (new). The method according to claim 30, wherein the total dose of cladribine reached at the end of the induction period is 3.5 mg/kg and the total dose of cladribine reached at the end of the maintenance period is 1.7 mg/kg.

32 (new). The method according to claim 30, wherein the formulation is to be orally administered at a daily dose of 3 to 30 mg cladribine.

33 (new). The method according to claim 32, wherein the pharmaceutical formulation is to be orally administered at a daily dose of 10 mg cladribine.

34 (new). The method according to claim 18, wherein the pharmaceutical formulation is orally administered 1 to 7 days per month during the induction period.

35 (new). The method according to claim 18, wherein the steps (iii) to (iv) are repeated at least one or two times.

36 (new). The method according to claim 18, wherein said cladribine formulation is to be administered in combination with interferon-beta.

37 (new). The method according to claim 30, wherein said cladribine formulation is to be administered in combination with interferon-beta.

Remarks

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16, 1.17, and 1.492 as required by this paper to Deposit Account No. 19-0065.

Respectfully submitted,

/FRANKCEISENSCHENK/

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl
Attachment: Abstract of the Disclosure

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Abstract of the Disclosure

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be orally administered and wherein re-treatments are possible.

Application Information

Application Type::	Regular (National Stage)
Subject Matter::	Utility
Suggested Classification::	None
Suggested Group Art Unit::	None
CD-ROM or CD-R?::	None
Number of CD disks::	None
Number of copies of CDs::	None
Sequence submission?::	No
Computer Readable Form?::	No
Number of Copies of CRF::	None
Title::	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
Attorney Docket Number::	SER-125
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	None
Total Drawing Sheets::	None
Small Entity?::	No
Petition included?::	No
Petition Type::	N/A
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Italy
Status::	Unknown
Inventor One Given Name::	Giampiero
Family Name::	DE LUCA
City of Residence::	Conches/Geneva
Country of Residence::	Switzerland
Street of Mailing Address::	Chemin des Conches 15B
City of Mailing Address::	Conches/Geneva
Country of Mailing Address::	Switzerland
Postal or Zip Code of Mailing Address::	CH-1231

Representative Information

Representative Customer Number::	000023557

Correspondence Information

Correspondence Customer Number::	000023557
Telephone Number One::	(352) 375-8100
Telephone Number Two::	
Fax Number::	(352) 372-5800
Electronic Mail Address::	fce@slspatents.com

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application is a	National Stage of	PCT/EP2005/056954	December 20, 2005
PCT/EP2005/056954	An application claiming the benefit under 35 USC 119(e) of	60/638,669	December 22, 2004

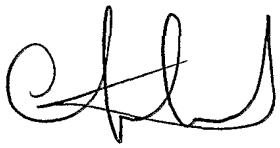
Foreign Priority Information

Country::	Application Number::	Filing Date::	Priority Claimed::
EP	04106909.7	December 22, 2004	Yes

Assignee Information

Assignee Name::	Laboratoires Serono S.A.
Street of Mailing Address::	Zone Industrielle de l'Ouriettaz
City of Mailing Address::	Aubonne
Country of Mailing Address::	Switzerland
Postal or Zip Code of Mailing Address::	CH-1170

VIII-4-1	**Declaration: Inventorship (only for the purposes of the designation of the United States of America)** Declaration of Inventorship (Rules 4.17(iv) and 51bis.1(a)(iv)) for the purposes of the designation of the United States of America:	I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought. This declaration is directed to international application PCT/EP2005/056954 (if furnishing declaration pursuant to Rule 26ter). I hereby declare that my residence, mailing address, and citizenship are as stated next to my name. I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications", by application number, country or Member of the World Trade Organization, day, month, and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.
VIII-4-1-1	Prior applications:	60/638,669, US, 22 December 2004 (22.12.2004) ;04106909.7, EP, 22 December 2004 (22.12.2004)

		I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.
VIII-4-1-1-1	Name (LAST, First)	DE LUCA, Giampiero
VIII-4-1-1-2	Residence: (city and either US State, if applicable, or country)	Conches, Switzerland
VIII-4-1-1-3	Mailing address:	Chemin de Conches 15B 1231 Conches Switzerland
VIII-4-1-1-4	Citizenship:	IT
VIII-4-1-1-5	Inventor's Signature: (if not contained in the request, or if declaration is corrected or added under Rule 26ter after the filing of the international application. The signature must be that of the inventor, not that of the agent)	
VIII-4-1-1-6	Date: (of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26ter after the filing of the international application)	

June 18, 2007

INFORMATION DISCLOSURE
STATEMENT
Patent Application
Docket No. SER-125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero de Luca
Filed	:	June 18, 2007
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§1.97 AND 1.98

Sir:

In accordance with 37 C.F.R. § 1.56, the references listed on the attached form PTO/SB/08 are being brought to the attention of the Examiner for consideration in connection with the examination of the above-identified patent application. A copy of each cited reference is enclosed.

It is respectfully requested that the references cited on the attached form PTO/SB/08 be considered in the examination of the subject application and that their consideration be made of record.

Applicant respectfully asserts that the substantive provisions of 37 C.F.R. §§ 1.97 and 1.98 are met by the foregoing statement.

Respectfully submitted,

/FRANKCEISENSCHENK/

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jps
Attachments: Form PTO/SB/08; copies of references cited therein.

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PTO/SB/08A (08-03)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Art Unit	
Examiner Name	
Attorney Docket Number	SER-125

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1	US-			
	U2	US-			
	U3	US-			
	U4	US-			
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code [5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T [6]
	F1	WO 04/087101 A2	10/14/2004	Ivax Corporation	All	
	F2	EP 0 626 853 B1	04/26/200	The Scripps Research Institute	All	
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 3

Complete if Known	
Application Number	
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Group Art Unit	
Examiner Name	
Attorney Docket Number	SER-125

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R1	BEUTLER, E. *et al.* "Marrow Suppression Produced by Repeated Doses of Cladribine", *Acta Haematol*, 1994, pp. 10-15, Vol. 91.	
	R2	BEUTLER, E. *et al.* "Treatment of Multiple Sclerosis and Other Autoimmune Diseases With Cladribine", *Seminars in Hematology*, January 1, 1996, pp. 45-52, Vol. 33, No. 1, Supplement 1.	
	R3	BEUTLER, E. *et al.* "The treatment of chronic progressive multiple sclerosis with cladribine", *Proc. Natl. Acad. Sci. USA*, February 1996, pp. 1716-1720, Vol. 93.	
	R4	ELLISON, G. *et al.* "Oral Cladribine for Multiple Sclerosis", *Neurology*, March 1997, P03.070, pp. A174-A175, Vol. 48, No. 3, XP008047069.	
	R5	GRIEB, P. *et al.* "Effect of Repeated Treatments with Cladribine (2-Chlorodeoxyadenosine) on Blood Counts in Multiple Sclerosis Patients", *Archivum Immunologiae et Therapiae Experimentalis*, 1995, pp. 323-327, Vol. 43, No. 5-6.	
	R6	KAZIMIERCZUK, Z. *et al.* "Synthesis of 2'-Deoxytubercidin, 2'-Deoxyadenosine, and Related 2'-Deoxynucleosides via a Novel Direct Stereospecific Sodium Salt Glycosylation Procedure", *J. Am. Chem. Soc.*, 1984, pp. 6379-6382, Vol. 106, No. 21.	
	R7	KURTZKE, J. "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)", *Neurology*, November 1983, pp. 1444-1452, Vol. 33.	
	R8	LANGTRY, H. *et al.* "Cladribine: A Review of its Use in Multiple Sclerosis", *Biodrugs*, May 1998, pp. 419-433, Vol. 9, No. 3.	
	R9	LASSMANN, H. *et al.* "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy", *TRENDS in Molecular Medicine*, March 2001, pp. 115-121, Vol. 7, No. 3.	
	R10	LUBLIN, F. *et al.* "Defining the clinical course of multiple sclerosis: Results of an international survey", *Neurology*, April 1996, pp. 907-911, Vol. 46.	
	R11	LUCCHINETTI, C. *et al.* "Multiple sclerosis: recent developments in neuropathology, pathogenesis, magnetic resonance imaging studies and treatment", *Current Opinion in Neurology*, 2001, pp. 259-269, Vol. 14.	
	R12	MATTSON, D. "Update on the diagnosis of multiple sclerosis", *Expert Review of Neurotherapeutics*, May 2002, pp. 319-327, Vol. 2, No. 3.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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PTO/SB/08B (08-03)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 3 of 3

Complete if Known	
Application Number	
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Group Art Unit	
Examiner Name	
Attorney Docket Number	SER-125

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R13	MCDONALD, W. *et al.* "Recommended Diagnostic Criteria for Multiple Sclerosis: Guidlines from the International Panel on the Diagnosis of Multiple Sclerosis", *Annals of Neurology*, July 2001, pp. 121-127, Vol. 50, No. 1.	
	R14	MILLER, R. *et al.* "Therapeutic advances in ALS", *Neurology*, 1996, pp. S217, Vol. 47, Suppl. 4.	
	R15	NOSEWORTHY, J. *et al.* "Multiple Sclerosis", *The New England Journal of Medicine*, September 28, 2000, pp. 938-952, Vol. 343, No. 13.	
	R16	POSER, C. *et al.* "New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols", *Annals of Neurology*, March 1983, pp. 227-231, Vol. 13, No. 3.	
	R17	RICE, G. *et al.* "Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial", *Neurology*, March 2000, pp. 1145-1155, Vol. 54.	
	R18	ROMINE, J. *et al.* "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis", *Proceedings of the Association of American Physicians*, *January*/February 1999, pp. 35-44, Vol. 111, No. 1.	
	R19	SCHUMACHER, G. *et al.* "Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis", *Annals New York Academy of Sciences*, March 31, 1965, pp. 552-568, Vol. 122.	
	R20	SELBY, R. *et al.* "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis", *Can. J. Neurol. Sci.*, 1998, pp. 295-299, Vol. 25.	
	R21	SIPE, J. *et al.* "A neurologic rating scale (NRS) for use in multiple sclerosis", *Neurology*, October 1984, pp. 1368-1372, Vol. 34.	
	R22	STELMASIAK, Z. *et al.* "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis", *Med. Sci Monit.*, 1998, pp. 4-8, Vol. 4, No. 1.	
	R23		
	R24		

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 626 853 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
26.04.2000 Bulletin 2000/17

(21) Application number: **93906071.1**

(22) Date of filing: **18.02.1993**

(51) Int. Cl.[7]: **A61K 31/70**

(86) International application number:
PCT/US93/01467

(87) International publication number:
WO 93/16706 (02.09.1993 Gazette 1993/21)

(54) USE OF SUBSTITUTED ADENINE DERIVATIVES FOR TREATING MULTIPLE SCLEROSIS

Verwendung von substituierten Adeninderivaten zur Behandlung von MultipleSklerose

UTILISATION DE DERIVES D'ADENINE SUBSTITUEE POUR LE TRAITEMENT DE LA SCLEROSE EN PLAQUES

(84) Designated Contracting States:
AT BE DE DK ES FR GB GR IE IT LU MC NL PT SE

(30) Priority: **19.02.1992 US 838546**

(43) Date of publication of application:
07.12.1994 Bulletin 1994/49

(73) Proprietor:
THE SCRIPPS RESEARCH INSTITUTE
La Jolla, CA 92037 (US)

(72) Inventor: **BEUTLER, Ernest**
La Jolla, CA 92037 (US)

(74) Representative:
Hedley, Nicholas James Matthew
Stephenson Harwood
One, St. Paul's Churchyard
London EC4M 8SH (GB)

(56) References cited:
EP-A- 0 379 145

- **J. CLIN. INVEST. vol. 86, no. 5, November 1990, pages 1480 - 1488 C.J. CARRERA ET AL. 'Potent toxicity of 2-chlorodeoxyadenosine toward human monocytes in vitro and in vivo.'**
- **Science, vol. 154, 1966, p.1044-1046**
- **Adv. Exp. Med. Biol., vol. 237, 1988, p.839-42**
- **Acta Neurol. Scand., vol. 75, 1987, p.352-355**
- **J. Exp. Med., vol. 160, 1984, p.310-316**
- **Nervenarzt, vol. 66, 1995, p.299-303**

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 0 626 853 B1

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Description

Technical Field

[0001] This invention relates to the use of substituted adenine derivatives for the manufacture of a medicament for treating multiple sclerosis.

Background of the Invention

[0002] Multiple sclerosis (MS) is the result of demyelination in the brain and spinal cord (central nervous system). Symptoms resulting from this demyelination include weakness, visual impairment, incoordination, and paresthesia (abnormal tingling). The course of the disease is largely unpredictable, but often progresses through a cycle of exacerbation of symptoms followed by remission.

[0003] Conventional treatments presently employ therapy with ACTH or corticosteroids such as prednisone. Controlled studies suggest that such treatments induce more rapid clearing of acute symptoms and signs but leave the long-term outcome of the disease unaffected. Long-term maintenance therapy with ACTH or corticosteroids is contraindicated. Evidence indicates that immunosuppressant agents have no long-term benefit. (Cecil, Textbook of Medicine, Beeson et al., eds., 15th ed., W.B. Saunders Company, Philadelphia, (1979) page 847)

[0004] The etiology of multiple sclerosis is unknown but is linked to a variety of genetic and environmental factors. Both cell-mediated and humoral immune responses, triggered by extraneous or autoantigens may contribute to the pathogenesis of multiple sclerosis. Certain immune response genes may be associated with an increased susceptibility to the disease. The disease may be mediated by T cells that recognize an as yet unidentified autoantigen. For example, experimental allergic encephalomyelitis (EAE), an animal model of demyelinating diseases such as multiple sclerosis, can be induced by immunizing mice with whole myelin or specific myelin components such as myelin basic protein.

[0005] In humans with multiple sclerosis, exacerbations are correlated with high levels of neopterin in blood and cerebrospinal fluid. Neopterin is a factor released from monocytes and macrophages in the presence of activated T-cells, thereby implicating these cells as being involved in multiple sclerosis exacerbations. (Fredrickson et al. (1987), Acta Neurol. Scand., 75:352-355; Huber et al. (1984), J. Exp. Med., 160:310-316). At the microscopic level, monocytes, microglial cells (macrophages of the central nervous system) and activated T-cells are found within the demyelinated regions of the nerve cells during multiple sclerosis exacerbations. (Cecil, Textbook of Medicine (1979), Beeson et al. (eds.), W.B. Saunders Co., Philadelphia, PA).

[0006] Various conventional treatment methodologies have been employed to ameliorate the symptoms of multiple sclerosis. Many of these are directed to use of palliative, anti-inflammatory agents. No treatment to date has had any consistent positive effect on the course of the disease.

[0007] Recently, the art has described the use of specific deoxyribosides as anti-inflammatory agents. For instance, U.S. Patent No. 4,481,197 (Rideout et al.) relates to the use of unsubstituted 3-deaza-2'-deoxyadenosine derivatives in the treatment of inflammation. U.S. Patent No. 4,381,344 (Rideout et al.) relates to a process for the synthesis of deoxyribosides that utilizes a bacterial phosphorylase.

[0008] A deoxyriboside derivative, 2-chloro-2'-deoxyadenosine (CdA), has been found to be an effective agent for the treatment of chronic lymphocytic leukemia and some T cell malignancies. (Carson et al. (1984) Proc. Natl. Acad. Sci. U.S.A., 81:2232-2236; Piro et al. (1988), Blood 72:1069-1073) The pharmacokinetics of orally and subcutaneously administered 2-chloro-2'-deoxyadenosine in the treatment of chronic lymphocytic leukemia have been described and compared. (Liliemark et al. (1992) Journal of Clinical Oncology, 10, (10): 1514-1518; Juliusson et al. (1992) Blood, 80 (Suppl. 1): 1427) Chronic lymphocytic leukemia is a malignancy of B lymphocytes that bear the Leu-I surface antigen.

[0009] The Leu-I B cells represent a minor proportion of the normal pool of B lymphocytes, usually less than 20 percent. The Leu-I B cells express surface markers that are typically found on monocytes (Mac-I antigen) and T-lymphocytes (Leu-I antigen). Approximately 10 percent of patients with chronic lymphocytic leukemia exhibit accompanying autoimmunity, and recently, Leu-I B cells have been implicated in the pathogenesis of autoimmune diseases.

[0010] Phase I clinical trials on human patients with chronic lymphocytic leukemia indicate that infusion of increasing doses of 2-chloro-2'-deoxyadenosine [0.1-0.5 milligrams per kilogram of body weight per day (mg/kg/day)] yielded increasing plasma concentrations of the drug [10-50 nanomolar (nM)]. Those infusions indicated that the drug was well tolerated and did not induce nausea, vomiting or fever. The dose-limiting toxicity was bone marrow suppression, which usually occurred at doses greater than about 0.2 mg/kg/day or at plasma levels of greater than about 20 nM.

[0011] Other studies, Montgomery et al. (1959) J. Am. Chem. Soc., 82:463-468, indicated that 2-fluoroadenosine exhibits a relatively high degree of cytotoxicity. Those workers reported that C57 black mice implanted with Adenocarcinoma 755 (Ad755) could tolerate only about 1 milligram per kilogram of body weight. 2-Fluoroadenosine was found to be inactive at that level against Ad755 as well as leukemia L1210 and the Erlich ascites tumor.

[0012] U.S. Patent No. 4,751,221 and its division No. 4,918,179 to Watanabe et al. describe the synthesis and use

of several 2-substituted-2'-deoxy-2'-fluoroarabino-furanosyl nucleosides including adenine derivatives. Those compounds were said to have anti-tumor and antitrypanosomal biological activities. Cytotoxicity data showing anti-tumor activity of 2-amino-6-thiopurine, guanine and thiopurine derivatives against murine and human cell lines were reported.

[0013] U.S. Patent No. 5,034,518 to Montgomery et al. teaches the synthesis of 2-substituted-2'-deoxy-2'-fluoroaraadenosines. Those compounds were said to have anticancer activity, and data for prolongation of life of mice transplanted with P388 leukemia cells were provided.

[0014] The biochemical activity of 2-CdA in cells has been reviewed by Ernest Beutler. (The Lancet (1992), 340: 952-956 - incorporated herein by reference)

[0015] The 2',3'-dideoxynucleosides are phosphorylated at the 5'-position in T cells to form the 5'-nucleotide triphosphate derivatives. Those derivatives are well known to be substrates for reverse transcriptase molecules. (Ono et al. (1986) Biochem. Biophys. Res. Comm., 2:498-507)

[0016] Those 2',3'-dideoxynucleoside 5'-triphosphates are also utilized by mammalian DNA polymerases beta and gamma. (Waquar et al. (1984) J. Cell. Physiol., 121:402-408) They are, however, poor substrates for DNA polymerase-alpha, the main enzyme responsible for both repair and replicative DNA synthesis in human lymphocytes. In part, these properties may explain the selective anti-HIV activity of the 2',3'-dideoxynucleosides.

[0017] Chan et al. (1982) J. Cell Physiol., 111:28-32 studied the pathways of pyrimidine nucleotide metabolism in murine peritoneal macrophages and monocytes, and reported undetectable levels of deoxycytidine kinase or thymidine kinase in these cells. High levels of adenosine kinase were found, however.

[0018] Similar high levels of adenosine kinase have been found in human monocytes and human monocyte-derived macrophages (MDM). MDM were found to exhibit about one-tenth to about one-fourth the nucleoside kinase activity of GEM T lymphoblasts (e.g. ATCC CCL 119) toward uridine, deoxycytidine and thymidine, and about two-thirds the adenosine kinase activity of GEM cells. In addition, that adenosine kinase activity of MDM cells was at least about 10-fold higher than any of the other kinase activities. Those studies also indicated relatively low levels of nucleoside phosphorylation using AZT, dideoxycytidine (ddC) and 2',3'-dideoxyadenosine (ddA) in intact GEM T lymphoblasts and still lower levels with the MDM.

[0019] Several 2-substituted adenosine derivatives have been reported not to be deaminated by adenosine deaminase. For example, Coddington (1965) Biochim. Biophys. Acta, 99:442-451 reported that deoxyadenosine-1-N-oxide, as well as 2-hydroxy-, 2-methyl-, 2-chloro-, 2-acetamido-, and 2-methylthio-adenosines were neither substrates nor inhibitors for adenosine deaminase. Montgomery, in Nucleosides, Nucleotides, and Their Biological Applications, Rideout et al. eds., Academic Press, New York, page 19 (1983) provides a table of comparative K_m and V_{max} data for the deamination of adenosine, 2-halo-adenosines 2-halo-deoxyadenosines and 2-fluoro-arabinoadenosine that also indicates that those 2-halo adenine derivatives are poor substrates for the enzyme relative to adenine itself. Stoeckler et al. (1982) Biochem. Pharm., 31:1723-1728 reported that the 2'-deoxy-2'-azidoribosyl and 2'-deoxy-2'-azidoarabinosyl-adenine derivatives were substrates for human erythrocytic adenosine deaminase, whereas work of others indicated 2-fluoroadenosine to have negligible activity with adenosine deaminase.

[0020] 2-Chloro-2'-deoxyadenosine is phosphorylated by non-dividing (normal) human peripheral blood lymphocytes and is converted to the 5'-triphosphate. This adenine derivative is not catabolized significantly by intact human cells or cell extracts, and is phosphorylated efficiently by T lymphocytes. (Carson et al. (1980) Proc. Natl. Acad. Sci. USA, 77:6865-6869)

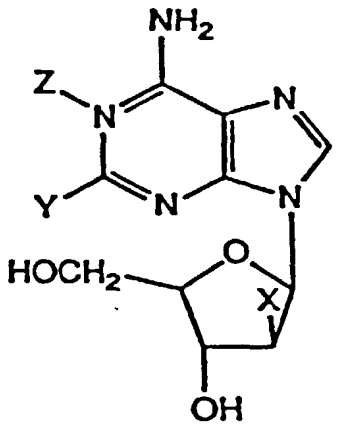
[0021] As discussed before, high levels of adenosine kinase have been found in murine peritoneal macrophages and in human monocytes. Adenosine kinase can phosphorylate 2'-deoxyadenosine derivatives, but does so less efficiently than deoxycytidine kinase. (Hershfield et al. (1982) J. Biol. Chem., 257:6380-6386)

[0022] Chemotherapeutic agents are described hereinafter that may be employed as therapeutic agents in the treatment of multiple sclerosis.

Summary of the Invention

[0023] The present invention relates the use of an substituted derivative for the preparation of a medicament for treating multiple sclerosis. The medicament has a pharmacologically acceptable carrier and a substituted adenine derivative dissolved or dispersed therein. The substituted adenine derivative is present in the pharmacologically acceptable carrier in an amount sufficient to provide a therapeutically effective dose over the course of treatment.

[0024] The substituted adenine derivatives useful for treating multiple sclerosis nay be represented by Formula I having a structural formula corresponding to:



wherein Z is O^- or absent,
Y is hydrogen or a substituent containing one to about 20 atoms that is free from net ionic charge at physiological pH values, provides a soluble adenine derivative and whose presence on the adenine moiety inhibits deamination of the adenine derivative by adenosine deaminase; and
X is hydrogen or fluoro, with the proviso that when Z is absent, Y is not hydrogen.

[0025] Particularly preferred compounds of Formula I are free of the Z group; i.e, Z is absent, and contain a halo group at the 2-position. The most preferred compounds are 2-chloro-2'-deoxyadenosine and 2-chloro-2'-deoxy-2'-arafluoroadenosine.

[0026] Methods for synthesizing all of the above compounds are indicated in U.S. Patent 5,106,837 (Carson et al., April 21, 1992, incorporated herein by reference).

[0027] The invention teaches that the disease condition of a patient having multiple sclerosis may be ameliorated by administration of an amount of the above-described composition having a sufficient quantity of the compound of Formula I to provide a therapeutically effective dose. Exemplary dosages range from about 0.04 to about 1.0 mg/kg/day, with dosages of about 0.04 to about 0.2 mg/kg/day being more preferred. Typically, the amount is sufficient to provide a concentration in the patient's plasma of about 0.5 nanomolar (nM) to about 50 nM, more preferably of about 1 nM to about 10 nM.

[0028] Preferably, the agent contemplated for use in the present invention is a 2-halo-2'-deoxyadenosine (2-halo-2'-deoxy-9,1'-beta-ribofuranosyladenine) or a 2-halo-2'-deoxy-2'-arafluoroadenosine, and most preferably the halo group is chloro.

[0029] A further aspect contemplated by the present invention comprises the use of subcutaneous injection for administering an effective amount of the active ingredient (agent) of the invention for treating multiple sclerosis.

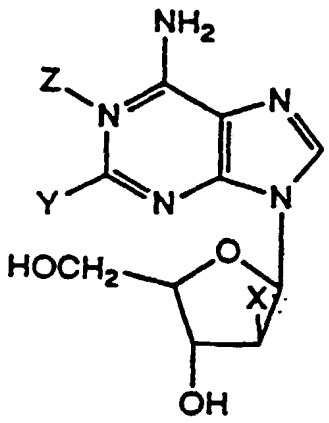
[0030] An alternative aspect contemplated by the present invention comprises the peroral administration of an effective amount of the active ingredient (agent) of the invention in a method of treating disease. Preferred compounds of Formula I for oral administration include compounds in which X is fluoro.

[0031] In each of the before-described methods, the substituted 2'-deoxyadenosine derivative is administered in a therapeutically effective amount. The effect of a compound of Formula I is dependent upon the route of administration and upon the time and dosage. As a consequence, one can tailor the dosage and duration for which a particular compound is administered to the stage of the disease and the condition of the patient being treated. Where the stage of multiple sclerosis is advanced or life-threatening, treatment may be more aggressive, and a therapeutically effective amount is an amount that is sufficient to kill at least 50 percent of the monocytes present but is less than that which substantially impairs bone marrow function as determined by usual procedures when administration is in vivo. The monocyte killing amount of a compound of Formula I is another measure of a therapeutically effective dose and monocyte death is measured at a time seven days after the initial administration.

Detailed Description of the Invention

A. Compounds

[0032] The present invention contemplates the use of substituted adenine derivatives, i.e. substituted-2'-deoxy-arabinofuranosyladenine, for treating multiple sclerosis. Preferred substituted adenine derivatives have a structure represented by the following formula, viz. Formula I:



wherein Z is an oxide radical (O^-) or is absent;
Y is hydrogen or a radical containing one to about twenty atoms that is free from net ionic charge at physiological pH values, provides a soluble adenine derivative, and whose presence on the adenine moiety inhibits deamination of the adenine derivative by adenosine deaminase; and
X is hydrogen or fluorine, with the proviso that Y is hydrogen only when Z is present.

[0033] Preferably, Y is chloro. Other Y substituents may be selected from the group consisting of lower alkyl, lower alkanoylamido, lower alkylthio and hydroxyl radicals. In particularly preferred embodiments, when Y is chloro, X is fluorine.

[0034] The preferred compound included in Formula I is 2-chloro-9,1'-beta-D-2'-deoxyribosyladenine, otherwise known as 2-chlorodeoxyadenosine or CdA.

[0035] Of the compounds of Formula I, those where X is fluoro are among the preferred compounds for use by oral administration.

[0036] Other illustrative compounds included in Formula I are:

2-bromo-9,1'-beta-D-2'-deoxyribosyladenine;
2-methyl-9,1'-beta-D-2'-deoxyribosyladenine;
2-fluoro-9,1'-beta-D-2'-deoxyribosyladenine;
2-acetoamido-9,1'-beta-D-2'-deoxyribosyladenine;
2-methylthio-9,1'-beta-D-2'-deoxyribosyladenine;
2-chloro-9,1'beta-2'-deoxy-2'-fluoro-D-arabinofuranosyl-adenine;
2-bromo-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyl-adenine;
2-(N-acetamido)-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine;
2-methylthio-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine.

[0037] Further illustrative of compounds of Formula I include the following arabinofuranosyl derivatives of adenine:

2-methyl-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyl-adenine;
2-isopropyl-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyl-adenine;
2-hydroxy-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyl-adenine;
2-chloro-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-l-N-oxide;
2-fluoro-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;
2-bromo-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;
2-methyl-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;
2-(N-acetamido)-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-1-N-oxide;
2-hydroxy-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-l-N-oxide;
2-(2-methylbutyl)-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine-l-N-oxide;
2-fluoro-9,1'-beta-D-2'-deoxyadenosine-l-oxide;
and
2-chloro-9,1'-beta-D-2'-deoxyadenosine-1-oxide.

[0038] It is noted that when X is hydrogen the sugar ring can be named as a 2'-deoxyribosyl or 2'-deoxyarabinofuranosyl radical. Both nomenclatures are utilized herein. When the class of compounds embraced by Formula I is discussed, all of the compounds are considered herein as derivatives of arabinose. However, when specific compounds of the subclass where X = H are discussed, the more familiar deoxyribose nomenclature is used, such as in deoxyadenosine. These compounds are also referred to herein more simply as adenine derivatives.

[0039] In the above formulas, and in all other formulas shown herein, hydrogen atoms on the purine and furanosidyl rings that are not needed to show conformation about a particular bond are not shown. Thus, the 8-position adenine hydrogen is not shown.

[0040] It is also to be understood that the D isomers of compounds of the formulas are the isomers contemplated. It is further to be noted that the designation "halo" used herein is meant to include fluorine, chlorine and bromine derivatives, and to exclude iodine derivatives, which are unstable and decompose, and astatine derivatives that are radioactive. Where specific halogen derivatives are intended, those compounds are named specifically.

[0041] As used herein, "a substituent free from net ionic charge" includes both charged and uncharged radicals, wherein when the substituent radical is charged, an internal zwitterionic charge pair is present that results in the absence of a net ionic charge for the molecule at physiologic pH values. N-oxide compounds are exemplary of such substituents.

[0042] As used herein, a "soluble adenine derivative" is an adenine derivative which is able to dissolve and remain soluble in a body fluid such as blood at a therapeutically effective dose as is discussed hereinafter.

[0043] As used herein, a "substituent whose presence on the adenine moiety inhibits deamination of an adenine derivative by adenosine deaminase" is one that, when 100 microliters of a 1 millimolar solution of the substituted adenine derivative is incubated for three hours at room temperature with 25 units of calf spleen adenosine deaminase (1 unit catalyzes the deamination of 1 micromole of adenosine per minute), produces a single UV-absorbing spot upon cellulose-thin layer chromatography of the reaction mixture whose R_f value is the same as that of the substituted adenine derivative used.

[0044] The metabolism of a compound by adenosine deaminase can be investigated by the following procedure. The individual nucleosides, at concentrations from 5-200 μM in 10 mM sodium phosphate, pH 7.5, are incubated at 18-20 degrees C with 0.01 EU/ml calf intestinal adenosine deaminase. The change in the optical density at 265 nm and 250 nm is monitored spectrophotometrically. The K_m and V_{max} values are determined by the Lineweaver-Burke method, utilizing the ΔE^{M}_{265} between adenosine and inosine.

[0045] The ratio V_{max}/K_m also provides a measure of relative efficiency of deamination by the enzyme. A substituent that provides a V_{max}/K_m ratio that is about 1 percent or less than that for the ratio obtained using 2'-deoxyadenosine is also a "substituent whose presence on the adenine moiety inhibits deamination of an adenine derivative by adenosine deaminase."

[0046] As used herein, lower alkyl radicals include C_1-C_6 straight chain, branched and cyclic alkyl groups, for example, methyl, ethyl, n-butyl, t-butyl, n-hexyl, 1-ethylbutyl, cyclopentyl, cyclohexyl and the like. Lower alkanoylamido radicals include C_1-C_6 radicals, for example, formamido, acetylamido, propionamido, hexamoylamido and the like. Lower alkylthio radicals include C_1-C_6 straight chain, branched and cyclic alkyl groups as discussed above linked to a thio radical.

[0047] The pharmacologically acceptable salts of a compound of the above Formula are also utilized. The phrase "pharmacologically acceptable salts," as used herein, refers to non-toxic acid addition salts that are generally prepared by reacting a compound with a suitable organic or inorganic acid. Representative salts include the hydrochloride, hydrobromide, sulfate, phosphate, citrate, acetate, maleate and the like.

B. Compositions

[0048] A compound of Formula I dissolved or dispersed in or together with a pharmacologically acceptable carrier constitutes a composition of this invention.

[0049] A compound of Formula I and its pharmacologically acceptable salts are useful in both short and long term treatment. For instance, a 2-substituted-9,1'-beta-2'-deoxy-2'-fluoro-D-arabinofuranosyladenine is administered to the patient internally, e.g., subcutaneously by injection, parenterally, orally, or rectally as a suppository, in an effective amount.

[0050] Although a compound of Formula I and its pharmacologically acceptable salts can be administered as the pure chemical, it is preferred that it be administered as a pharmaceutical composition. In either event, it is administered in an amount sufficient to provide a therapeutically effective dose as is discussed hereinafter.

[0051] Accordingly, the present invention utilizes a pharmaceutical composition comprising a therapeutically effective dose of a compound of Formula I or a pharmacologically acceptable salt thereof, hereinafter referred to as the "active ingredient" or "agent," dissolved or dispersed in a pharmacologically acceptable carrier or diluent.

[0052] A pharmaceutical composition is prepared by any of the methods well known in the art of pharmacy all of which involve bringing into association the active compound and the carrier therefor. For therapeutic use, a compound utilized in the present invention can be administered in the form of conventional pharmaceutical compositions. Such compositions can be formulated so as to be suitable for oral, subcutaneous, or parenteral administration, or as suppositories. In these compositions, the agent is typically dissolved or dispersed in a physiologically tolerable carrier.

[0053] A carrier or diluent is a material useful for administering the active compound and must be "pharmacologically acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. Thus, as used herein, the phrases "physiologically tolerable" and "pharmacologically acceptable" are used interchangeably and refer to molecular entities and compositions that do not produce an allergic or similar untoward reaction, such as gastric upset, dizziness and the like, when administered to a mammal. The physiologically tolerable carrier can take a wide variety of forms depending upon the preparation desired for administration and the intended route of administration.

[0054] As an example of a useful composition, a compound of Formula I can be utilized in liquid compositions such as sterile suspensions or solutions, or as isotonic preparations containing suitable preservatives. Particularly well-suited for the present purposes are injectable media constituted by aqueous injectable isotonic and sterile saline or glucose solutions. Additional liquid forms in which these compounds can be incorporated for administration include flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil, peanut oil, and the like, as well as elixirs and similar pharmaceutical vehicles.

[0055] The agents can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain stabilizers, preservatives, excipients, and the like in addition to the agent. The preferred lipids are the phospholipids and the phosphatidyl cholines (lecithins), both natural and synthetic.

[0056] Methods to form liposomes are known in the art. See, for example, Prescott, Ed., Methods in Cell Biology, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

[0057] An agent of Formula I can also be used in compositions such as tablets or pills, preferably containing a unit dose of the compound. To this end, the agent (active ingredient) is mixed with conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, gums, or similar materials as non-toxic, physiologically tolerable carriers. The tablets or pills can be laminated or otherwise compounded to provide unit dosage forms affording prolonged or delayed action.

[0058] It should be understood that in addition to the aforementioned carrier ingredients the pharmaceutical formulation described herein can include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like, and substances included for the purpose of rendering the formulation isotonic with the blood of the intended recipient.

[0059] The tablets or pills can also be provided with an enteric layer in the form of an envelope that serves to resist disintegration in the stomach and permits the active ingredient to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, including polymeric acids or mixtures of such acids with such materials as shellac, shellac and cetyl alcohol, cellulose acetate phthalate, and the like. A particularly suitable enteric coating comprises a styrene-maleic acid copolymer together with known materials that contribute to the enteric properties of the coating. Methods for producing enteric coated tablets are described in U.S. Patent 4,079,125 to Sipos, which is herein incorporated by reference.

[0060] The term "unit dose", as used herein, refers to physically discrete units suitable as unitary dosages for

administration to patients, each such unit containing a predetermined quantity of the agent calculated to produce the desired therapeutic effect in association with the pharmaceutically acceptable diluent. Examples of suitable unit dosage forms in accord with this invention are tablets, capsules, pills, powder packets, granules, wafers, cachets, teaspoonfuls, dropperfuls, ampules, vials, segregated multiples of any of the foregoing, and the like.

[0061] Administration of the compound by subcutaneous injection is a particularly attractive mode of administration due to the favorable pharmacokinetics of this mode of administration.

[0062] Oral administration of the compound is also an attractive mode of administration. One drawback usually associated with oral administrations of bioactive nucleoside compounds, however, is their potential decomposition in the acidic conditions of the stomach. That is, the glycosidic bond tends to hydrolyze under acid conditions.

[0063] However, where oral administration is desired, substitutions on the 2-position of the adenine ring of the compound of Formula I are utilized along with a 2'-fluoro-substituted arabinofuranosidyl ring.

[0064] Marquez et al. (1987) Biochem. Pharm., 36:2719-2722 reported preparation of 2'-fluoro-2',3'-dideoxyribose and 2'-fluoro-2',3'-dideoxyarabinose derivatives of adenine. Their findings stated that both derivatives were stable at a pH value of 1 at 37 degrees C, whereas dideoxyadenosine had a half-time of 35 seconds under those conditions.

[0065] The ability of an adenine derivative to be or not to be a substrate for adenosine deaminase is more a function of the 2-substituent or lack thereof on the adenine portion of the molecule than a function of substituents on the linked sugar ring portion, at least as far as the substituents on both rings herein are concerned.

C. Methods

[0066] As noted earlier, a method of treating multiple sclerosis is contemplated herein. Broadly in that method, a patient having multiple sclerosis is treated with a composition containing a pharmacologically acceptable carrier having dissolved or dispersed therein, as an active ingredient, a substituted adenine derivative (substituted 2'-deoxy-adenosine) whose structure corresponds to that of previously discussed Formula I. The substituted adenine derivative is present in the composition in an amount sufficient to provide a therapeutically effective dose over the period of contacting. The above treatment is typically repeated periodically such as weekly or monthly over a time period of several months to about one year.

[0067] The amount of a compound of Formula I present in a composition and used in a method as described above is a function of several variables. Among those variables is the method of administration. Exemplary concentrations for various modes of administration are illustrated hereinafter.

[0068] When the administration is in vivo, the amount administered is less than that which substantially impairs bone marrow functions as determined by usual procedures. An amount sufficient to kill at least about 50 percent of the monocytes originally present while not substantially impairing bone marrow function over the course of the administration of the agent is one way of defining a therapeutic dose.

[0069] The above amount of a 2'-deoxyadenine derivative of Formula I or its pharmacologically acceptable salt present in the composition is also an amount sufficient to provide about 0.04 to about 1.0 mg/kg of body weight of the treated host mammal per day, more preferably about 0.04 to about 0.20 mg/kg/day, more preferably still at about 0.05 to about 0.15 mg/kg/day and most preferably about 0.1 mg/kg/day, when given in vivo. This amount is another way of defining a therapeutically effective dose that is particularly useful when a compound of Formula I is administered by infusion.

[0070] The molar plasma concentration of the compound of Formula I or the pharmacologically acceptable salts thereof during treatment is preferably in the range of about 1 nanomolar (nM) to about 100 nM, particularly about 5 nM to about 50 nM, and more preferably about 10 nM to about 20 nM. Molarity of the 2'-deoxyadenine derivative in plasma of the treated (administered to) patient thus provides still another measure of a therapeutically effective dose from which the amount in a composition can be calculated.

[0071] It is to be understood that the above therapeutically effective dosages need not be the result of a single administration, and are usually the result of the administration of a plurality of unit doses. Those unit doses can in turn comprise portions of a daily or weekly dosage, and thus, the therapeutically effective dose is determined over the period of treatment (contacting).

[0072] Oral administration and subcutaneous injection are preferred modes of administration, as already noted. To achieve the desired plasma concentration of the agent, a range of doses can be employed depending upon the specific mode of administration, objective of the particular treatment, the particular compound being used, and like considerations.

[0073] For example, for oral administration, the daily dose can be about 0.04 to about 1.0 mg/kg of body weight, more preferably about 0.04 to about 0.20 mg/kg/day, more preferably still at about 0.05 to about 0.15 mg/kg/day, and most preferably about 0.1 mg/kg body weight. In general, the amount of active substituted adenine derivative administered can vary over a relatively wide range to achieve, and preferably maintain, the desired plasma concentration.

[0074] Unit dosage forms of the adenine derivative can contain about 0.1 milligrams to about 15 milligrams thereof.

A preferred unit dosage form contains about 0.1 to about 1 milligram of agent and can be administered 2 to 5 times per day. However, it should be noted that continuous infusion at a rate designed to maintain the above described plasma concentration is also contemplated.

[0075] Duration of a particular treatment can also vary, depending on severity of the disease, whether the treatment is intended for an acute manifestation or for prophylactic purposes, and like considerations. Typical administration lasts for a time period of about 5 to about 14 days, with a 7-day time course being usual. Courses (cycles) of administration can also be repeated at monthly intervals, or parenteral unit dosages can be delivered at weekly intervals. Oral unit dosages can be administered at intervals of one to several days to provide the determined therapeutically effective dose. Thus, in vivo administration of a before-discussed dosage over a time period of about 5 to about 14 days or at weekly or daily intervals provides an amount sufficient to kill at least about 50 percent of the originally present monocytes.

[0076] This method of treatment produces a decrease in the level of monocytes in the blood due to the toxicity of the utilized compounds of Formula I toward monocytes. This method can be used to reduce the number of monocytes circulating in a treated mammal's blood stream by about 90 percent of the number present prior to treatment over a seven day treatment period with the level of circulating monocytes returning to pretreatment levels about two weeks after the treatment stopped. This exemplary study is illustrated hereinafter.

[0077] A less aggressive treatment regimen is also therefore contemplated. Here, a before-described dosage, e.g., plasma concentration, is again utilized, but for a shorter contact time course so that monocyte function is impaired, but the monocytes are not substantially killed as is the result of the before- discussed treatment regimen. Impairment of monocyte function is herein defined as a reduction of at least about 25 percent in the spontaneous secretion of interleukin-6 (IL-6) by monocytes cultured in the presence of a compound of Formula I for a time period of 72 hours. A useful assay for monocyte impairment is discussed hereinafter.

[0078] In an exemplary treatment regimen, a compound of Formula I is administered in an amount of about 0.04 to about 1.0 mg/kg/day, more preferably about 0.04 to 0.20 mg/kg/day, more preferably still about 0.05 to about 0.15 mg/kg/day, and most preferably about 0.1 mg/kg/day. Such treatments typically provide a plasma concentration of about 0.5 nM to about 50 μM, and more preferably about 10 nM to about 10 μM. That single administration is repeated periodically such as weekly over a time period of several months, e.g. about three to about nine months. In usual practice, treatments are administered over a period of about five to seven days and are repeated at about three to about four week intervals for several months, e.g. about three to about nine months.

[0079] Such an administration can be carried out on an out-patient basis for humans using an intravenous infusion lasting about 2 to about 4 hours in a doctor's office. As such, the treatment is far less invasive than is a continuous infusion over a period of several days that usually requires a hospital stay for the host mammal; i.e., human patient. A less invasive continuous infusion method that employs a pump linked to a catheter that automatically infuses a predetermined dosage permits the patient to be ambulatory during the infusion.

[0080] Any of the before-discussed methods can be carried out while the patient is continuing therapy with a previous drug or drugs, or after cessation of such prior treatment. When a patient is removed from a prior even partially effective treatment, a flare-up (exacerbation) of symptoms sometimes occurs that typically abates after several months. In addition, where a prior treatment regimen is halted while an above method is practiced, that prior treatment can be continued after cessation of an above method, often with quite positive results.

[0081] Dosage schedules and protocols for administering 2-chlorodeoxyadenosine to treat patients having disease conditions other than multiple sclerosis have been reviewed in the literature. (Ernest Beutler (1992), The Lancet, 340: 952-956) To a first approximation, the pharmacokinetics of 2-chlorodeoxyadenosine and its effect upon monocyte levels are independent of the disease condition being treated.

D. Compound Synthesis

[0082] A compound useful herein where Z is absent can be prepared by condensing an appropriately substituted adenine directly with an appropriately substituted sugar ring as by the techniques described in Montgomery et al., (1986) J. Med. Chem., 29:2389-2392, by the method taught in U.S. Patent No. 4,082,911, or as described in the citations of Herdewijn at al. (1987) J. Med. Chem., 30:2131-2137, which disclosures are incorporated herein by reference. An appropriately substituted adenine can be prepared by following reported literature syntheses or analogous syntheses. Still further, Wright et al. (1987) J. Org. Chem., 35:4617-4618 recently prepared 2-chloro- and 2-bromo-2'-deoxyadenosines by direct reaction of the appropriate 2,6-dihalo purine with a 3',5'-protected-alpha-l-chlororibose using sodium hydride in acetonitrile, followed by treatment with methanolic ammonia at 60 degrees C to deprotect the resulting 3',5'-hydroxyls and form the 6-amino group of the finally produced adenosine. Fukukawa et al. (1983) Chem. Pharm. Bull., 31(5):1582-1592 also report syntheses of 2'-deoxy-2'-arahalo-substituted adenosine derivatives.

[0083] The 2'-deoxy-2'-fluoroarabinofuranosyladenine compounds of the present invention are produced as described hereinafter in the Examples. The synthesis is similar to that taught in Marquez at al. (1987) Biochem. Pharmacol., 36:2719-2722, herein incorporated by reference, in which 6-chloropurine is condensed with 3-O-acetyl-5-O-

benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide. The functionalized halosugar is produced according to the method reported by Reichnan et al. (1975) J. Carbohyd. Res., 42:233 and the 2'-deoxy-2'-fluoro-arabinofuranosyladenine compound is obtained by ammonolysis with concentrated methanolic ammonia which removes the protective groups. Syntheses of 2-substituted-2'-deoxy-2'-arafluoroadenosines are also described in U.S. Patents No. 4,918,179 and No. 5,034,518, whose disclosures are incorporated by reference.

[0084] The adenosine-1-N-oxide group of compounds, i.e, where Z is present, is of particular interest since those materials, per se, are most likely not incorporated into a growing polynucleotide chain because the presence of the N-oxide group probably interferes with hydrogen bonding during that synthesis. Rather, it is believed that the N-oxide compounds are reduced by an endogenous reductase prior to their incorporation into and termination of the growing chain.

[0085] Nevertheless, being free from a net ionic charge, but possessing an internal zwitterionic charge pair, the N-oxide compounds can penetrate cell membranes. Those compounds are also somewhat more water-soluble than are the corresponding un-oxidized compounds.

[0086] Without wishing to be bound by theory, it is nevertheless believed that the N-oxide compounds enter the cell and are phosphorylated, in keeping with the report of such phosphorylation in Lindberg et al. (1967) J. Biol. Chem., 242:350-356. A pool of such derivatives is maintained intracellularly until such time as the N-oxide function is reduced and the nucleotide is incorporated to terminate the appropriate, growing polynucleotide chain.

[0087] The 1-N-oxide compounds are readily prepared by the method of Klenow et al. (1961) Biochim. Biophys. Acta, 52:386-389, with slight modification, as discussed hereinafter.

[0088] The present invention is further illustrated by the following examples which are not intended to limit the scope of the invention in any way.

Example 1

Treatment of Multiple Sclerosis with CdA

[0089] A study of four patients with chronic multiple sclerosis was undertaken. Each patient was first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values. Each of the patients was then treated with CdA dissolved in sterile preservative-free isotonic saline. The CdA was administered intravenously at a dosage of 0.1 mg/kg each day for a total of seven days. Each patient received six courses of intravenous therapy, once monthly for a total of six months. Patients were examined on a daily basis while hospitalized. During that time, daily blood counts and twice weekly blood chemistries were performed on each patient. CdA levels were also measured in blood and spinal fluid.

[0090] The neurologic function of each of these patients was measured using the expanded Krutzke disability status scale (EDSS), and the Scripps neurologic rating scale (SNRS).

[0091] There was no evidence of any significant toxic side effects. None of the four patients exhibited any nausea, vomiting, skin rash, or hepatic or renal dysfunction. Each of the patients developed lymphopenia (reduction in the level of lymphocytes in the blood), with absolute lymphocyte counts being suppressed 0.5 to about 10 percent for more than one year.

[0092] Monocyte levels dropped after each treatment. For example, in one patient, monocytes dropped 40 percent after the first treatment, and were substantially absent after each of the remaining five treatments. For another patient, monocytes were substantially absent after two treatments, and depleted by about 85, 50, 40 and 73 percents after the other four treatments.

[0093] In some cases, there was leukopenia (reduction in the level of total white blood cells). There was also a modest macrocytosis in all patients lasting for six to eight months after cessation of treatment. However, the platelet counts of all four patients remained within the normal range. In essence, there was no evidence of toxicity in these four patients with normal marrow, hepatic and renal functions. Likewise, the side effects of CdA were imperceptible in these four patients.

[0094] Measurement of neurologic function using the EDSS and SNRS scales provided evidence of improvement in all four patients during treatment with CdA. Cerebrospinal fluid studies (CSF) showed a marked drop in lymphocyte counts and, quite remarkably, complete disappearance of IgG oligoclonal bonds in all cases. There was no significant change in total CFS IgG.

[0095] In particular, the SNRS data demonstrated between 5 and 50 percent improvement from baseline pre-treatment values in all patients. One of the four patients was completely bed-ridden at the beginning of the treatment, and this patient was able to walk with the aid of a walker by the end of the treatment. All patients reported subjective feelings of improved energy and stamina.

Example 2

Treatment of Multiple Sclerosis with CdA

[0096] The study indicated above in Example 1 involving four patients was then enlarged. A double-blind placebo study involving 50 patients was performed to further demonstrate the effectiveness of 2-CdA for treating multiple sclerosis. The dosage schedules and protocols for this second study were similar or substantially the same as the dosage schedules and protocols employed in Example 1. The same two neurologic rating scales were employed, i.e. the SNRS scale and the EDSS scale. 28 patients were tested with the SNRS scale; 23 patients were tested with the EDSS scale. The SNRS scale is substantially more sensitive than the EDSS scale. The inventor's most recent data indicate that a highly significant improvement (p=0.0004) was observed in patients treated with 2-CdA as compared with placebo in the 28 patients tested for changes in the SNRS scale.

Table I

Changes in SNRS

	Absolute	Relative	
CdA	4.83 ± 5.71	0.076 ± 0.089	(N=14)
Placebo	-4.40 ± 5.14	-0.062 ± 0.071	(N=14)
	p=0.0004	p=0.0005	

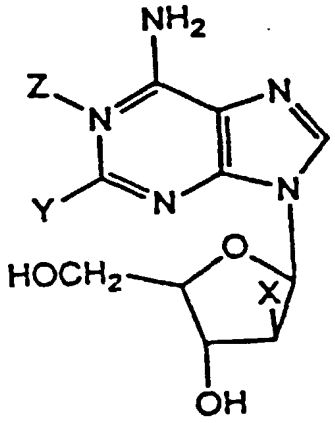
Changes in EDSS

	Absolute	Relative	
CdA	-0.018 ± 0.222	-0.011 ± 0.081	(N=12)
Placebo	0.038 ± 0.9233	0.039 ± 0.240	(N=11)
	p=0.84	p=0.50	

SNRS	0	100
EDSS	10	1
	Worst	Best

Claims

1. Use of a substituted adenine derivative having a structure represented by the formula:



or a pharmacologically acceptable salt thereof
where:

Z is O^- or absent;
Y is hydrogen or a substituent containing one to about 20 atoms that is free from net ionic charge at physiological pH values, produces a soluble adenine derivative, and whose presence on the adenine moiety inhibits deamination of said adenine derivative by adenosine deaminase; and
X is hydrogen or fluoro,
with the proviso that when Z is absent, Y is not hydrogen for the preparation of a medicament for treating multiple sclerosis.

2. The use of claim 1, wherein Z is absent and Y is halo group.

3. The use of claim 1 wherein said substituted adenine is 2-chloro-2'-deoxyadenosine.

4. The use of any one of claims 1 to 3, wherein the treatment is by application of the adenine derivative to the patient's serum.

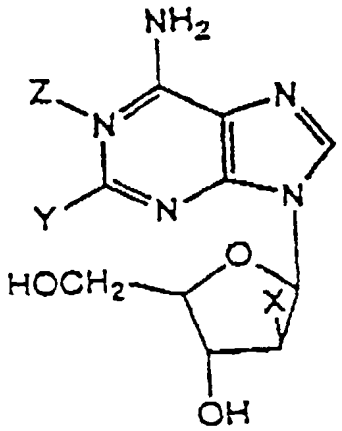
5. The use of any one of claims 1 to 4, wherein the medicament is in the form of a subcutaneous injectable medium.

6. The use of any one of claims 1 to 4, wherein the medicament is in the form of an intravenous infusion.

7. The use of any one of claims 1 to 4, wherein the medicament is in the form of capsules, powders or granules, in the form of tablets or pills that are optionally provided with an enteric layer, in the form of a suppository, in the form of a solution, suspension or elixir or in the form of liposomes.

Patentansprüche

1. Verwendung eines substituierten Adeninderivats mit einer Struktur der Formel:



oder eines pharmakologisch annehmbaren Salzes davon,
worin:

Z O^- ist oder nicht vorliegt;

Y Wasserstoff oder ein Substituent ist, welcher 1 bis etwa 20 Atome aufweist, der frei ist von einer Netto-Ionenladung bei physiologischen pH-Werten, ein lösliches Adeninderivat erzeugt und dessen Anwesenheit auf dem Adeninrest eine Desaminierung des Adeninderivats durch Adenosindesaminase inhibiert; und

X Wasserstoff oder Fluor ist,

mit der Maßgabe, daß, wenn Z nicht vorliegt, Y nicht Wasserstoff ist, für die Herstellung eines Medikamentes zur Behandlung von Multiple Sklerose.

2. Verwendung gemäß Anspruch 1, worin Z nicht vorliegt und Y eine Halogengruppe ist.

3. Verwendung gemäß Anspruch 1, worin das substituierte Adenin 2-Chlor-2'-desoxyadenosin ist.

4. Verwendung gemäß einem der Ansprüche 1 bis 3, worin die Behandlung durch die Anwendung des Adeninderivats auf das Serum des Patienten geschieht.

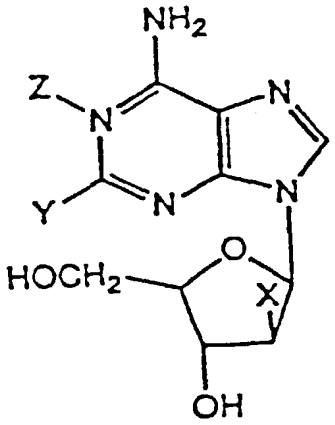
5. Verwendung gemäß einem der Ansprüche 1 bis 4, wobei das Medikament in Form eines subkutanen injizierbaren Mediums vorliegt.

6. Verwendung gemäß einem der Ansprüche 1 bis 4, wobei das Medikament in Form einer intravenösen Infusion vorliegt.

7. Verwendung gemäß einem der Ansprüche 1 bis 4, wobei das Medikament in Form von Kapseln, Pulvern oder Granulaten, in der Form von Tabletten oder Pillen, welche vorzugsweise mit einer enterischen Schicht versehen sind, in der Form ein Zäpfchens, in der Form einer Lösung, einer Suspension oder eines Elixiers oder in der Form von Liposomen vorliegt.

Revendications

1. Utilisation d'un dérivé d'adénine substituée ayant la structure représentée par la formule :



ou d'un sel pharmacologiquement acceptable d'un tel dérivé

formule dans laquelle :
Z représente O^- ou est absent ;
Y représente l'hydrogène ou un substituant contenant de 1 à environ 20 atomes qui est dépourvu de charge ionique nette aux valeurs de pH physiologiques, produit un dérivé soluble de l'adénine et dont la présence sur le motif adénine inhibe la désamination dudit dérivé de l'adénine par l'adénosine-désaminase ; et
X représente l'hydrogène ou fluoro,
étant entendu que lorsque Z est absent, Y ne représente pas l'hydrogène,
pour la préparation d'un médicament pour le traitement de la sclérose en plaques.

2. Utilisation selon la revendication 1, dans laquelle Z est absent et Y est un groupe halogéno.

3. Utilisation selon la revendication 1, dans laquelle ladite adénine substituée est la 2-chloro-2'-déoxyadénosine.

4. Utilisation selon l'une quelconque des revendications 1 à 3, dans laquelle le traitement se fait par application du dérivé de l'adénine au sérum du patient.

5. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le médicament est sous la forme d'un milieu injectable par voie sous-cutanée.

6. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le médicament est sous la forme d'une perfusion intraveineuse.

7. Utilisation selon l'une quelconque des revendications 1 à 4, dans laquelle le médicament est sous la forme de capsules, poudres ou granules, sous la forme de comprimés ou de pilules qui sont éventuellement pourvus d'une couche entérique, sous la forme d'un suppositoire, sous la forme d'une solution, d'une suspension ou d'un élixir ou sous la forme de liposomes.

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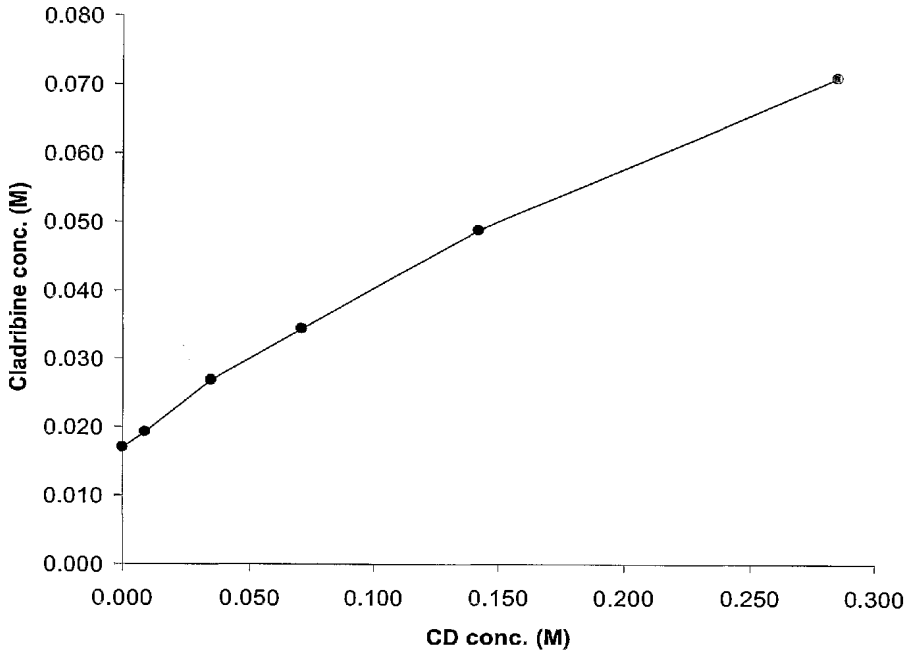
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[Continued on next page]

(54) Title: ORAL FORMULATIONS OF CLADRIBINE



(57) Abstract: ABSTRACT OF THE DISCLOSURE Provided are compositions of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine.

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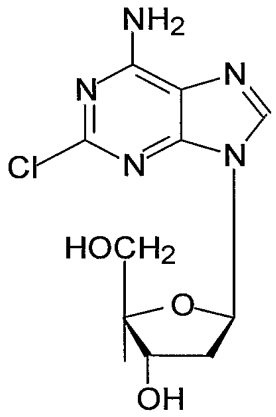
ORAL FORMULATIONS OF CLADRIBINE

FIELD OF THE INVENTION

The invention relates to a composition comprising a complex cladribine-cyclodextrin complex formulated into a solid oral dosage form and to a method for enhancing the oral bioavailability of cladribine.

BACKGROUND OF THE INVENTION

Cladribine, which is an acid-labile drug, has the chemical structure as set forth below:



It is also known as 2-chloro-2′-deoxyadenosine or 2-CdA. Cladribine exists as a white, nonhydroscopic, crystalline powder, consisting of individual crystals and of crystalline aggregates.

Cladribine is an antimetabolite which has use in the treatment of lymphoproliferative disorders. It has been used to treat experimental leukemias such as L1210 and clinically for hairy cell leukemia and chronic lymphocytic leukemia as well as Waldenstrom's macroglobulinaemia. It has

also been used as an immunosuppressive agent and as a modality for the treatment of a variety of autoimmune conditions including rheumatoid arthritis, inflammatory bowel disease (*e.g.*, Crohn's disease, ulcerative colitis) and multiple sclerosis (see *e.g.*, J. Liliemark, *Clin. Parmacokinet*, 32(2): 120-131, 1997). It has also been investigated, either experimentally or clinically in, for example, lymphomas, Langerhan's cell histiocytosis, lupus erythematosus, chronic plaque psoriasis, Sezary syndrome, Bing-Neel syndrome, recurrent glioma, and solid tumors.

Oral delivery of drugs is often preferred to parenteral delivery for a variety of reasons, foremost patient compliance, or for cost or therapeutic considerations. Patient compliance is enhanced insofar as oral dosage forms alleviate repeated health care provider visits, or the discomfort of injections or prolonged infusion times associated with some active drugs. At a time of escalating health care costs, the reduced costs associated with oral administration versus parenteral administration costs gain importance. The cost of parenteral administration is much higher due to the requirement that a health care professional administer the cladribine in the health care provider setting, which also includes all attendant costs associated with such administration. Furthermore, in certain instances, therapeutic considerations such as the need for a slow release of cladribine over a prolonged period of time may be practically met only by oral or transmucosal delivery.

However, to date the oral delivery of cladribine has been plagued by low bioavailability (see, *e.g.*, J. Liliemark *et al., J. Clin. Oncol.*, 10(10): 1514-1518, 1992), and suboptimal interpatient variation (see, *e.g.*, J. Liliemark, *Clin. Pharmacokinet*, 32 (2): 120-131, 1997). See also, A. Tarasuik, *et al.* reporting poor absorption and pH dependent lability (*Arch. Immunol. et Therapiae Exper.*, 42: 13-15, 1994).

Cyclodextrins are cyclic oligosaccharides composed of cyclic α-(1→4) linked D-glucopyranose units. Cyclodextrins with six to eight units have

been named α-, β- and γ-cyclodextrin, respectively. The number of units determines the size of the cone-shaped cavity which characterizes cyclodextrins and into which drugs may be included to form stable complexes. A number of derivatives of α-, β- and γ-cyclodextrin are known in which one or more hydroxyl groups is/are replaced with ether groups or other radicals. These compounds are thus known complexing agents and have been previously used in the pharmaceutical field to form inclusion complexes with water-insoluble drugs and to thus solubilize them in aqueous media.

Recently, Schultz *et al.*, in U.S. Patent No. 6,194,395 B1, have described complexing and solubilizing cladribine with cyclodextrin. The Schultz *et al.* patent primarily addresses the problems inherent in previously described aqueous formulations of cladribine, particularly for subcutaneous and intramuscular injection. Schultz *et al.* have found that cladribine is not only significantly more soluble in aqueous media when formulated with cyclodextrin, but also is more stable against acid-catalyzed hydrolysis when combined with cyclodextrin. The latter finding is taught to be of particular benefit in the formulation of solid oral dosage forms, where the compound would normally undergo hydrolysis in the acid pH of the stomach contents. Schultz *et al.* do not appear to have described any actual work in connection with solid oral dosage forms. In fact, they describe only one method of preparing the solid dosage form, which is a melt extrusion process, in which the cladribine and cyclodextrin are mixed with other optional additives and then heated until melting occurs. Furthermore, the broad dosage ranges of 1 mg to 15 mg of cladribine and 100 mg to 500 mg of cyclodextrin listed in the patent suggest no criticality to the particular amount of cyclodextrin to be present with a given amount of cladribine in a solid oral dosage form. Indeed, these dosage ranges include many combinations which may be suitable as mixtures but not for complex formation. For example, a ratio of 1 mg of cladribine to 500 mg of cyclodextrin contains too much cyclodextrin, so

that the drug would not readily leave the complex and achieve its therapeutic function. On the other hand, 15 mg of cladribine and only 100 mg of cyclodextrin would not be enough to complex that amount of cladribine.

The Schultz *et al.* patent does suggest improving the stability of cladribine in oral dosage forms by combining/complexing it with cyclodextrin, but does not suggest improving the drug's oral bioavailability by such means; in fact, the patent does not describe or suggest a method for enhancing or maximizing the bioavailability of cladribine from a solid oral dosage form of cladribine and cyclodextrin, or a composition specially designed to do so.

Many workers have studied the solubility of specific drugs in water containing various concentrations of selected cyclodextrins in order to demonstrate that increasing concentrations of cyclodextrins increase the solubility of the drugs at selected temperatures and pH levels, as for example reported in the Schultz *et al.* patent. Phase solubility studies have also been performed by various workers in order to elucidate the nature of the complex formation, for example, whether the cyclodextrin and drug form a 1:1 complex or a 1:2 complex; see, for example, Harada *et al.* U.S. Patent No. 4,497,803, relating to inclusion complexes of lankacidin-group antibiotics with cyclodextrin, and Shinoda *et al.* U.S. Patent No. 4,478,995, relating to a complex of an acid addition salt of (2'-benzyloxycarbonyl)phenyl trans-4-guanidinomethylcyclohexanecarboxylate with a cyclodextrin.

While Schultz *et al.* teach that a cladribine-cyclodextrin complex improves the water solubility and acid stability of cladribine, the art does not suggest how to maximize or enhance the benefits of the complexation in terms of bioavailability and interpatient variation when the complex is to be administered in a solid oral dosage form.

SUMMARY OF THE INVENTION

It has now been found that amorphous cyclodextrins can be combined with cladribine to form a particularly advantageous product which can be incorporated into a solid oral dosage form. This product is a complex cladribine-cyclodextrin complex, and the solid oral dosage form containing it improves oral bioavailability and/or achieves lower interpatient and/or intrapatient variation of the drug.

The present invention provides a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, and a pharmaceutical composition comprising said complex, formulated into a solid oral dosage form. Thus, the cyclodextrin itself is amorphous, the inclusion complex with cladribine is amorphous (and is preferably saturated with cladribine) and the free cladribine which forms the non-inclusion complex is amorphous.

The invention also provides a method for increasing or enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof, a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form which maximizes the amount of cladribine in the inclusion and non-inclusion complexes.

The invention further provides for treatment of conditions responsive to administration of cladribine in mammals by administering thereto the composition of the invention. Use of cladribine in the preparation of the pharmaceutical compositions of the invention for administration to treat

cladribine-responsive conditions and for enhancing the oral bioavailability of cladribine is also provided.

Still further, the invention provides a process for the preparation of a complex cladribine-cyclodextrin complex which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

In yet a further aspect the invention provides a pharmaceutical composition obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

BRIEF DESCRIPTION OF THE DRAWING

A more complete appreciation of the invention and its many attendant advantages will be readily understood by reference to the following detailed description and the accompanying drawing, wherein the sole Figure is a graphical representation of the results of a phase solubility study where various molar concentrations of hydroxypropyl-β-cyclodextrin (HPβCD) are plotted against various cladribine molar concentrations, with (●) representing

the data points obtained for complexation under conditions specified in EXAMPLE 2 below.

DETAILED DESCRIPTION OF THE INVENTION

Throughout the instant specification and claims, the following definitions and general statements are applicable.

The patents, published applications, and scientific literature referred to herein establish the knowledge of those with skill in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

The term "inclusion complex" as used herein refers to a complex of cladribine with the selected cyclodextrin wherein the hydrophobic portion of the cladribine molecule (the nitrogen-containing ring system) is inserted into the hydrophobic cavity of the cyclodextrin molecule. This is often referred to simply as a cyclodextrin complex of the drug.

The term "non-inclusion complex" refers to a complex which is not an inclusion complex; rather than the hydrophobic portion of cladribine being inserted in the cyclodextrin cavity, the non-inclusion complex is formed primarily by hydrogen-bonding of the hydroxyls and amino group on "free" cladribine, (*i.e.* cladribine not in the inclusion complex) to the hydroxyls on the exterior of the cyclodextrin torus (*e.g.* in the case of hydroxypropyl-β-cyclodextrin, hydroxypropyl and hydroxyl groups on the glucose rings). This is a more loosely-held association than an inclusion complex.

As used herein, whether in a transitional phrase or in the body of a claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a composition, the term "comprising" means that the composition includes at least the recited features or components, but may also include additional features or components.

The terms "consists essentially of" or "consisting essentially of" have a partially closed meaning, that is, they do not permit inclusion of steps or features or components which would substantially change the essential characteristics of a process or composition; for example, steps or features or components which would significantly interfere with the desired properties of the compositions described herein, *i.e.,* the process or composition is limited to the specified steps or materials and those which do not materially affect the basic and novel characteristics of the invention. The basic and novel features herein are the provision of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, so as to provide improved bioavailability and/or lower interpatient and/or intrapatient variation following administration. Essential to the invention is the combination of the amorphous nature of the starting cyclodextrin, and the level of water solubility exhibited by cladribine (about 5 mg/ml at room temperature), and consequently its capability for hydrogen bonding, which can be taken advantage of under particular conditions described hereinafter, and which afford a special amorphous mixture uniquely well-suited for optimizing the oral bioavailability of cladribine.

The terms "consists of" and "consists" are closed terminology and allow only for the inclusion of the recited steps or features or components.

As used herein, the singular forms "a," "an" and "the" specifically also encompass the plural forms of the terms to which they refer, unless the content clearly dictates otherwise.

The term "about" is used herein to means approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" or "approximately" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

The term "amorphous" is used herein to refer to a noncrystalline solid. The cyclodextrins encompassed herein themselves are amorphous because they are each composed of a multitude of individual isomers, and their complexes with cladribine are also amorphous. Further, conditions for complexation can be selected (elevated temperature and prolonged complexation times, as described hereinafter) so that a supersaturated cladribine solution will be formed. When cooled, because of the amorphous nature of the complex and the cyclodextrin, some excess free cladribine does not precipitate but rather is trapped in amorphous form in intimate admixture with the (preferably saturated) amorphous cladribine-cyclodextrin inclusion complex. This excess cladribine forms a loosely-held association, or non-inclusion complex, with the cyclodextrin through hydrogen bonding. This, then, further increases the amount of cladribine in the product; this additional cladribine, because it is amorphous and also because it is in intimate admixture with the amorphous inclusion complex, is expected to be somewhat protected from degradation by stomach acid (although it may not be as protected as the cladribine which is in the form of the inclusion complex).

The term "saturated" when used in conjunction with a complex of cladribine in amorphous cyclodextrin means that the complex is saturated with cladribine, that is, the complex contains the maximum amount of cladribine which can be complexed (by means of both inclusion and non-inclusion complexes) with a given amount of cyclodextrin under the conditions of complexation used. A phase solubility study can be used to provide this information, as described in more detail hereinafter. (Conditions for the complexation are also described in more detail below.) Alternatively, a saturated complex may be arrived at empirically by simply adding cladribine to an aqueous solution of the selected cyclodextrin until no more cladribine goes into solution; ultimately, excess cladribine, if any, is removed (by filtration or centrifugation) and the solution lyophilized to provide the dry saturated complex.

The expression "substantially', as in "substantially free" means within 20% of the exact calculated amount, preferably within 10%, most preferably within 5%.

The term "interpatient variability" refers to variation among patients to which a drug is administered. The term "intrapatient variability" refers to variation experienced by a single patient when dosed at different times.

As used herein, the recitation of a numerical range for a variable is intended to convey that the invention may be practiced with the variable equal to any of the values within that range. Thus, for a variable which is inherently discrete, the variable can be equal to any integer value of the numerical range, including the end-points of the range. Similarly, for a variable which is inherently continuous, the variable can be equal to any real value of the numerical range, including the end-points of the range. As an example, a variable which is described as having values between 0 and 2, can be 0, 1 or 2 for variables which are inherently discrete, and can be 0.0,

0.1, 0.01, 0.001, or any other real value for variables which are inherently continuous.

In the specification and claims, the singular forms include plural referents unless the context clearly dictates otherwise. As used herein, unless specifically indicated otherwise, the word "or" is used in the "inclusive" sense of "and/or" and not the "exclusive" sense of "either/or."

Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present invention pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Standard reference works setting forth the general principles of pharmacology include Goodman and Gilman's *The Pharmacological Basis of Therapeutics*, 10th Ed., McGraw Hill Companies Inc., New York (2001).

Reference is made hereinafter in detail to specific embodiments of the invention. While the invention will be described in conjunction with these specific embodiments, it will be understood that it is not intended to limit the invention to such specific embodiments. On the contrary, it is intended to cover alternatives, modifications, and equivalents as may be included within the spirit and scope of the invention as defined by the appended claims. In the following description, numerous specific details are set forth in order to provided a thorough understanding of the present invention. The present invention may be practiced without some or all of these specific details. In other instances, well-known process operations have not been described in detail, in order not to unnecessarily obscure the present invention.

There is provided by the present invention compositions, as well as methods of making and of using pharmaceutical compositions, useful to achieve desirable pharmacokinetic properties. Such compositions stem from the discovery that solutions of cyclodextrin and cladribine in which cladribine is in a high thermodynamic state, when presented to the gastric mucosa

through which they are absorbed are associated with improved cladribine absorption, as reflected by higher bioavailability and/or lower interpatient variation.

It is postulated, without wishing to so limit the invention, that upon dissolution (*e.g.*, by contact with a fluid, such as a bodily fluid), dry compositions according to the invention form a locally saturated cladribine solution in which cladribine is in the state of highest thermodynamic activity (HTA), thus favoring absorption. Cladribine has a fairly low, although not insignificant, intrinsic aqueous solubility; it is in fact somewhat water soluble. The free cladribine formed from dissociation of the inclusion and non-inclusion complexes in a saturated aqueous solution seeks a more stable activity level by being absorbed through the gastric mucosa.

In view of the foregoing, it is apparent that to produce optimal pharmaceutical compositions, in a solid oral dosage form, these dosage forms should be formulated to release a localized saturated cladribine solution, upon contact of the solid dosage forms with body fluid at the mucosa, in which cladribine is in its HTA state. To provide such a localized saturated solution *in vivo*, it is important to first identify the optimal ratio of cladribine to amorphous cyclodextrin, which ratio is referred to herein as the HTA ratio, to be used in the solid dosage form.

The HTA ratio is empirically determined and is identified as the ratio of cladribine to amorphous cyclodextrin which corresponds to the maximum amount of cladribine that can be complexed with a given amount of the cyclodextrin. The HTA ratio may be determined using an empirical method such as a phase solubility study to determine the saturation concentration of cladribine that can be solubilized with different concentrations of amorphous cyclodextrin solutions. Hence, the method identifies the concentrations at which a saturated cladribine-cyclodextrin complex is formed. It is noted that the molar ratio represented by a point on the phase solubility graph shows

how many moles of amorphous cyclodextrin are the minimum needed to maintain the drug in the complex, under given conditions; this may then be converted to a weight ratio. For example, if a phase solubility diagram shows that 9 moles of a given cyclodextrin are needed to maintain the cladribine in a saturated complex, then multiplying the number of moles of cladribine by its molecular weight and multiplying the number of moles of the selected cyclodextrin by its molecular weight, one can arrive at the ratio of the products as an appropriate optimized weight ratio. A phase solubility study also provides information about the nature of the cladribine-cyclodextrin inclusion complex formed, for example whether the inclusion complex is a 1:1 complex (1 molecule of drug complexed with 1 molecule of cyclodextrin) or a 1:2 complex (1 molecule of drug complexed with 2 molecules of cyclodextrin).

In accordance with the present invention, one can start using either the selected amorphous cyclodextrin, such as hydroxypropyl-β-cyclodextrin (HPβCD) or hydroxypropyl-γ-cyclodextrin, or cladribine as the fixed variable to which an excess of the other is added to identify various solubility data points (indicating saturated cladribine-cyclodextrin complexes) and draw the resultant line. Typically, cladribine is added to an aqueous solution having a known concentration of amorphous cyclextrin under conditions empirically found to promote complex formation. Generally, the complexation is conducted with heating, for example at about 45 to about 60°C for a significant period of time, *e.g.*, at least 6-9 hours; it is believed that even better results can be obtained by heating at up to about 80°C for up to 24 hours. Excess precipitated cladribine is then removed and the cladribine concentration is subsequently measured. This concentration represents the amount of cladribine solubilized for a given amorphous cyclodextrin concentration. This process is repeated for a different known concentration of cyclodextrin until several data points are obtained. Each data point represents the concentration of the cladribine dissolved in a known

concentration of the selected amorphous cyclodextrin. The data points are then plotted to show the concentration of cladribine against the various cyclodextrin concentrations used. The graph is a phase solubility diagram which can be used to determine the amount of cladribine for any specific concentration of cyclodextrin used to form the solution under a given set of complexation conditions. It will be appreciated that the aqueous solubility of cladribine is about 5 mg/ml at room temperature and would be higher at elevated temperature. Consequently, the data points correspond to the amount of cladribine dissolved in aqueous HPβCD or other amorphous cyclodextrin under the selected conditions; when later lyophilized, the solution yields a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex. If equilibrium conditions are reached during the complexation, the amorphous cladribine-cyclodextrin complex will be saturated with cladribine.

One of skill in the art will appreciate that concentrations at which saturated complexes of cladribine with amorphous cyclodextrins are formed (and thus HTA ratios as well) may be identified by a variety of alternative methodologies. Accordingly, any method known in the field suitable to identify these concentrations is within the scope of the invention.

It has been discovered that desirable pharmacological properties (improved bioavailability and/or coefficient of variation as compared to traditional approaches) are associated with mixtures of inclusion complexes and non-inclusion complexes of cladribine and cyclodextrin.

Using intrinsically amorphous cyclodextrins, for example hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated cyclodextrins, and the like, with cladribine, which is a somewhat water soluble compound (capable of H-bonding through its free hydroxyl and

amino groups), the cladribine provides increased solubility in solutions of these cyclodextrins. Not only is there increased water solubility but also H-bonded association of the cladribine with the cyclodextrin, separately from the actual inclusion complexed material.

One of skill in the art will appreciate that the phase solubility diagram for each given starting concentration ratio represents the starting point of one's investigation on the basis of which variables (reactants' concentrations, temperature and time) may be altered to promote inclusion complex and non-inclusion complex associations favoring a higher or lower proportion of either type of association in the final product. Departure from the ratio of cladribine to cyclodextrin, the temperature and/or the dilution empirically found to promote equilibrium towards complex formation is then analyzed to promote the formation of mixtures of inclusion complexes and non-inclusion complexes of cladribine and cyclodextrin in various proportions according to the invention.

Thus, for example, by starting with more diluted cyclodextrin (*i.e.*, larger water volumes than that used for solubility plot analysis) logically will accommodate more cladribine in solution sequestering more of the same from complex formation. Upon evaporation, some of the solubilized cladribine will tend to associate with cyclodextrin in a non-inclusion complex fashion. By altering the initial dilution, one may shift equilibrium towards inclusion complex or non-inclusion complex formation. Similarly, by increasing complexation temperature, the water solubility of cladribine may be increased while decreasing the stability of inclusion complexes, thus promoting non-inclusion complexes. Thus, by altering complexation temperature, one may shift equilibrium towards inclusion complex or non-inclusion complex formation. Finally, complexation time may be altered to favor the formation of mixtures of inclusion complexes and non-inclusion complexes of cladribine and cyclodextrin according to the invention.

As exemplified hereinafter, it is possible to maximize the cladribine in solid amorphous mixtures, by forcing additional cladribine into solution (using more dilute solutions of cyclodextrin, higher temperatures and longer complexation times, as indicated above). When the solution is cooled off, the extensively amorphous nature of these cyclodextrins does not allow crystallization of an excess amount of cladribine beyond that which forms an inclusion complex with the cyclodextrin; and upon freeze-drying/lyophilization, one obtains an amorphous mixture of cladribine-cyclodextrin inclusion complex (which is amorphous) and amorphous free cladribine, loosely associated with uncomplexed cyclodextrin (and even with complexed cyclodextrin) by hydrogen-bonding, that is, the non-inclusion complex.

As shown in the EXAMPLES, this may be done by maximizing solubilization by elevating the temperature (for example, to about 50°to 80°C), and stirring for many hours (up to 24 hours) before freeze-drying. The weight/weight ratios obtained were about 1:14 and 1:11. The apparent optimum weight/weight ratio under these exemplified conditions is the higher of these, or about 1:14 of cladribine: cyclodextrin. If too much excess caldribine is added to the complexation medium, then crystallization of some of the cladribine takes place, which would in turn result in some crystalline cladribine in the product; this undesired excess cladribine is not in solution and is not H-bonded to the amorphous cyclodextrin and lowers the weight ratio. Therefore, it is desirable to carefully control the amount of excess cladribine beyond that which will form the inclusion complex to only the amount which will dissolve in the solution. The desired amorphous mixture of amorphous inclusion complex and amorphous free cladribine can be termed a "complex cladribine-cyclodextrin complex," which includes both inclusion and non-inclusion/H-bonded complexes. The inclusion complex is a complex of cladribine inserted into the hydrophobic cavity of the selected amorphous cyclodextrin, while the non-inclusion/H-bonded complex is

amorphous free cladribine loosely hydrogen-bonded to the cyclodextrin. It is estimated that about two-thirds (60 to 70%) of the cladribine will be in the non-inclusion complex, with the remaining one third (30 to 40%) being in the inclusion complex when the product is obtained as exemplified hereinbelow (17% HPβCD solution, 45 to 50°C complexation temperature for about 9 hours); by increasing the percentage of cyclodextrin used and/or manipulating the temperature, products can be readily obtained in which a much greater proportion of the amorphous mixture is in the form of the inclusion complex. In the case of a representative amorphous cyclodextrin, hydroxypropyl-β-cyclodextrin (HPβCD) a cladribine:cyclodextrin weight ratio of from about 1:10 to about 1:16 is appropriate for the exemplified conditions; the ratio is expected to be the same for hydroxypropyl-γ-cyclodextrin under those conditions. The material obtained is characterized by rapid dissolution of the cladribine in aqueous media.

Freeze-drying, also known as lyophilization, comprises three basic stages: first a freezing stage, then a primary drying stage and finally a secondary drying stage. EXAMPLE 2 below provides details of lyophilization as conducted on the batches described therein. This procedure can be further optimized by following the principles described by Xiaolin (Charlie) Tang and Michael J. Pikal in *Pharmaceutical Research*, Vol. 21, No. 2, February 2004, 191-200, incorporated by reference herein in its entirety and relied upon.

The above-described method requires amorphous cyclodextrins rather than originally crystalline cyclodextrins which have relatively low water solubilities, such as α-, β- or γ-cyclodextrin, 2,6-dimethyl-β-cyclodextrin and the like, because these cyclodextrins would allow crystallization of cladribine in excess of that forming an inclusion complex and therefore would not afford the desired amorphous mixture. The method also would not be useful if cladribine were highly hydrophobic/lipophilic, because in such a situation the drug would not have intrinsic aqueous solubility/H-bonding capability and

could not provide the unique mixture obtained herein. However, in point of fact, cladribine has an aqueous solubility of 5 mg/ml at room temperature, thus a significant amount of the drug will be simply soluble in the water phase especially at higher than room temperature; also, as in the case of HPβCD, for example, some of the cladribine will be associated by hydrogen-bonding to the 2-hydroxypropyl and free glucose-OH groups in the cyclodextrin via the two hydroxy functions found in the deoxyadenosine moiety of the cladribine.

The cyclodextrins within the scope of this invention are amorphous derivatives of the natural cyclodextrins α-, β- or γ-cyclodextrin wherein one or more of the hydroxy groups are substituted, for example, by alkyl, hydroxyalkyl, carboxyalkyl, alkylcarbonyl, carboxyalkoxyalkyl, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl or hydroxy-(mono or polyalkoxy)alkyl groups; and wherein each alkyl or alkylene moiety preferably contains up to six carbons. Although commonly referred to as a single entity, an amorphous cyclodextrin is actually a mixture of many different entities, since the substituent groups can be located on various hydroxyls of the basic cyclodextrin structure. This in turn results in the amorphous nature of these cyclodextrins, which is indeed well-known. Moreover, these cyclodextrins can be obtained in varying degrees of substitution, for example from 1 to 14, preferably from 4 to 7; the degree of substitution is the approximate average number of substituent groups on the cyclodextrin molecule, for example, the approximate number of hydroxypropyl groups in the case of the hydroxpropyl-β-cyclodextrin molecule, and all such variations are within the ambit of this invention. Substituted amorphous cyclodextrins which can be used in the invention include polyethers, for example, as described in U.S. Patent No. 3,459,731. Further examples of substituted cyclodextrins include ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxy-C_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl-

C_{1-6}alkyl groups or mixed ethers thereof. In particular, such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxy-C_{2-4}alkyl or carboxy-C_{1-2}alkyl or more particularly by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxymethyl or carboxyethyl. The term "C_{1-6}alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms such as methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like. Other cyclodextrins contemplated for use herein included glucosyl-β-cyclodextrin and maltosyl-β-cyclodextrin. Of particular utility in the present invention are randomly methylated β-cyclodextrin and polyethers such as hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, and hydroxyethyl-γ-cyclodextrin, as well as sulfobutyl ethers, especially β-cyclodextrin sulfobutyl ether. In addition to simple cyclodextrins, branched cyclodextrins and cyclodextrin polymers may also be used. Other cyclodextrins are described, for example, in *Chemical and Pharmaceutical Bulletin* 28: 1552-1558 (1980); Yakugyo Jiho No. 6452 (28 March 1983); *Angew. Chem. Int. Ed. Engl.* 19: 344-362 (1980); U.S. Patent Nos. 3,459,731 and 4,535,152; European Patent Nos. EP 0 149 197A and EP 0 197 571A; PCT International Patent Publication No. WO90/12035; and UK Patent Publication GB 2,189,245.

References describing cyclodextrins for use in the compositions according to the present invention, and/or which provide a guide for the preparation, purification and analysis of cyclodextrins include the following: *Cyclodextrin Technology* by Jozsef Szejtli, Kluwer Academic Publishers (1988) in the chapter Cyclodextrins in Pharmaceuticals; *Cyclodextrin Chemistry* by M. L. Bender *et al.*, Springer-Verlag, Berlin (1978); *Advances in Carbohydrate Chemistry*, Vol. 12, Ed. By M. L. Wolfrom, Academic Press, New York in the chapter "The Schardinger Dextrins" by Dexter French, pp. 189-260; *Cyclodextrins and their Inclusion Complexes* by J. Szejtli,

Adakemiai Kiado, Budapest, Hungary (1982); I. Tabushi, *Acc. Chem. Research*, 1982, 15, pp. 66-72; W. Sanger, *Angewandte Chemie*, 92, p. 343-361 (1981); A. P. Croft *et al., Tetrahedron*, 39, pp. 1417-1474 (1983); Irie *et al. Pharmaceutical Research*, 5, pp. 713-716 (1988); Pitha *et al., Int. J. Pharm.* 29, 73 (1986); U.S. Patent Nos. 4,659,696 and 4,383,992; German Patent Nos. DE 3,118,218 and DE-3,317,064; and European Patent No. EP 0 094 157A. Patents describing hydroxyalkylated derivative of β- and γ-cyclodextrin include Pitha U.S. Patent Nos. 4,596,795 and 4,727,064, Müller U.S. Patent Nos. 4,764,604 and 4,870,060 and Müller *et al.* U.S. Patent No. 6,407,079.

Amorphous cyclodextrins of particular interest for complexation with cladribine include: hydroxyalkyl, *e.g.* hydroxyethyl or hydroxypropyl, derivatives of β- and γ-cyclodextrin; carboxyalkyl, *e.g.* carboxymethyl or carboxyethyl, derivatives of β- or γ-cyclodextrin; β-cyclodextrin sulfobutyl ether; and randomly methylated β-cyclodextrin. 2-Hydroxypropyl-β-cyclodextrin (HPβCD), 2-hydroxypropyl-γ-cyclodextrin (HPγCD), randomly methylated β-cyclodextrin, β-cyclodextrin sulfobutyl ether, carboxymethyl-β-cyclodextrin (CMβCD) and carboxymethyl-γ-cyclodextrin (CMγCD) are of special interest, especially hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin.

Compositions of an amorphous mixture of amorphous free cladribine and an amorphous, preferably saturated, cladribine-cyclodextrin inclusion complex for use in the present invention can be prepared under conditions favoring complex formation in a liquid environment as described and as exemplified herein. The resultant liquid preparations can be subsequently converted to a dry form suitable for administration as a solid oral or transmucosal dosage form.

One of skill will appreciate that a variety of approaches are available in the field to prepare compositions as described herein. One available

method exemplified herein includes the steps of mixing the cladribine in an aqueous solution of an amorphous cyclodextrin, separating un-dissolved cladribine (*e.g.*, by filtering or centrifugation), and lyophilizing or freeze-drying the saturated solution to form a solid amorphous mixture.

Pharmaceutical compositions according to the invention may optionally include one or more excipients or other pharmaceutically inert components. One of the advantages of the invention, however, is that cladribine drug forms as described herein can be prepared with the minimal amount of excipients necessary for shaping and producing the particular form, such as a tablet or patch. Excipients may be chosen from those that do not interfere with cladribine, with cyclodextrin or with complex formation.

Dosage forms are optionally formulated in a pharmaceutically acceptable vehicle with any of the well-known pharmaceutically acceptable carriers, diluents, binders, lubricants, disintegrants, scavengers, flavoring agents, coloring agents, and excipients (see *Handbook of Pharmaceutical Excipients*, Marcel Dekker Inc., New York and Basel (1998); Lachman *et al.* Eds., *The Theory and Practice of Industrial Pharmacy*, 3rd Ed., (1986); Lieberman *et al.*, Eds. *Pharmaceutical Dosage Forms,* Marcel Dekker Inc., New York and Basel (1989); and *The Handbook of Pharmaceutical Excipients*, 3rd Ed., American Pharmaceutical Association and Pharmaceutical Press, 2000); see also *Remington's Pharmaceutical Sciences*, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA (1990) and *Remington: The Science and Practice of Pharmacy*, Lippincott, Williams & Wilkins, (1995)). A simple solid oral dosage form consists of the amorphous mixture of amorphous free cladribine and amorphous cladribine-cyclodextrin complex (preferably saturated) as described above, *i.e.* the complex cladribine-cyclodextrin complex, compressed with a small amount (*e.g.* about 1% by weight) of a suitable binder or lubricant such as magnesium stearate.

In certain instances, oral absorption may be further facilitated by the addition of various excipients and additives to increase solubility or to enhance penetration, such as by the modification of the microenvirionment.

The methods and pharmaceutical compositions described herein offer novel therapeutic modalities for the treatment of patients in need of treatment with cladribine. As shown herein, the invention addresses the problems of poor bioavailability traditionally associated with oral cladribine.

The compositions of the invention are particularly suitable as modalities for the treatment of any cladribine-responsive disease. Several disease states responsive to cladribine are well-documented in the literature (see *infra*). For any target disease state, an effective amount of the complex cladribine-cyclodextrin comples, *i.e.* the amorphous mixture of the optimized amorphous saturated cladribine-amorphous cyclodextrin complex with amorphous free cladribine as described above is used (*e.g.*, an amount affective for the treatment of multiple sclerosis, rheumatoid arthritis, or leukemia).

The term "therapeutically effective amount" or "effective amount" is used to denote treatments at dosages effective to achieve the therapeutic result sought. Therapeutically effective dosages described in the literature include those for hairy cell leukemia (0.09 mg/kg/day for 7 days), for multiple sclerosis (from about 0.04 to about 1.0 mg/kg/day (see U.S. Patent No. 5,506,214)); for other diseases, see also U.S. Patent Nos. 5,106,837 (autohemolytic anemia); 5,310,732 (inflammatory bowel disease); 5,401,724 (rheumatoid arthritis); 5,424,296 (malignant astrocytoma); 5,510,336 (histiocytosis); 5,401,724 (chronic myelogenous leukemia); and 6,239,118 (atherosclerosis).

Further, various dosage amounts and dosing regimens have been reported in the literature for use in the treatment of multiple sclerosis; see, for example: Romine et al., *Proceedings of the Association of American*

Physicians, Vol. 111, No. 1, 35-44 (1999); Selby et al., *The Canadian Journal of Neurological Sciences*, 25, 295-299 (1998); Tortorella et al., *Current Opinion in Investigational Drugs*, 2 (12), 1751-1756 (2001); Rice et al., *Neurology,* 54, 1145-1155 (2000); and Karlsson et al., *British Journal of Haematology*, 116, 538-548 (2002); all of which are incorporated by reference herein in their entireties and relied upon.

Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability obtain after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment. For further dosing information, see also U.S. Provisional Patent Application No. _____ [IVAX0021-P-USA/Attorney Docket No. 033935-011], and U.S. Provisional Patent Application No. _____ [IVAX0022-P-USA/Attorney Docket No. 033935-012], both entitled "Cladribine Regimen for Treating Multiple Sclerosis", both filed on March 25, 2004 and incorporated by reference herein in their entireties.

Furthermore, one of skill will appreciate that the therapeutically effective amount of cladribine administered herein may be lowered or increased by fine tuning and/or by administering cladribine according to the invention with another active ingredient. The invention therefore provides a method to tailor the administration/treatment to the particular exigencies specific to a given mammal. Therapeutically effective amounts may be easily determined, for example, empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of beneficial effect.

As noted in the preceding paragraph, administration of cladribine in accord with this invention may be accompanied by administration of one or more additional active ingredients for treating the cladribine-responsive condition. The additional active ingredient will be administered by a route of administration and in dosing amounts and frequencies appropriate for each additional active ingredient and the condition being treated. For example, in the treatment of multiple sclerosis, other useful drugs include interferon beta (Rebif®, Betaseron®/Betaferon®, Avonex®), identical to the naturally occurring protein found in the human body; glatiramer acetate (Copaxone®), a random chain (polymer) of the amino acids glutamic acid, lysine, alanine and tyrosine; natalizumab (Antegren®), a monoclonal antibody; alemtuzumab (Campath-1H®), a humanized anti-CD52 monoclonal antibody; 4-aminopyridine (also known as 4-AP and Fampridine), a drug that blocks the potassium channels in neurons; and amantadine, an anti-viral agent which improves muscle control and reduces muscle stiffness and is used to alleviate the symptoms of fatigue in multiple sclerosis, a purpose for which pemoline (Cylert®) and L-Carnitine (a herbal product) may also be useful. In the treatment of hairy cell leukemia, additional active ingredients may include interferon alpha, pentostatin, fludarabine, rituximab (an anti-CD 20 monoclonal antibody) and the anti-CD22 recombinant immunotoxin BL 22; other additional active ingredients may be appropriate in other types of

leukemias. In the treatment of rheumatoid arthritis, there are many other active ingredients which may be selected. These include NSAIDS (non-steroidal anti-inflammatory drugs), which are of three types: salicylates such as aspirin, traditional NSAIDS such as ibuprofen and indomethacin, and COX-2 inhibitors such as celecoxib (Celebrex®), rofecoxib (Vioxx®), meloxicam (Mobic®), valdecoxib (Bextra®), lumiracoxib (Prexige®) and etoricoxib (Arcoxia®). Other drugs useful in treating rheumatoid arthritis which may be used in conjunction with the present invention include DMARDS, glucocorticoids, biological response modifiers and non-NSAID analgesics. DMARDS are disease-modifying anti-rheumatic drugs which include methotrexate, plaquenil, leflunomide (Arava®), sulfasalazine, gold, penicillamide, cyclosporine, methyl cyclophosamide and azathioprine. Glucocorticoids include dexamethasone, prednisolone, triamcinolone and many others. Biological response modifiers (which restore the disease-fighting ability of the immune system), include etanercept (Enrel®), a tumor-necrosis factor inhibitor, infliximab (Remicade®), which is also an anti-TNF drug, anakinra (Kineret®), a selective IL-1 blocker, and Humira®, a human monoclonal antibody which is another anti-TNF drug. The non-NSAID analgesics include acetaminophen as well as narcotic analgesics such as hydrocodone, oxycodone and propoxyphene. Generally speaking, those drugs which work by a mechanism different from that of cladribine are particularly useful for concomitant therapy with the cladribine composition described herein. Those drugs which are effective by the oral route of administration and which are compatible with the instant cladribine complexes in a single dosage form may be incorporated into the instant dosage forms; otherwise, they should of course be separately administered in amounts, frequencies and via administration routes suitable to them.

As used herein, "treating" means reducing, preventing, hindering the development of, controlling, alleviating and/or reversing the symptoms in the individual to which a compound of the invention has been administered, as

compared to the symptoms of an individual not being treated according to the invention. A practitioner will appreciate that the complexes, compositions, dosage forms and methods described herein are to be used in concomitance with continuous clinical evaluations by a skilled practitioner (physician or veterinarian) to determine subsequent therapy. Such evaluation will aid and inform in evaluating whether to increase, reduce or continue a particular treatment dose, and/or to alter the mode of administration.

The methods of the present invention are intended for use with any subject/patient that may experience the benefits of the methods of the invention. Thus, in accordance with the invention, the terms "subjects" as well as "patients" include humans as well as non-human subjects, particularly domesticated animals.

Any suitable materials and/or methods known to those of skill can be utilized in carrying out the present invention. However, preferred materials and methods are described. Materials, reagents and the like to which reference are made in the following description and examples are obtainable from commercial sources, unless otherwise noted.

The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein.

EXAMPLES

EXAMPLE 1

PHASE SOLUBILITY STUDY

A phase solubility study can be carried out as follows. Excess cladribine is added to cyclodextrin solutions of various concentrations of

hydroxypropyl-β-cyclodextrin (HPβCD) and allowed to complex as described in EXAMPLE 2 below. The excess, undissolved cladribine is removed by filtration. The amount of cladribine in the complexation solution is measured to obtain a data point. This process is repeated with different known concentrations of HPβCD until several data points are obtained. These data points are then plotted graphically, each data point representing the amount of cladribine that can be dissolved in water with a specific concentration of cyclodextrin. Points on the line generated by the data points represent ratios for the product. One of skill in the art will realize the same results will be generated if excess cyclodextrin is added to cladribine solutions of known concentration.

The molar concentrations of cladribine to cyclodextrin obtained are plotted and presented graphically. A representative phase solubility diagram is shown in the Figure. The plotted lines for cladribine-HPβCD represent cladribine solubilization for the conditions tested, that is, the ratio of the concentration of cladribine to the concentration of cyclodextrin. The area above each of the plotted lines represents conditions where excess insoluble cladribine is present. The area below each of the plotted lines represents the conditions where cyclodextrin is in excess.

The plot for cladribine-HPβCD shown in the Figure is approximately linear; this is indicative of a 1:1 complex, in which one molecule of the drug is complexed with one molecule of cyclodextrin. The Figure also shows that additional cyclodextrin is needed to maintain the cladribine in the complex. For example, about 0.14 mole of HPβCD is needed to maintain about 0.049 mole of cladribine dissolved under the selected conditions, which will ultimately provide the amorphous mixture of the amorphous, preferably saturated, cladribine-HPβCD inclusion complex and amorphous free cladribine (as a non-inclusion complex). Under the conditions of EXAMPLE 2 below, a significant portion of the cladribine in the product can be expected to be not in the inclusion complex but rather in amorphous form loosely held

in intimate admixture therewith by hydrogen bonding as a non-inclusion complex.

EXAMPLE 2

PREPARATION OF CLADRIBINE-CYCLODEXTRIN COMPLEX FOR HUMAN TRIALS

Cladribine is complexed with HPβCD by the following method.

In 825 mL of distilled water, 172.5 g of hydroxypropyl-β-cyclodextrin are dissolved (forming an approximately 17% solution), then cladribine is added and the mixture is stirred at about 45 to about 50°C for about nine hours. Stirring is continued for an additional 6 to 9 hours at room temperature. Any undissolved cladribine is removed by filtration and the solution is cooled to room temperature. To form the amorphous mixture of amorphous cladribine-cyclodextrin complex and amorphous free cladribine, the aqueous cladribine-cyclodextrin solution is dried by lyophilization prior to incorporation into solid oral tablets. The lyophilization procedure comprises a freezing stage of rapidly bringing the complexation solution to about -40°C to about -80°C (e.g., about -45°C) for approximately 2 to 4 hours (preferably about 3 to 4 hours), followed by a primary drying stage at about -25°C for approximately 80-90 hours, typically under low pressure, and a second drying stage at about 30°C for about 15-20 hours.

Product made by the foregoing general procedure can be analyzed by HPLC (utilizing a Hypersil ODS 3 micron column and an acetonitrile based mobile phase, with UV detection at 264 nm) to find the weight ratio of cladribine to cyclodextrin in the final product. Final product preparations can be further characterized by methods known in the art, including, for example by inspecting appearance, ascertaining the overall impurity content by HPLC, ascertaining the water content using a Karl Fischer titrator, determining the dissolution profile by a standard method, for example using USP<711>Apparatus II equipment and UV detection at 264 nm, inspecting

the content uniformity and performing quantitative assay by HPLC analysis of the active ingredient.

Two batches of cladribine/cyclodextrin product, FD04 and FD05, were made by the foregoing general procedure as follows:

Purified water (825 mL) was pre-heated at 48°C (target range 45°C to 50°C) in a 1-liter glass vessel by immersion in a water bath. The heated water was stirred to achieve a controlled central vortex. 2-hydroxypropyl-β-cyclodextrin (172.50 g) was weighed and slowly added to the heated water over a period of 40 minutes. The resulting solution was stirred for a further 10 minutes to ensure complete dissolution of the cyclodextrin. Cladribine (12.00 g for FD04 and 18.75 g for FD05) was weighed and added to the stirred cyclodextrin solution, which turned cloudy before becoming clear. The resulting clear solution was maintained at 48°C and continually stirred for 9 hours. Stirring continued for a further 7 hours while the solution cooled to room temperature.

Use of a larger amount of cladribine in the preparation of FD05 was part of an attempt to optimize the procedure; however, it was found that the initial amount of cladribine in that case was too great and precipitation was observed at the end of the cooling step for batch FD05. The solution was filtered to remove the precipitate. Analysis of the resultant product revealed (assay value = 87.2%) that 16.35 g of cladribine had been incorporated into the cyclodextrin complex in the case of FD05. No filtration was required for batch FD04, indicating that the amounts used in the preparation of FD04 were more appropriate and that the FD05 procedure could be optimized by beginning with a smaller amount of cladribine (16.35 g rather than 18.75 g), thus avoiding the filtration step.

After cooling to room temperature and, in the case of FD05, filtering, the solutions were filled into 100 mL lyophilization vials (20 mL solutions per vial), the filled vials were partially stoppered and lyophilized. The

lyophilization included freezing at -45°C for about 200 minutes, a primary drying phase at -25°C under a pressure of 100 mTorr for about 5,200 minutes and a secondary drying phase at 30°C for about 1,080 minutes as set forth below:

TABLE I

Step	Process	Temperature	Pressure (mTorr)	Time (min)
1	Load	4°C		
2	Load Hold	4°C	n/a	120
3	Ramp	-45°C	n/a	120
4	Freezing	-45°C	n/a	200
5	Ramp	-25°C	100	120
6	Primary drying	-25°C	100	5200
7	Ramp	30°C	50	240
8	Secondary drying	30°C	50	1080
9	Finish	30°C	Vials closed under vacuum	

The FD04 and FD05 batches of cladribine/cyclodextrin product made by the foregoing procedure were analyzed by HPLC (utilizing a Hypersil ODS 3 micron column and an acetonitrile based mobile phase with UV detection at 264 nm) and empirically found to have the following characteristics:

TABLE II

Lot No.	Cladribine: HPβCD w/w	Cladribine: HPβCD Weight Ratio
FD04	12.00g:172.50g	1:14.38
FD05	16.35g:172.50g	1:10.55

The products were analyzed by DSC thermograms and X-ray diffraction methods to determine any free crystalline cladribine in the lyophilized material. Importantly, the samples exhibited no transitions in the region of 210°C to 230°C, which is associated with the melting of crystalline cladribine. In both cases, no significant thermal activity was recorded in the range of 210°C to 230°C, suggesting that the complexes obtained at the end of the lyophilization do not have any significant amount of free crystalline cladribine, considering the sensitivity of the analytical method (up to 3% w/w). This conclusion was supported by the absence of peaks for crystalline cladribine from X-ray diffraction traces for both complexes FD04 and FD05.

The products are amorphous mixtures of amorphous cladribine-HPβCD inclusion complex and amorphous free cladribine hydrogen-bonded to the cyclodextrin as a non-inclusion complex. The cladribine:HPβCD weight ratios obtained were about 1:14 and 1:11.

Generally speaking, amorphous mixtures within the scope of the present invention have cladribine:HPβCD weight ratios of from about 1:10 to 1:16.

EXAMPLE 3

PREPARATION OF ORAL TABLETS

Tablets were manufactured using batches of amorphous mixtures FD04 and FD05 described in EXAMPLE 2 for use in a clinical study.

Batch N0120 was manufactured using cladribine-2-HPβCD complex mixture DF05 to a batch size of 3,000 tablets and batch N0126 was manufactured using cladribine-HPβCD complex mixture FD04 to a batch size of 800 tablets. The master formulations for the two batches are shown in TABLE III. Batch N0120 represented 3.0 g tablets and Batch N0126 represented 10 mg tablets for clinical study.

TABLE III

Constituent	Lot Number	mg/tablet 3.0 mg Batch N0120	mg/tablet 10.0 mg Batch N0126
Cladribine-HPβCD complex mix	FD05	30.60*	
Cladribine-HPβCD complex mix	FD04		153.75**
Sorbitol powder NF	1007403	68.4	44.25
Magnesium stearate NF	1006280	1.00	2.00
Total		100.00	200.00

*Equivalent to 3.0 mg cladribine per tablet.
**Equivalent to 10.0 mg cladribine per tablet.

The following table sets forth the method of manufacture of the Batch N0120 and N0126 tablets.

TABLE IV

1.	Pre-mix the magnesium stearate with an approximately equal quantity of sorbitol power.
2.	Pass the cladribine-HPβCD complex and the remainder of the sorbitol powder into a one-liter glass jar via a 40-mesh screen.
3.	Blend the contents for 10 minutes at 12 rpm.
4.	Pass the magnesium stearate/sorbitol powder pre-mix into the glass jar via the 40-mesh screen.
5.	Blend the final mixture for 5 minutes at 12 rpm.
6.	Compress into 3.0 mg and 10.0 mg tablets at a target compression weight of 100 mg and 200 mg, respectively.

Both the Batch N0120 3.0 mg tablets and the Batch N0126 10.0 mg tablets were round, with one side flat-beveled edged and the other side shallow convex. The Batch N0120 3.0 mg tablets had an average weight of 100 mg, a thickness of 2.7 mm, a friability of 0.2%, a hardness of 4 Kp and a disintegration time of 3 minutes. The Batch N0126 10.0 mg tablets had an average weight of 198 mg, a thickness of 4.2 mm, a friability of 1%, a hardness of 2.8 Kp and a disintegration time of 5 minutes 42 seconds.

The Batch N0120 3.0 mg and N0126 10.0 mg tablets were used in the clinical study summarized in EXAMPLE 5 below.

EXAMPLE 4

CLINICAL STUDY: RELATIVE BIOAVAILABILITY

The objective of this study was to assess the relative bioavailability of three oral cladribine formulations: (1) a cyclodextrin-based formulation according to the instant invention (Tablet 1: complex FD05, i.e. Batch No. N0120 tablets described above); (2) a mucoadhesive formulation (Tablet 2: containing 3.0 mg cladribine, 10 mg of Carbopol 71G NF, 22.2 mg of dicalcium phosphate, 64.3 mg of lactose and 0.5 mg of magnesium stearate, Batch No. N0121); and (3) a hard-gel capsule (Capsule containing 3.0 mg cladribine, 5.0 mg Carbopol 974P, 91.3 mg Avicel PH101, 100.0 mg Avicel PH102, 0.2 mg colloidal silicon dioxide and 0.5 mg magnesium stearate, Batch No. RD03030) in comparison with one fixed subcutaneous clardribine administration (reference formulation) in patients with MS (multiple sclerosis).

This study was a 2 center, open-label, randomized, 4-way crossover single dose study using twelve patients with MS. Patients received randomly three different fixed oral doses (3.0 mg) and a fixed subcutaneous dose of 3.0 mg. The four treatment days were separated by a drug-free interval of at

least 5 days. In each treatment period, blood samples were collected over a 24-hour period for evaluation of plasma cladribine.

The plasma concentration of cladribine was measured by a HPLC/MS/MS method. Using this method, the relationship between concentration versus peak area ratio was found to be linear within the range of 100 pg/ml to 50,000 pg/ml for cladribine. The limit of quantification was 100 pg/ml. Analysis of samples was carried out in 16 runs. No calibrator had to be excluded from fitting of the calibration curve and accuracy of each quality control sample met the GLP requirements.

576 clinical plasma samples were analyzed and concentration values of cladribine were determined. The results were compiled and are summarized in the tables below (Tables V and VI). In these tables, the following definitions are applicable: T_{max} is the time to reach maximum concentration in the plasma; $T_{½}$ is the half-life of cladribine in the plasma; C_{MAX} is the maximum concentration of cladribine in the plasma; AUC_{inf} is the area under the curve for the measured data from zero extrapolated to infinity; AUC_t is the area under the curve for the measured data (from zero to the last time point); Geom Mean is the geometric mean; CV is the coefficient of variation (relative standard deviation); LL is the lower limit; UL is the upper limit.

TABLE V
Summary Statistics for Pharmacokinetic Parameters for Cladribine Study Obtained via Non-Compartmental Analyses. (n=12).

Pharmacokinetic Parameter	3.0 mg subcutaneous			3mg Tablet 1			3mg Tablet 2			3 mg Capsule		
	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)
T_{max}(hr)	N/A	.313 ±.113	36.2	N/A	.521 ±.167	32.1	N/A	1.25 ±.839	67.1	N/A	2.25 ±.622	27.7
$T_{½}$(hr)	N/A	6.69 ±2.01	30.1	N/A	7.55 ±2.50	33.1	N/A	6.73 ±2.82	41.9	N/A	6.27 ±2.31	36.9
C_{max}(pg/ml)	23186	N/A	40.1	6597	N/A	24.7	5041	N/A	52.6	3818	N/A	36.8
AUC_{inf} (hr·pg/ml)	57254	N/A	44.4	24936	N/A	28.8	21676	N/A	42.7	22604	N/A	39.5
AUC_t (hr·pg/ml)	54725	N/A	43.8	23182	N/A	28.0	20063	N/A	42.1	20951	N/A	42.0

**CV=SD/mean for T_{max} and $T_{½}$ and CV% geometric mean for C_{max}, AUC_{inf} and AUC_t.

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TABLE VI

Ratios of Oral to Subcutaneous Pharmacokinetic Parameters and Corresponding Two-Sided 90% Confidence Intervals for Cladribine Study (n=12).

Pharmacokinetic Parameter	3 mg Tablet 1		3mg Tablet 2		3mg Capsule	
	Ratio*	LL, UL	Ratio*	LL, UL	Ratio*	LL, UL
AUC_{inf}	43.1	35.7, 52.1	38.4	31.8, 46.4	38.9	32.1, 47.0
AUC_t	41.9	34.6, 50.8	37.2	30.7, 45.0	37.6	31.0, 45.5

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

EXAMPLE 5

CLINICAL STUDY: DOSE RESPONSE AND ABSOLUTE BIOAVAILABILITY

The objective of this study was to assess the systemic availability of cladribine after oral administration in two different fixed oral doses, in comparison with one fixed intravenous administration (reference formulation) in patients with MS (multiple sclerosis), and to evaluate the safety and tolerability of cladribine in this population.

This study was a 3 center, open-label, randomized, 3-way crossover single dose study using twenty-six patients with MS. Patients received randomly two different fixed oral doses (3.0 mg and 10.0 mg) and a fixed intravenous dose of 3.0 mg (administered as a 1 hour infusion). The three treatment days were separated by a drug-free interval of at least 5 days. In

each treatment period blood samples were collected over a 24-hour period for evaluation of plasma cladribine.

The plasma concentrations of cladribine were measured by a HPLC/MS/MS method. Using this method the relationship between concentrations versus peak area ratios was found to be linear within the range of 100 pg/ml to 50,000 pg/ml for cladribine. The limit of quantification was 100 pg/ml. Analysis of samples was carried out in 16 runs. Except the first run (which had to be rejected because of equipment failure), all other runs could be accepted. No calibrator had to be excluded from fitting of the calibration curve and accuracy of each quality control sample met the GLP requirements.

858 clinical plasma samples were analyzed and concentration values of cladribine were determined. The results were compiled and are summarized in the tables below [TABLES VII through X]. In these tables, the following definitions are applicable: T_{max} is the time to reach maximum concentration in the plasma; $T_{1/2}$ is the half-life of cladribine in the plasma; C_{max} is the maximum concentration of cladribine in the plasma; AUC_{inf} is the area under the curve for the measured data from zero extrapolated to infinity; AUC_t is the area under the curve for the measured data (from zero to the last time point); Geom Mean is the geometric mean; CV is the coefficient of variation (relative standard deviation); LL is the lower limit; UL is the upper limit; σ^2 is the mean variance; σ_B^2 is the mean variance between subjects; σ_W^2 is the mean variance within subjects; CV_T is the total coefficient of variation; and CV_W is the coefficient of variation within subjects.

TABLE VII

Summary Statistics for Pharmacokinetic Parameters for Cladribine Study Obtained via Non-Compartmental Analysis (n=26)

Pharmaco-kinetic Parameter	3.0 mg IV infusion			Oral Administration					
				3.0 mg			10.0 mg		
	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)	Geom Mean	Mean ± SD	CV** (%)
T_{max}(hr)	N/A	.817 ±.397	48.6	N/A	.548 ±.300	54.8	N/A	.558 ±.204	36.5
$T_{½}$(hr)	N/A	6.50 ±1.27	19.5	N/A	5.85 ±1.18	20.2	N/A	5.60 ±0.75	13.3
C_{max}(pg/ml)	21425	N/A	27.6	5608	N/A	49.5	21242	N/A	50.5
AUC_{inf} (hr·pg/ml)	58528	N/A	24.0	20159	N/A	35.0	76690	N/A	30.3
AUC_t (hr·pg/ml)	56396	N/A	24.0	19166	N/A	36.9	74532	N/A	30.3

**CV=SD/mean for T_{max} and $T_{½}$ and CV% geometric mean for C_{max}, AUC_{inf} and AUC_t.

TABLE VIII

Ratios of Oral to I.V. Pharmacokinetic Parameters and Corresponding Lower Limit (LL) for the one-sided 95% Confidence Interval for Cladribine Study (n=26)

Pharmacokinetic Parameter	Oral Administration			
	3.0 mg		10.0 mg	
	Ratio*	LL	Ratio*	LL
AUC_{inf}	34.5	31.7	39.1	35.9
AUC_t	34.0	31.2	39.4	36.1

*Ratios (dose normalized) and Corresponding 95% LL obtained via inverse transformation of log-transformed data.

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TABLE IX

Ratios and Corresponding two-sided 90% Confidence Intervals for Cladribine Study (n=26)

Pharmacokinetic Parameter	10.0 mg/3.0 mg		
	Ratio*	LL	UL
C_{max}	112.6	95.1	133.3
AUC_{inf}	113.3	104.2	123.3
AUC_t	115.8	106.1	126.5

*Ratios (dose normalized) and Corresponding 90% CI obtained via inverse transformation of log-transformed data.

TABLE X

Variance components for Cladribine Study (n=26)

Source of variation	C_{max}	AUC_{inf}	AUC_t
Between (σ_B^2)	.0380	.0487	.0492
With (σ_W^2)	.1315	.0330	.0357
TOTAL ($\sigma_B^2 + \sigma_W^2$)	.1695	.0816	.0849
CV_T(%)	43.0	29.2	29.8
CV_W(%)	37.5	18.3	19.1

Where PK parameters are dose-adjusted and $CV = \sqrt{\exp(\sigma^2) - 1}$

The foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents thereof may be resorted to, falling within the scope of the invention claimed.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form.

2. The pharmaceutical composition according to Claim 1, wherein the complex is saturated with cladribine.

3. The composition according to Claim 1 or 2, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. The composition according to Claim 1 or 2, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

5. The composition according to Claim 1 or 2, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

6. The composition according to any one of Claims 1 to 3, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

7. The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

8. The composition according to Claim 7, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

9. The composition according to Claim 7, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

10. The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

11. The composition according to any one of Claims 1 to 10, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

12. The composition according to any one of Claims 1 to 11, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

13. A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form.

14. The method according to Claim 13, wherein the complex is saturated with cladribine.

15. The method according to Claim 13 or 14, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

16. The method according to Claim 13 or 14, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

17. The method according to Claim 13 or 14, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

18. The method according to any one of Claims 13 to 15, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

19. The method according to Claim 18, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

20. The method according to Claim 19, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

21. The method according to Claim 19, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

22. The method according to Claim 18, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

23. The method according to any one of Claims 13 to 22, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin

corresponds to a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin.

24. The method according to any one of Claims 13 to 23, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form.

26. The method according to Claim 25, wherein the complex is saturated with cladribine.

27. The method according to Claim 25 or 26, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

28. The method according to Claim 27, wherein the cladribine-responsive condition is multiple sclerosis.

29. The method according to Claim 25, 26, 27 or 28, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin,

hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

30. The method according to any one of Claims 25 to 29, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

31. The method according to any one of Claims 25 to 30, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

32. The method according to Claim 31, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

33. The method according to Claim 31, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

34. The method according to Claim 25, 26, 27 or 28, wherein the amorphous cyclodextrin is hydropropyl-γ-cyclodextrin.

35. The method according to any one of Claims 25 to 34, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

36. Use of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, in the formulation of a solid oral dosage form, for administration in the treatment of symptoms of a cladribine-responsive condition.

37. Use according to Claim 36, wherein the complex is saturated with cladribine.

38. Use according to Claim 36 or 37, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

39. Use according to Claim 38, wherein the cladribine-responsive condition is multiple sclerosis.

40. Use according to Claim 36, 37, 38 or 39, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

41. Use according to any one of Claims 36 to 40, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

42. Use according to any one of Claims 36 to 41, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

43. Use according to Claim 42, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

44. Use according to Claim 42, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

45. Use according to any one of Claims 36 to 41, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

46. Use according to any one of Claims 36 to 45, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

47. Use of a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, in the formulation of a solid oral dosage form, for enhancing the oral bioavailability of cladribine.

48. Use according to Claim 47, wherein the complex is saturated with cladribine.

49. Use according to Claim 47 or 48, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

50. Use according to any one of Claims 47 to 49, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

51. Use according to any one of Claims 47 to 50, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

52. Use according to Claim 51, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

53. Use according to Claim 51, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

54. Use according to any one of Claims 47 to 50, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

55. Use according to any one of Claims 47 to 54, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

56. A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex.

57. The complex according to Claim 56, saturated with cladribine.

58. The complex according to Claim 56 or 57, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

59. The complex according to Claim 56 or 57, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

60. The complex according to Claim 56 or 57, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

61. The complex according to any one of Claims 56 to 58, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

62. The complex according to Claim 61, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

63. The complex according to Claim 62, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

64. The complex according to Claim 62, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

65. The complex according to Claim 61, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

66. The complex according to any one of Claims 56 to 65, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

67. A process for the preparation of a complex cladribine-cyclodextrin complex which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

68. A process according to Claim 67, further comprising a filtration step following step (ii).

69. A process according to Claim 67 or 68, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

70. A process according to any one of Claims 67 to 69, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

71. A process according to Claim 69 or 70, wherein step (i) is performed with stirring.

72. A process according to Claim 71, wherein step (i) is performed for a period of from about 6 to about 9 hours.

73. A process according to any one of Claims 67 to 72, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

74. A process according to any one of Claims 67 to 73, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

75. A process according to Claim 74, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

76. A process according to any one of Claims 67 to 75, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

77. A process according to any one of Claims 67 to 75, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

78. A process according to Claim 76 or 77, wherein 825 parts by volume of water are introduced in step (i).

79. A process according to any one of Claims 67 to 78, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

80. A process according to Claim 79, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

81. A process according to Claim 79 or 80, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

82. A pharmaceutical composition obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about 40 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

83. A pharmaceutical composition according to Claim 82, wherein the process further comprises a filtration step following step (i) or (ii).

84. A pharmaceutical composition according to Claim 82 or 83, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

85. A pharmaceutical composition according to any one of Claims 82 to 84, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

86. A pharmaceutical composition according to Claim 84 or 85, wherein step (i) of the process is performed with stirring.

87. A pharmaceutical composition according to Claim 86, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

88. A pharmaceutical composition according to any one of Claims 82 to 87, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

89. A pharmaceutical composition according to any one of Claims 82 to 88, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80°C, and held at said temperature for a period of from about 2 to about 4 hours.

90. A pharmaceutical composition according to Claim 89, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

91. A pharmaceutical composition according to any one of Claims 82 to 90, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

92. A pharmaceutical composition according to any one of Claims 82 to 90, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

93. A pharmaceutical composition according to Claim 91 or 92, wherein 825 parts by volume of water are introduced in step (i) of the process.

94. A pharmaceutical composition according to any one of Claims 82 to 93, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

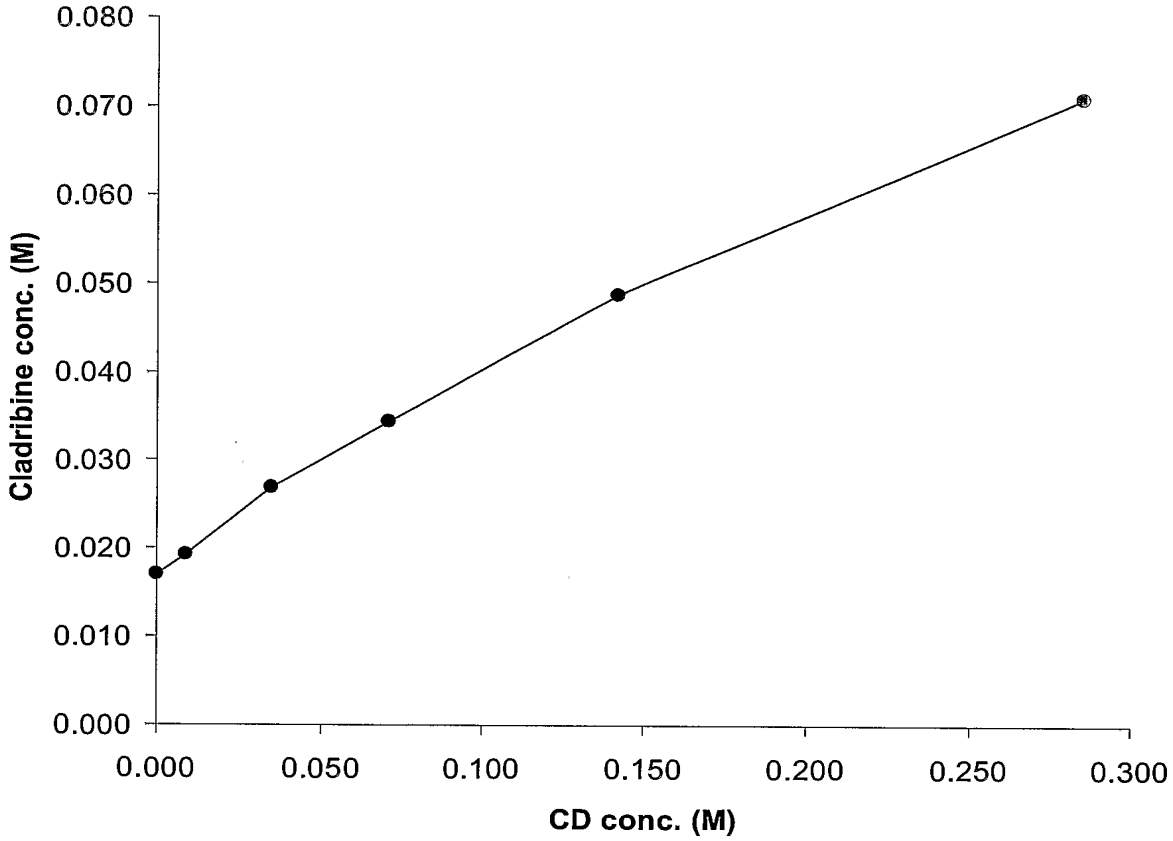
95. A pharmaceutical composition according to Claim 94, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

96. A pharmaceutical composition according to Claim 94 or 95, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

97. A pharmaceutical composition according to any one of Claims 82 to 96, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

98. A pharmaceutical composition according to Claim 97, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

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0.080
0.070
0.060
0.050
0.040
0.030
0.020
0.010
0.000
Cladribine conc. (M)
0.000
0.050
0.100
0.150
0.200
0.250
0.300
CD conc. (M)

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	GIAMPIERO DE LUCA
Filer:	Frank Christopher Eisenschenk/Sherry Loke
Attorney Docket Number:	SER-125

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
National Stage Fee	1631	1	300	300
Natl Stage Search Fee - Report provided	1642	1	400	400
National Stage Exam - all other cases	1633	1	200	200
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**900**

Electronic Acknowledgement Receipt

EFS ID:	1881928
Application Number:	11722018
International Application Number:	PCT/EP05/56954
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	GIAMPIERO DE LUCA
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Sherry Loke
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER-125
Receipt Date:	18-JUN-2007
Filing Date:	
Time Stamp:	14:43:50
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	$900
RAM confirmation Number	6690
Deposit Account	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)	Multi Part /.zip	Pages (if appl.)

1		PreAmd.pdf	302711	yes	8

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Preliminary Amendment	1	1
Specification	2	2
Claims	3	6
Applicant Arguments/Remarks Made in an Amendment	7	7
Abstract	8	8

Warnings:					
Information:					
2	Application Data Sheet	ADS.pdf	95541	no	3
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Information:					
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3	Oath or Declaration filed	executed-Dec.pdf	77284	no	2
Warnings:					
Information:					
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Warnings:					
Information:					
6	NPL Documents	BEUTLER-2.pdf	733855	no	8
Warnings:					

Information:					
7	NPL Documents	BEUTLER-3.pdf	636437	no	5
Warnings:					
Information:					
8	NPL Documents	ELLISON.pdf	298199	no	2
Warnings:					
Information:					
9	Foreign Reference	EP00626853.pdf	65243	no	14
Warnings:					
Information:					
10	NPL Documents	GRIEB.pdf	821536	no	5
Warnings:					
Information:					
11	NPL Documents	KAZIMIERCZUK.pdf	543725	no	4
Warnings:					
Information:					
12	NPL Documents	KURTZKE.pdf	888621	no	9
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13	NPL Documents	LANGTRY.pdf	1732215	no	15
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14	NPL Documents	LASSMANN.pdf	973628	no	7
Warnings:					
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15	NPL Documents	LUBLIN.pdf	571910	no	5
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16	NPL Documents	LUCCHINETTI.pdf	1233109	no	11
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17	NPL Documents	MATTSON.pdf	1297977	no	9
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18	NPL Documents	MCDONALD.pdf	612160	no	7
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19	NPL Documents	MILLER.pdf	141122	no	1
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20	NPL Documents	NOSEWORTHY.pdf	2342135	no	15
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21	NPL Documents	POSER.pdf	477588	no	5
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22	NPL Documents	RICE.pdf	1348545	no	11
Warnings:					
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23	NPL Documents	ROMINE.pdf	753434	no	10
Warnings:					
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24	NPL Documents	SCHUMACHER.pdf	1241812	no	17
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25	NPL Documents	SELBY.pdf	546095	no	5
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26	NPL Documents	SIPE.pdf	508511	no	5
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27	NPL Documents	STELMASIAK.pdf	593050	no	5
Warnings:					
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28	Foreign Reference	WO04087101.pdf	2796486	no	56
Warnings:					
Information:					
29	Fee Worksheet (PTO-06)	fee-info.pdf	8433	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	24474778		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/722,018	06/18/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☒ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 06/18/2007

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 20	Minus	** 20	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	***3	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT 06/18/2007

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 20	Minus	** 20	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/GLORIA NORRIS/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on August 16, 2007.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

Patent Application
Docket No. SER-125
Serial No. 11/722,018

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF POWER OF ATTORNEY AND CORRESPONDENCE ADDRESS INDICATION FORM

Sir:

Transmitted herewith for filing in connection with the above-identified patent application are Power of Attorney and Correspondence Address Indication Forms executed by the inventor.

Respectfully submitted,

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jps
Attachments: Power of Attorney forms

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PTO/SB/81 (04-05)
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POWER OF ATTORNEY and CORRESPONDENCE ADDRESS INDICATION FORM

Application Number	11/722,018
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Title	Cladribine Regimen for Treating ...
Art Unit	
Examiner Name	
Attorney Docket Number	SER-125

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☑ Practitioners associated with the Customer Number: 23557

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☑ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☑ Applicant/Inventor.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	12/07/2007
Name	GIAMPIERO DE LUCA	Telephone	
Title and Company			

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

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Patentanmeldung Nr. Patent application No. Demande de brevet n°

04106909.7

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Cladribine regimen for treating Multiple Sclerosis

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Cladribine regimen for treating Multiple Sclerosis

Field of the Invention

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

Background of the Invention

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (*Lublin and Reingold, Neurology, 1996, 46:907-911*).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exarcerbation but also from insidious progression between exacerbations (*Lublin and Reingold above).* 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5 % of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (*Lassmann et al., 2001, Trends Mol. Med., 7, 115-121; Lucchinetti et al., Curr. Opin. Neurol., 2001, 14, 259-269*).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic (*Noseworthy et al., The New England Journal of Medicine, 2000, 343, 13, 938-952*). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (*Mc Donald et al., 2001, Ann. Neurol., 50:121-127*).

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatimarer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved..

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (*EP 626853B1 and US 5,506,214*).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (*Selby et al., 1998, Can. J. Neurol. Sci., 25:295-299*) and Relapsing-Remitting MS respectively (*Romine et al., 1999, Proceedings of the Association of American Physicians, 111, 1, 35-44*).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (*Rice at al., 2000, Neurology, 54, 5, 1145-1155).* In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (*Beutler et al., 1996, Proc. Nat. Acad. Sci. USA, 93, 1716-1720; Romine et al., 1999 above)*. Phase III study results, were positive on the significant reduction of MRI-measured brain lesions (*Rice at al., 2000, above*).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (*Selby et al., 1998, above; Beutler et al., 1994, Acta hematol., 91:10-15*). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or s.c. administration. As a result, *Beutler et al. (Beutler et al., 1996, Seminars in Hematology, 33, 1(S1), 45-52)* excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible.

Summary of the Invention

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting

multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i).

Detailed Description of the invention

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments.

Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of **(i)** an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and **(ii)** a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months.

A "Maintenance Treatment" consists in the sequential succession of **(i)** a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during the induction treatment and **(ii)** a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria *(Schumacher et al., 1965, Ann. NY Acad. Sci. 1965; 122:552-568; Poser et al., 1983, Ann. Neurol. 13(3): 227-31).*

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the

presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology, 47(Suppl 4): S217; Evans et al., 1997, Ann. Neurology, 41:125-132*).

The observation of the reduction and/or suppression of MRI T_1 gadolinium -enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328.*

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 14444-1452*). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the

contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (*EP 173,059; WO 04/028462; WO 04/028462; US 5,208,327; WO 00/64918*) and *Robins et al., J. Am. Chem. Soc., 1984, 106: 6379*. Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers

include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Compositions of this invention may also be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, nonaqueous vehicles and preservatives. Suspending agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Nonaqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

According to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions and in the same or different routes of administration.

In one embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.
IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.
Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be

administered sub-cutaneously every second day at a dosage of about of 250 to 300 μg or 8 MIU to 9.6 MIU per person.

In accordance with the present invention, where IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intra-muscularly once a week at a dosage of about of 30μg to 33 μg or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μg or 6 MIU to 12 MIU per person.

Patients

Patients according to the invention are patients suffering from multiple sclerosis, preferably RRMS or early SPMS.

In an embodiment of the invention, patients are selected from human males or females between 18 and 55 years age.

In another embodiment of the invention, patients had at least one relapse within the prior 12 months of the treatment.

Use according to the invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months or up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period (ii) lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of multiple sclerosis wherein the medicament is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

Examples

The following abbreviations refer respectively to the definitions below:

kg (kilogram), µg (microgram), **mg** (milligram), **AEs** (Adverse effects), CNS (Cnetral nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale, **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra -veinous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **UI** (International unit).

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

Example 1: Oral cladribine in the treatment of relapsing forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

Table 1:

Group	2CdA
1	-
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 2 below:

Table 2:

Name of ingredients	Formula mg/tablet	Formula mg/tablet
Cladribine-2-hydroxypropyl-ß-cyclodextrin- complex*	153.75 equivalent to 10 mg 2CdA	30.60 equivalent to 3 mg 2CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

* Cladribine is complexed and lyophilised with 2-hydroxypropyl-ß-cyclodextrin as a separate process as described in WO 2004/087101.

Examples of administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable.

Table 3:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	**Mid range**	**Max**	**Min**	**Max**	**Month 1**	**Month 2**	**Total**
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14

Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	Mid range	Max	Min	Max	Month 1	Month 2	Total
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

Table 4:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1 patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailablility of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailablility of about 40%); followed by 8 months of no treatment.

Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.

Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.

Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in *Miller et al., 1996, above; Evans et al., 1997, above*; *Sipe et al., 1984, above*; and *Mattson, 2002, above*. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.
The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-fee patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

Claims:

1. Use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:
   (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
   (ii) A Cladribine-free period wherein no Cladribine is administered;
   (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);
   (iv) A Cladribine-free period wherein no Cladribine is administered.

2. Use according to claim 1 wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

3. Use according to claims 1 or 2 wherein the induction period lasts up to about 2 months.

4. Use according to any of the preceding claims wherein the induction period lasts up to about 4 months.

5. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

6. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

7. Use according to any of the preceding claims wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months, or up to about 8 months.

8. Use according to any of the preceding claims wherein the Cladribine-free (iv) period lasts up to about 10 months.

9. Use according to any of the preceding claims wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2 months.

10. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

11. Use according to claim 1 wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 8 months or up to about 10 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total

dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

12. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine.

13. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 10 mg Cladribine.

14. Use according to any of the preceding claims wherein the pharmaceutical formulation is orally administered about 1 to about 7 days per month during the induction period.

15. Use according to any of the preceding claims wherein the steps (iii) to (iv) are repeated at least one or two times.

16. Use according to any of the preceding claims wherein wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

Abstract of the invention:

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be the orally administered and wherein re-treatments are possible.

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T. LAWRENCE
Certifying Officer

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Express Mail Label No. ED 290333676 US

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Giampiero	De Luca	Conches, Switzerland

Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

Cladribine Regimen for Treating Multiple Sclerosis

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 30
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Respectfully submitted,

SIGNATURE _____

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Cladribine regimen for treating Multiple Sclerosis

Field of the Invention

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

Background of the Invention

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

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Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (*Lublin and Reingold, Neurology, 1996, 46:907-911*).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exarcerbation but also from insidious progression between exacerbations (*Lublin and Reingold above).* 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5 % of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (*Lassmann et al., 2001, Trends Mol. Med., 7, 115-121; Lucchinetti et al., Curr. Opin. Neurol., 2001, 14, 259-269*).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic (*Noseworthy et al., The New England Journal of Medicine, 2000, 343, 13, 938-952*). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (*Mc Donald et al., 2001, Ann. Neurol., 50:121-127*).

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Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatimarer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved.

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (*EP 626853B1 and US 5,506,214*).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (*Selby et al., 1998, Can. J. Neurol. Sci., 25:295-299*) and Relapsing-Remitting MS respectively (*Romine et al., 1999, Proceedings of the Association of American Physicians, 111, 1, 35-44*).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (*Rice at al., 2000, Neurology, 54, 5, 1145-1155).* In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

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The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (*Beutler et al., 1996, Proc. Nat. Acad. Sci. USA, 93, 1716-1720; Romine et al., 1999 above).* Phase III study results, were positive on the significant reduction of MRI-measured brain lesions (*Rice at al., 2000, above*).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (*Selby et al., 1998, above; Beutler et al., 1994, Acta hematol., 91:10-15*). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or s.c. administration. As a result, *Beutler et al. (Beutler et al., 1996, Seminars in Hematology, 33, 1(S1), 45-52*) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible.

Summary of the Invention

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting

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multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

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(ii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i).

Detailed Description of the invention

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments.

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Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of **(i)** an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and **(ii)** a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months.

A "Maintenance Treatment" consists in the sequential succession of **(i)** a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during the induction treatment and **(ii)** a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

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Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria *(Schumacher et al., 1965, Ann. NY Acad. Sci. 1965; 122:552-568; Poser et al., 1983, Ann. Neurol. 13(3): 227-31).*

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the

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presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology*, 47 (Suppl 4):5217; *Evans et al., 1997, Ann. Neurology, 41:125-132*).

The observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328.*

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 14444-1452*). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the

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contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (*EP 173,059; WO 04/028462; WO 04/028462; US 5,208,327; WO 00/64918*) and *Robins et al., J. Am. Chem. Soc., 1984, 106: 6379.* Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers

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include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Compositions of this invention may also be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, nonaqueous vehicles and preservatives. Suspending agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Nonaqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

According to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions and in the same or different routes of administration.

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In one embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.
IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.
Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be

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administered sub-cutaneously every second day at a dosage of about of 250 to 300 μg or 8 MIU to 9.6 MIU per person.

In accordance with the present invention, where IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intra-muscularly once a week at a dosage of about of 30μg to 33 μg or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μg or 6 MIU to 12 MIU per person.

Patients

Patients according to the invention are patients suffering from multiple sclerosis, preferably RRMS or early SPMS.

In an embodiment of the invention, patients are selected from human males or females between 18 and 55 years age.

In another embodiment of the invention, patients had at least one relapse within the prior 12 months of the treatment.

Use according to the invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

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(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

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In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months or up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period (ii) lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

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In another further embodiment, the invention provides a use according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

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(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

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In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of multiple sclerosis wherein the medicament is to be orally administered following the sequential steps below:

(v) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(vi) A Cladribine-free period wherein no Cladribine is administered;

(vii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(viii) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

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In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

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In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg;

(v) A Cladribine-free period wherein no Cladribine is administered;

(vi) A maintenance period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(vii) A Cladribine-free period wherein no Cladribine is administered.

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In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

Examples

The following abbreviations refer respectively to the definitions below:

kg (kilogram), **µg** (microgram), **mg** (milligram), **AEs** (Adverse effects), CNS (Cnetral nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale, **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra-veinous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **UI** (International unit).

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The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

Example 1: Oral cladribine in the treatment of relapsing forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

Table 1:

Group	2CdA
1	-
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 2 below:

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Table 2:

Name of ingredients	Formula mg/tablet	Formula mg/tablet
Cladribine-2-hydroxypropyl-ß-cyclodextrin- complex*	153.75 equivalent to 10 mg 2CdA	30.60 equivalent to 3 mg 2CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

* Cladribine is complexed and lyophilised with 2-hydroxypropyl-ß-cyclodextrin as a separate process as described in WO 2004/087101.

Examples of administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable.

Table 3:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	Mid range	Max	Min	Max	Month 1	Month 2	Total
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14

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Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	Mid range	Max	Min	Max	Month 1	Month 2	Total
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

Table 4:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37

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Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1 patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailablility of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailablility of about 40%); followed by 8 months of no treatment.

Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.

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Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.

Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in *Miller et al., 1996, above; Evans et al., 1997, above*; *Sipe et al., 1984, above*; and *Mattson, 2002, above*. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.
The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-fee patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

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Claims:

1. Method of treating multiple sclerosis, with 2-CdA wherein, 2-CdA is orally administered following the sequential steps below:
   (i) Administering 2-CdA, such that the total dose of 2-CdA reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;
   (ii) Administering no 2-CdA during a Cladribine free period;
   (iii) Administering 2-CdA such that the total dose of 2-CdA reached at the end of a maintenance period is lower than the total dose of 2-CdA reached at the end of the induction period (i);
   (iv) And optionally, a Cladribine-free period wherein no 2-CdA is administered.

2. The method of claim 1, wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

3. The method of claim 1, wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

4. The method of claim 1, wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months, or up to about 8 months.

5. The method of claim 1, wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2 months.

6. The method of claim 1, wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

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7. The method of claim 1, wherein the maintenance period is followed by a Cladribine-free period.

8. The method of claim 1, comprising the following:

(i) An induction period wherein 2-CdA is administered and wherein the total dose of 2-CdA reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no 2-CdA is administered;

(iii) A maintenance period wherein the total dose of 2-CdA reached at the end of the maintenance period is lower than the total dose of 2-CdA reached at the end of the induction period (i); and,

(iv) Optionally a Cladribine-free period wherein no 2-CdA is administered.

wherein the induction period lasts up to about 4 months, or up to about 3 months or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 8 months or up to about 10 months; the maintenance period lasts up to about 2 months; the optional Cladribine-free period lasts up to about 10 months; the total dose of 2-CdA reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

9. The method of claim 1 to 8, wherein 2-CdA is to be orally administered at a daily dose of about 3 to about 30 mg.

10. The method of claim 1 to 8, wherein 2-CdA is to be orally administered at a daily dose of about 10 mg.

11. The method of claim 1 to 8, wherein 2-CdA is orally administered about 1 to about 7 days per month during the induction period.

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12. The method of claim 1 to 8, wherein the steps (iii) are repeated at least one or two times.

13. The method of claim 1 to 8, wherein 2-CdA is to be administered in combination with interferon-beta.

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Abstract of the invention:

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be the orally administered and wherein re-treatments are possible.

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(54) Title: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

(57) Abstract: The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be the orally administered and wherein re-treatments are possible.

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Cladribine regimen for treating Multiple Sclerosis

Field of the Invention

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

Background of the Invention

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (*Lublin and Reingold, Neurology, 1996, 46:907-911*).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exarcerbation but also from insidious progression between exacerbations (*Lublin and Reingold above).* 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5 % of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (*Lassmann et al., 2001, Trends Mol. Med., 7, 115-121; Lucchinetti et al., Curr. Opin. Neurol., 2001, 14, 259-269*).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic (*Noseworthy et al., The New England Journal of Medicine, 2000, 343, 13, 938-952*). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (*Mc Donald et al., 2001, Ann. Neurol., 50:121-127*).

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatimarer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone

(Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved.

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (*EP 626853B1 and US 5,506,214*).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (*Selby et al., 1998, Can. J. Neurol. Sci., 25:295-299*) and Relapsing-Remitting MS respectively (*Romine et al., 1999, Proceedings of the Association of American Physicians, 111, 1, 35-44*).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (*Rice at al., 2000, Neurology, 54, 5, 1145-1155).* In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (*Beutler et al., 1996, Proc. Nat. Acad. Sci. USA, 93, 1716-1720; Romine et al., 1999 above).* Phase III study results, were positive on the significant reduction of MRI-measured brain lesions (*Rice at al., 2000, above*).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (*Selby et al., 1998, above; Beutler et al., 1994, Acta hematol., 91:10-15*). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or s.c. administration. As a result, *Beutler et al. (Beutler et al., 1996, Seminars in Hematology, 33, 1(S1), 45-52*) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Grieb et al. reported a small trial in 11 patients with remitting-relapsing multiple sclerosis (*Grieb et al., 1995, Archivum Immunologiae et Therapiae Experimentalis, 43 (5-6), 323-327*) wherein Cladribine has been orally administered during 6 monthly courses of 5 days at a total dose of about 4-5.7 mg/kg (patients of about 52 and about 75 kilos, respectively) i.e. a total effective dose of 2-2.85 mg/kg. For some patients, a single re-treatment of 5 days was performed at a cumulative dose of 0.4-0.66 mg/kg after a cladribine free-period of 3 or 6 months. The side effects observed with the regimen above were said to be less severe than the ones observed in the study on patients suffering from chronic progressive multiple sclerosis treated by i.v. infusion of Cladribine (*Sipe et al., 1994, Lancet, 344, 9-13*) but were still present. In addition, the therapeutic efficacy of the oral regimen above versus the i.v. infusion therapy was questioned (*Grieb et al., 1995, above*) and a group of "non-responders" has been identified (*Stelmasiak et al., 1998, Laboratory Investigations, 4(1), 4-8*).

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible. A sustained benefit of Cladribine treatment between the treatment periods is also desirable.

Summary of the Invention

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

Detailed Description of the invention

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg or the total dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days is 1.7 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg or the total effective dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 0.7 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments. Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of **(i)** an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and **(ii)** a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months, typically at least of about 8 months.

A "Maintenance Treatment" consists in the sequential succession of **(i)** a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during

the induction treatment and **(ii)** a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinctic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.
Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria *(Schumacher et al., 1965, Ann. NY Acad. Sci. 1965; 122:552-568; Poser et al., 1983, Ann. Neurol. 13(3): 227-31).*

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also

not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the presence or absence of new lesions in the CNS as detected using methods such as MRI technique (*Miller et al., 1996, Neurology, 47(Suppl 4): S217; Evans et al., 1997, Ann. Neurology, 41:125-132*).

The observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (*Sipe et al., 1984, Neurology, 34, 1368-1372*). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in *Mattson, 2002, Expert Rev. Neurotherapeutics, 319-328.*

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (*Kurtzke, 1983, Neurology, 33, 1444-1452*). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (*WO 96/19230; WO 96/19229; US 6,194,395; US 5,506,214; WO 2004/087100; WO 2004/087101*), the contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (*EP 173,059; WO 04/028462; WO 04/028462; US 5,208,327; WO 00/64918*) and *Robins et al., J. Am. Chem. Soc., 1984, 106: 6379.* Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants,

disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Compositions of this invention may also be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, nonaqueous vehicles and preservatives. Suspending agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Nonaqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

According to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions and in the same or different routes of administration.

In one embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.
IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.
Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be

administered sub-cutaneously every second day at a dosage of about of 250 to 300 μg or 8 MIU to 9.6 MIU per person.

In accordance with the present invention, where IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intra-muscularly once a week at a dosage of about of 30μg to 33 μg or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μg or 6 MIU to 12 MIU per person.

Patients

Patients according to the invention are patients suffering from multiple sclerosis, preferably RRMS or early SPMS.

In an embodiment of the invention, patients are selected from human males or females between 18 and 55 years age.

In another embodiment of the invention, patients had at least one relapse within the prior 12 months of the treatment.

Use according to the invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months or up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period (ii) lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free periods (ii) and/or (iv) last between about 8 and about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period (iii) is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period (iii) is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of multiple sclerosis wherein the medicament is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the maintenance period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily

dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period and wherein the pharmaceutical formulation is a pharmaceutical formulation described in WO 2004/087101 or in WO 2004/087100.

In another embodiment, the invention provides a use of Cladribine according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a method of treating multiple sclerosis with Cladribine, wherein Cladribine is orally administered following the sequential steps below:

(i) Administering Cladribine, such that the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) Administering no Cladribine during a Cladribine free period;

(iii) Administering Cladribine such that the total dose of Cladribine reached at the end of a maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) And optionally, a Cladribine-free period wherein no Cladribine is administered.

In a further preferred embodiment, the invention provides a method wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months, or up to about 8 months.

In a further preferred embodiment, the invention provides a method wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the maintenance period is followed by a Cladribine-free period.

In another further embodiment, the invention provides a method according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 3 to about 30 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 10 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is orally administered about 1 to about 7 days per month during the induction period.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) are repeated at least one or two times.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be administered in combination with interferon-beta.

Examples

The following abbreviations refer respectively to the definitions below:

kg (kilogram), **µg** (microgram), **mg** (milligram), **AEs** (Adverse effects), CNS (Cnetral nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale, **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra-veinous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **2-CdA** (2-chloro-2'deoxyadenosine or Cladribine), **UI** (International unit).

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

Example 1: Oral cladribine in the treatment of relapsing forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

Table 1:

Group	2-CdA
1	-
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2-CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2-CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 2 below:

Table 2:

Name of ingredients	**Formula mg/tablet**	**Formula mg/tablet**
Cladribine-2-hydroxypropyl-ß-cyclodextrin- complex*	153.75 equivalent to 10 mg 2-CdA	30.60 equivalent to 3 mg 2-CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

* Cladribine is complexed and lyophilised with 2-hydroxypropyl-ß-cyclodextrin as a separate process as described in WO 2004/087101.

Examples of administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable.

Table 3:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 1.75 mg/kg		Number of pills (10 mg)/induction period		
Min	Mid range	Max	Min	Max	Month 1	Month 2	Total
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

Table 4:

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24

Patient weight ranges (kg)			Total target dose (kg) equivalent to 3.5 mg/kg		Number of pills (10 mg)/induction period				
Min	Mid range	Max	Min	Max	Month 1	Month 2	Month 3	Month 4	Total
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1 patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2-CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailablility of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2-CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailablility of about 40%); followed by 8 months of no treatment.

Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with

the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.

Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.

Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in *Miller et al., 1996, above; Evans et al., 1997, above*; *Sipe et al., 1984, above*; and *Mattson, 2002, above*. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.
The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-fee patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2-CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

Claims:

1. Use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:
   (i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from 1.7 mg/kg to 3.5 mg/kg;
   (ii) A Cladribine-free period wherein no Cladribine is administered;
   (iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);
   (iv) A Cladribine-free period wherein no Cladribine is administered.

2. Use according to claim 1 wherein the induction period lasts up to 4 months, or up to 3 months, or up to 2 months.

3. Use according to claims 1 or 2 wherein the induction period lasts up to 2 months.

4. Use according to any of the preceding claims wherein the induction period lasts up to 4 months.

5. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is 1.7 mg/kg.

6. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is 3.5 mg/kg.

7. Use according to any of the preceding claims wherein the Cladribine-free period lasts up to 10 months, or up to 9 months, or up to 8 months.

8. Use according to any of the preceding claims wherein the Cladribine-free (iv) period lasts up to 10 months.

9. Use according to any of the preceding claims wherein the maintenance period lasts up to 4 months, or up to 3 months or up to 2 months.

10. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the maintenance period is 1.7 mg/kg.

11. Use according to claim 1 wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from 1.7 mg/kg to 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to 4 months, or up to 3 months or up to 2 months; the Cladribine-free period (ii) lasts up to 10 months, or up to 8 months or up to 10 months; the maintenance period (iii) lasts up to 2 months; the Cladribine-free period (iv) lasts up to 10 months; the total dose of Cladribine reached at the end of the maintenance period is 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

12. Use according to any of the preceding claims wherein the total dose of Cladribine reached at the end of the induction period is 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is 1.7 mg/kg.

13. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine 3 to 30 mg Cladribine.

14. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine 10 mg Cladribine.

15. Use according to any of the preceding claims wherein the pharmaceutical formulation is orally administered 1 to 7 days per month during the induction period.

16. Use according to any of the preceding claims wherein the steps (iii) to (iv) are repeated at least one or two times.

17. Use according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/056954

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7076 A61K38/21 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRIEB PAWEL ET AL: "Effect of repeated treatments with cladribine (2-chlorodeoxyadenosine) on blood counts in multiple sclerosis patients" ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS, vol. 43, no. 5-6, 1995, pages 323-327, XP008047072 ISSN: 0004-069X cited in the application abstract page 324, column 1, paragraph 3 page 326, column 2, paragraph 3 ------ -/--	1,7-9, 13-16

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 2006	15/05/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STELMASIAK Z ET AL: "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting- relapsing multiple sclerosis" MEDICAL SCIENCE MONITOR 1998 POLAND, vol. 4, no. 1, 1998, pages 4-8, XP008047060 ISSN: 1234-1010 cited in the application abstract page 5, column 1, paragraph 2 - column 2, paragraph 1 page 7, column 1, paragraph 3	1,7-9, 13-16
X	WO 2004/087101 A (IVAX CORPORATION; BODOR, NICHOLAS, S; DANDIKER, YOGESH) 14 October 2004 (2004-10-14) cited in the application page 5, lines 1-7 page 12, lines 4-12 page 23, lines 15-28 page 24, lines 10-26 page 33, line 24 - page 34, line 2; example 4 page 36, line 17 - page 37, line 2; example 5 claims 25,28,36,39	1,2,4, 7-9, 13-15,17
X	LANGTRY H D ET AL: "Cladribine: A review of its use in multiple sclerosis" BIODRUGS 1998 NEW ZEALAND, vol. 9, no. 5, 1998, pages 419-433, XP008047073 ISSN: 1173-8804	1,7-9, 13-16
A	page 422, column 1, paragraph 3 - page 423, column 1, paragraph 1 page 423, column 2, paragraphs 1,2 page 424, column 1, paragraph 5 table III page 430, column 1, paragraph 3 table IV	17
A	ELLISON GEORGE W ET AL: "Oral cladribine for multiple sclerosis" NEUROLOGY, vol. 48, no. 3 SUPPL. 2, 1997, pages A174-A175, XP008047069 & 49TH ANNUAL MEETING OF THE AMERICAN ACADEMY OF NEUROLOGY; BOSTON, MASSACHUSETTS, USA; APRIL 12-19, 1997 ISSN: 0028-3878 the whole document	1-15

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/056954

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 626 853 A (THE SCRIPPS RESEARCH INSTITUTE) 7 December 1994 (1994-12-07) cited in the application page 3, paragraph 23 page 4, paragraphs 25,30 page 8, paragraphs 62-66,71-73 page 8, paragraph 74 - page 9, paragraph 75 page 9, paragraph 78	1-16

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/056954

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004087101 A	14-10-2004	AU 2004226437 A1	14-10-2004
		BR PI0408848 A	04-04-2006
		CA 2520523 A1	14-10-2004
		EP 1608344 A2	28-12-2005
EP 0626853 A	07-12-1994	AT 192045 T	15-05-2000
		AU 682818 B2	23-10-1997
		AU 3724993 A	13-09-1993
		BR 9305907 A	21-10-1997
		CA 2130275 A1	02-09-1993
		CH 684310 A5	31-08-1994
		DE 69328474 D1	31-05-2000
		DE 69328474 T2	28-09-2000
		DK 626853 T3	07-08-2000
		FI 943805 A	19-10-1994
		HU 68030 A2	29-05-1995
		JP 2688113 B2	08-12-1997
		JP 7507540 T	24-08-1995
		NO 942765 A	13-09-1994
		NO 20000762 A	13-09-1994
		RU 2130308 C1	20-05-1999
		WO 9316706 A1	02-09-1993

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
11/722,018	GIAMPIERO DE LUCA	SER-125

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
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GAINESVILLE, FL 32614-2950

INTERNATIONAL APPLICATION NO.	
PCT/EP2005/056954	
I.A. FILING DATE	PRIORITY DATE
12/20/2005	12/22/2004

CONFIRMATION NO. 5532
371 FORMALITIES LETTER



Date Mailed: 11/26/2008

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Filing Date Granted

Applicant is given **TWO MONTHS FROM THE DATE OF THIS NOTICE** within which to comply with the sequence rules, 37 CFR §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR § 1.821(g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR § 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period. Direct the response to: Mail Stop Missing Parts, Commissioner for Patents, P.O. Box 1450, Alexandria VA 22313-1450.

- This application clearly fails to comply with the requirements of 37 CFR. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper or compact disc copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**. Applicant must also provide a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.
- A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e). If the effective filing date is on or after September 8, 2000, see the final rulemaking notice published in the Federal Register at 65 FR 54604 (September 8, 2000) and 1238 OG 145 (September 19, 2000). Applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing" and a statement that the content of the sequence listing information recorded in computer readable form is identical to the written (on paper or compact disc) sequence listing and, where applicable, includes no new matter, as required by 37 CFR 1.821(e), 1.821(f), 1.821(g), 1.825(b), or 1.825(d). If applicant desires the sequence listing in the instant application to be identical with that of another application on file in the U.S. Patent and Trademark Office, such request in accordance with 37 CFR 1.821(e) may be submitted in lieu of a new CRF.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

For questions regarding compliance to 37 CFR 1.821-1.825 requirements, please contact:

- **For Rules Interpretation, call (571) 272-0951**
- **For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.**
- **Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov**

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

VONDA M WALLACE

Telephone: (703) 308-9140 EXT 225

PATENT APPLICATION FEE DETERMINATION RECORD

Effective December 8, 2004

Application or Docket Number: 11/722,018

CLAIMS AS FILED - PART I

	(Column 1)	(Column 2)
U.S. NATIONAL STAGE FEES		
BASIC FEE		
EXAMINATION FEE		
SEARCH FEE		
FEE FOR EXTRA SPEC. PGS.	minus 100 =	/ 50 =
TOTAL CHARGEABLE CLAIMS	20 minus 20 =	
INDEPENDENT CLAIMS	1 minus 3 =	
MULTIPLE DEPENDENT CLAIM PRESENT		☐

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY		OR	LARGE ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE		OR	BASIC FEE	300
EXAM. FEE			EXAM. FEE	200
SEARCH FEE			SEARCH FEE	400
X $ 125 =			X $ 250 =	
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL		OR	TOTAL	900

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X $ 25 =		OR	X $ 50 =	
X $ 100 =		OR	X $ 200 =	
+ $ 180 =		OR	+ $ 360 =	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '20', enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than '3', enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET

(FOR USE WITH FORM PTO-875)

SERIAL NO.	FILING DATE
11/732,018	
APPLICANT(S)	

CLAIMS

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
1	1		1			
2		1				
3		2				
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50						
TOTAL IND.	1		1			
TOTAL DEP.	17		19			
TOTAL CLAIMS	18		20			

	AS FILED		AFTER 1st AMENDMENT		AFTER 2nd AMENDMENT	
	IND.	DEP.	IND.	DEP.	IND.	DEP.
51						
52						
53						
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99						
100						
TOTAL IND.						
TOTAL DEP.						
TOTAL CLAIMS						

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on December 10, 2008.

Frank C. Eisenschenk

Frank C. Eisenschenk, Ph.D., Patent Attorney

Patent Application
Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PCT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Sir:

A Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures was received in the above-referenced patent application dated November 26, 2008. The Notice indicates that the subject application does not comply with the sequence requirements of 37 CFR §§1.821-1.825. Applicant's undersigned representative respectfully submits that the as-filed specification does not contain any sequences. Accordingly, a sequence listing on paper and in computer readable format is not required. However, if the Patent Office believes that there are sequences contained in the subject specification, Applicant respectfully requests that the next communication provide the page and line number.

J:\SER\125\PTO-Misc\Resp-Not2Comply.doc/DNB/sl

Applicants believe that no fees are due in connection with filing this Response. However, should the Patent Office determine that fees are due, the Commissioner is authorized to charge any fees as required under 37 CFR §§1.16 or 1.17 to Deposit Account No. 19-0065.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Telephone No.: (352) 375-8100
Facsimile No.: (352) 372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl

J:\SER\125\PTO-Misc\Resp-Not2Comply.doc\DNB/sl

Electronic Acknowledgement Receipt

EFS ID:	4431481
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	GIAMPIERO DE LUCA
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Sherry Loke
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER-125
Receipt Date:	10-DEC-2008
Filing Date:	
Time Stamp:	16:19:15
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Pre-Exam Sequence Notice	Resp-Not2Comply.pdf	107558 e60f33fd153135e97baa1f48d060f17706927560	no	2

Warnings:	
Information:	

Total Files Size (in bytes):	107558

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
11/722,018	Giampiero De Luca	SER-125

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

INTERNATIONAL APPLICATION NO.	
PCT/EP2005/056954	
I.A. FILING DATE	PRIORITY DATE
12/20/2005	12/22/2004

CONFIRMATION NO. 5532
371 ACCEPTANCE LETTER

OC000000033563838

Date Mailed: 12/12/2008

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495), has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

06/18/2007	06/22/2007
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF COMPLETION OF ALL 35 U.S.C. 371 REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 (c)(1), (c)(2) and (c)(4) REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- Copy of the International Application filed on 06/18/2007
- Copy of the International Search Report filed on 06/18/2007
- Preliminary Amendments filed on 06/18/2007
- Information Disclosure Statements filed on 06/18/2007
- Oath or Declaration filed on 06/18/2007
- U.S. Basic National Fees filed on 06/18/2007
- Priority Documents filed on 06/18/2007
- Power of Attorney filed on 08/16/2007
- Specification filed on 06/18/2007
- Claims filed on 06/18/2007
- Abstracts filed on 06/18/2007

FORM PCT/DO/EO/903 (371 Acceptance Notice)

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

VONDA M WALLACE

Telephone: (703) 308-9140 EXT 225

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
11/722,018	Giampiero De Luca	SER-125

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

INTERNATIONAL APPLICATION NO.	
PCT/EP2005/056954	
I.A. FILING DATE	PRIORITY DATE
12/20/2005	12/22/2004

CONFIRMATION NO. 5532
371 WITHDRAWAL NOTICE

OC000000033563814

Date Mailed: 12/12/2008

Letter Regarding a New Notice and/or the Status of the Application

If a new notice or Filing Receipt is enclosed, applicant may disregard the previous notice mailed on 11/26/2008. The time period for reply runs from the mail date of the new notice. Within the time period for reply, applicant is required to file a reply in compliance with the requirements set forth in the new notice to avoid abandonment of the application.

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If the Office previously granted a petition to withdraw the holding of abandonment or a petition to revive under 37 CFR 1.137, the status of the application has been returned to pending status.

VONDA M WALLACE

Telephone: (703) 308-9140 EXT 225

FORM PCT/DO/EO/WITH (371 Withdrawal Notice)

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/722,018	06/18/2007	1614	900	SER-125	20	1

CONFIRMATION NO. 5532

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO BOX 142950
GAINESVILLE, FL 32614-2950

FILING RECEIPT



Date Mailed: 12/12/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Giampiero De Luca, Conches, SWITZERLAND;

Assignment For Published Patent Application

Laboratoires Serono S.A., Aubonne, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 23557

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2005/056954 12/20/2005
which claims benefit of 60/638,669 12/22/2004

Foreign Applications

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

If Required, Foreign Filing License Granted: 12/10/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/722,018**

Projected Publication Date: 03/26/2009

Non-Publication Request: No

Early Publication Request: No

Title

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/722,018	06/18/2007	Giampiero De Luca	SER-125

CONFIRMATION NO. 5532

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

PUBLICATION NOTICE

OC000000035186128

Title:CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Publication No.US-2009-0081163-A1
Publication Date:03/26/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

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In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	06/18/2007	Giampiero De Luca	SER-125	5532

23557 7590 08/03/2009

SALIWANCHIK LLOYD & SALIWANCHIK
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EXAMINER	
BALLARD, KIMBERLY	
ART UNIT	PAPER NUMBER
1649	
MAIL DATE	DELIVERY MODE
08/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/722,018	DE LUCA, GIAMPIERO	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/18/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Claims 1-17 have been canceled and new claims 18-37 have been added as requested in the preliminary amendment filed on June 18, 2007.

2. Claims **18-37** are pending and under examination in the current office action.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed June 18, 2007 has been considered and is of record.

Claim Objections

4. Claim 30 is objected to because of the following informalities: in step (iv) the claim recites that "the cladribine-free period (ii) lasts up to 10 months, or up to 8 months *or up to 10 months*" (emphasis added), wherein the phrase "up to 10 months" has been unnecessarily repeated. Appropriate correction is required.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 18-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 2004/087101 A2 by Bodor et al. (published October 14, 2004; priority to March 28, 2003; listed on IDS) and US Patent 5,506,214 to Beutler (issued April 9, 1996), in view of US Patent 4,964,848 to Bloom (issued October 23, 1990).

The claims recite a method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine, wherein the formulation is administered following the steps of: (i) an induction period wherein the total dose of cladribine reached at the end of this period is from 1.7 mg/kg to 3.5 mg/kg; (ii) a cladribine-free period wherein no formulation is administered; (iii) a maintenance period wherein said formulation is administered and wherein the total dose of cladribine reached at the end of this period is lower than the total dose of cladribine reached at the end of the induction period (i); and (iv) a cladribine-free period wherein no cladribine formulation is administered.

The teachings of Bodor et al. and Beutler are cumulative. Both references teach the use of cladribine for the treatment of multiple sclerosis. Specifically, Bodor discloses treatment of multiple sclerosis comprising administering to a patient in need

thereof a therapeutically effect amount of a composition comprising cladribine, wherein the composition is formulated for oral administration (see, for example, pages 5 and 22). In particular, Bodor teaches that for the treatment of multiple sclerosis, 10 mg of cladribine in solid dosage form is to be administered orally once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively, the patient may be treated with 10 mg of cladribine in the dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment (see page 23, lines 7-24). Further, Bodor discloses that one of skill in the art will appreciate that the therapeutically effective amount of cladribine administered may be lowered or increased by fine tuning and/or by administering cladribine with another active ingredient (see page 24, lines 1-4).

Hence, the teachings of Bodor et al. address the following recited limitations of the instant claims: an induction period lasting up to 4 months, or up to 3 months, or up to 2 months (claims 19-23 and 30); the cladribine-free period (step iv) lasts up to 10 months (claims 26, 27 and 30); the maintenance period lasts up to 4 months, or up to 3 months, or up to 2 months (claims 28 and 30); the formulation is to be orally administered at a daily dose of 3 to 30 mg cladribine (claim 32) or at a daily dose of 10 mg cladribine (claim 33); and the pharmaceutical formulation is administered 1 to 7 days per month during the induction period (claim 34).

Finally, regarding claims 36 and 37, Bodor discloses administration of cladribine in conjunction with the administration of one or more additional active ingredients. For

example, in the treatment of multiple sclerosis, Bodor teaches co-administration of interferon beta (see page 24, lines 10-18).

In accord with the teachings of Bodor et al., Beutler discloses a method of treating multiple sclerosis by administration of 2-chloro-2'-deoxyadenosine (a.k.a. cladribine) (see abstract), wherein oral administration is a preferred mode of administration (see column 10, lines 47-48). Beutler teaches that for oral administration, a therapeutically effective daily dose can range from about 0.04 mg/kg to about 1.0 mg/kg/day (see column 10, lines 53-54). Typical administration lasts for a time period of about 5 to about 14 days, with a 7-day time course being usual. Courses (cycles) of administration can also be repeated at monthly intervals. Oral unit dosages can be administered at intervals of one to several days to provide the therapeutically effective dose (see column 11, lines 1-15).

Thus, for an average adult human weighing 150 lbs (68 kg), according to the claimed invention, if the total dose reached at the end of the induction period is 3.5 mg/kg and the total dose reached at the end of the maintenance period is 1.7 mg/kg, for example, this would amount to 238 mg and 115.6 mg cladribine, respectively. According to Beutler, a 68 kg adult receiving oral cladribine therapy for 7 days, for example, could receive a total dose of between 19.04 and 476 mg cladribine, which encompasses the instantly recited doses of claims 18, 24, 25, and 29-31.

Thus, Beutler notes, *in vivo* administration of the above dosages over a time period of about 5 to about 14 days or at weekly or day intervals provides an amount sufficient to kill at least 50 percent of the originally present monocytes (which acts to

down-regulate the autoimmune aspect of MS) (see column 11, lines 1-15). Beutler further teaches that the daily administration course can be repeated periodically over a period of several months, e.g. about three to about nine months. In usual practice, this means that treatments are administered over a period of about 5-7 days and are repeated at about 3 to about 4 week intervals for several months, e.g. about 3 to about 9 months (see column 11, lines 37-50). Therefore, for a 7 day administration period (i.e., the induction period), the total dose of cladribine reached at the end of the 7 days would be in the range of 0.28 to 7.0 mg/kg, which would encompass the instantly recited range of 1.7 to 3.5 mg/kg. And in addition to addressing presently claimed limitations regarding the frequency of the administration cycles, Beutler's disclosure also addresses instantly recited limitations of claims 30 and 35, which state that the maintenance (iii) step and cladribine-free period (iv) step are repeated at least one, two or three times.

Taken together, the combined teachings of Bodor et al. and Beutler provide for method of treating multiple sclerosis comprising oral administration of cladribine, wherein a typical treatment course comprises the daily administration of cladribine for 1-7 days (i.e., induction phase) followed by a cladribine-free period and then another course of daily cladribine for 1-7 days in a subsequent treatment such as the second month (i.e., maintenance phase), followed by up to 10 months of no treatment, wherein a weekly treatment course can be repeated periodically for several months. However, neither of the above references teach that the total dose of cladribine reached at the

end of the maintenance phase is lower than the total dose reached at the end of the induction phase.

Bloom discusses the treatment of multiple sclerosis and other autoimmune diseases, wherein effective treatment requires an intense induction phase lasting from about five to seven weeks during which time lymphocytes are continuously depleted from circulation to a level of less than 500 cells/μl, followed by a maintenance phase in a lower intensity treatment regimen is employed to hold the overall blood lymphocyte count to less than 500 cells/μl (see columns 3-4). While the initial induction phase of treatment is accomplished here by lymphoctapheresis and the maintenance phase is accomplished with the use of immunosuppressive or immunomodulatory agents other than cladribine, the principle of Bloom's teachings remains the same: effective treatment of multiple sclerosis requires an intense induction phase with substantial depletion of blood lymphocytes followed by a more moderate maintenance phase to hold the cell numbers down. Even with respect to the immunomodulatory agents employed in the maintenance phase, Bloom teaches that treatment dosages are lowered with each successive use of the drug (see, for example, column 4, lines 39-49 regarding the use of azathioprine (AZA) and prednisone.

Thus, as evidenced by the prior art, the skilled artisan would have known that effective treatment of multiple sclerosis involves the removal of the majority (e.g., up to 90%; see Beutler, column 11) of activated lymphocytes from the patient in an initial phase of the treatment, followed by a maintenance phase in which the numbers of lymphocytes are maintained at a reduced level. The artisan would have also been

aware that cladribine is useful for the treatment of multiple sclerosis, as cladribine is an immunosuppressive agent that functions by killing activated lymphocytes (and in particular, monocytes, which are presumably activated against self-antigens). Particularly in view of the chronic nature of multiple sclerosis, in order to reduce the severity or duration of future relapses (or to prevent them altogether) the artisan would have been aware that in order for long-term treatment to be successful, it must be sustainable and well-tolerated by the patient.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat multiple sclerosis with oral cladribine according to a cyclic treatment regimen, wherein treatment involves an induction phase and a maintenance phase, and wherein the total dosage administered in the maintenance phase is less than the total dosage administered in the induction phase. Additionally, even though cladribine therapy is generally well-tolerated with a low incidence of adverse effects (see, for example, Examples 1 and 2 in the Beutler patent), in order to reduce overall treatment costs associated with cladribine therapy and further lessen the risk of negative side effects, the artisan would have been motivated to use a lower dose in the maintenance phase that is still sufficient to sustain a therapeutically-effective immunosuppressive state. Regardless, each of the recited doses, treatment durations, and frequencies are clearly result effective parameters that a person of ordinary skill in the art would routinely optimize (see MPEP § 2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Indeed, both Bodor et al. and Beutler assert that it is within the level and skill of the

artisan to fine-tune cladribine dosages and treatment protocols in order to achieve a desired therapeutic effect. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization would have been obvious at the time of applicant's invention. Furthermore, as was noted by the United States Supreme Court, if a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one method (e.g., Bloom's method of high dose, no dose, low dose), and a person of ordinary skill would recognize that it would improve similar methods (e.g., Bodor et al. or Beutler) in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *KSR,* 127 S. Ct. at 1740. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show it was obvious under 35 U.S.C. 103." *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1742, 82USPQ2d 1385, 1396 (2007).

Conclusion

7. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard
Art Unit 1649

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646

Notice of References Cited	Application/Control No. 11/722,018	Applicant(s)/Patent Under Reexamination DE LUCA, GIAMPIERO	
	Examiner Kimberly Ballard	Art Unit 1649	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,964,848	10-1990	Bloom, Philip M.	604/6.03
*	B	US-5,506,214	04-1996	Beutler, Ernest	514/46
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
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	L	US-			
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*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
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	S					
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*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11722018	DE LUCA, GIAMPIERO
	Examiner	Art Unit
	Kimberly Ballard	1649

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
Inventor search (PALM, EAST, NPL)	07/28/2009	KAB
EAST (USPAT, USOCR, PGPUB, DERWENT, FPRS, EPO, JPO)	07/28/2009	KAB
STN (MEDLINE, BIOSIS, CAPLUS, EMBASE)	07/28/2009	KAB

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BIB DATA SHEET

CONFIRMATION NO. 5532

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/722,018	06/18/2007	514	1649	SER-125

APPLICANTS

Giampiero De Luca, Conches, SWITZERLAND;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2005/056954 12/20/2005
which claims benefit of 60/638,669 12/22/2004

**** FOREIGN APPLICATIONS ***************************

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/10/2008

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/KIMBERLY BALLARD/ Examiner's Signature	☐ Initials	SWITZERLAND	0	20	1

ADDRESS

SALIWANCHIK LLOYD & SALIWANCHIK
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PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

TITLE

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
900	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	25	De-luca-gia$.in.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2009/07/28 19:37
L2	5077	cladribine leustatin (2-chlorodeoxyadenosine) (2-chloro-2'deoxyadenosine)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2009/07/28 19:38
L3	61883	multiple adj sclerosis	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2009/07/28 19:39
L4	1466	l2 and l3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2009/07/28 19:39
L5	1372	l4 and oral	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2009/07/28 19:39
L6	136	l2 same l3	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2009/07/28 19:41

7/28/2009 7:43:17 PM
C:\Documents and Settings\kballard\My Documents\EAST\Workspaces\11.722018.wsp

June 18, 2007

INFORMATION DISCLOSURE
STATEMENT
Patent Application
Docket No. SER-125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Giampiero de Luca

Filed : June 18, 2007

For : Cladribine Regimen for Treating Multiple Sclerosis

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

INFORMATION DISCLOSURE STATEMENT
UNDER 37 CFR §§1.97 AND 1.98

Sir:

In accordance with 37 C.F.R. § 1.56, the references listed on the attached form PTO/SB/08 are being brought to the attention of the Examiner for consideration in connection with the examination of the above-identified patent application. A copy of each cited reference is enclosed.

It is respectfully requested that the references cited on the attached form PTO/SB/08 be considered in the examination of the subject application and that their consideration be made of record.

Applicant respectfully asserts that the substantive provisions of 37 C.F.R. §§ 1.97 and 1.98 are met by the foregoing statement.

Respectfully submitted,

/FRANKCEISENSCHENK/

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jps
Attachments: Form PTO/SB/08; copies of references cited therein.

J:\SER\125\PTO-Misc\IDS.doc/DNB/jps

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B./

PTO/SB/08A (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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Substitute for form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Art Unit	
Examiner Name	K. Ballard
Attorney Docket Number	SER-125

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1	US-			
	U2	US-			
	U3	US-			
	U4	US-			
	U5	US-			
	U6	US-			
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code [5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T [6]
	F1	WO 04/087101 A2	10/14/2004	Ivax Corporation	All	
	F2	EP 0 626 853 B1	04/26/200	The Scripps Research Institute	All	
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

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This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B./

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PTO/SB/08B (08-03)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 3

Complete if Known	
Application Number	
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Group Art Unit	
Examiner Name	K. Ballard
Attorney Docket Number	SER-125

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R1	BEUTLER, E. *et al.* "Marrow Suppression Produced by Repeated Doses of Cladribine", *Acta Haematol*, 1994, pp. 10-15, Vol. 91.	
	R2	BEUTLER, E. *et al.* "Treatment of Multiple Sclerosis and Other Autoimmune Diseases With Cladribine", *Seminars in Hematology*, January 1, 1996, pp. 45-52, Vol. 33, No. 1, Supplement 1.	
	R3	BEUTLER, E. *et al.* "The treatment of chronic progressive multiple sclerosis with cladribine", *Proc. Natl. Acad. Sci. USA*, February 1996, pp. 1716-1720, Vol. 93.	
	R4	ELLISON, G. *et al.* "Oral Cladribine for Multiple Sclerosis", *Neurology*, March 1997, P03.070, pp. A174-A175, Vol. 48, No. 3, XP008047069.	
	R5	GRIEB, P. *et al.* "Effect of Repeated Treatments with Cladribine (2-Chlorodeoxyadenosine) on Blood Counts in Multiple Sclerosis Patients", *Archivum Immunologiae et Therapiae Experimentalis*, 1995, pp. 323-327, Vol. 43, No. 5-6.	
	R6	KAZIMIERCZUK, Z. *et al.* "Synthesis of 2'-Deoxytubercidin, 2'-Deoxyadenosine, and Related 2'-Deoxynucleosides via a Novel Direct Stereospecific Sodium Salt Glycosylation Procedure", *J. Am. Chem. Soc.*, 1984, pp. 6379-6382, Vol. 106, No. 21.	
	R7	KURTZKE, J. "Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS)", *Neurology*, November 1983, pp. 1444-1452, Vol. 33.	
	R8	LANGTRY, H. *et al.* "Cladribine: A Review of its Use in Multiple Sclerosis", *Biodrugs*, May 1998, pp. 419-433, Vol. 9, No. 3.	
	R9	LASSMANN, H. *et al.* "Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy", *TRENDS in Molecular Medicine*, March 2001, pp. 115-121, Vol. 7, No. 3.	
	R10	LUBLIN, F. *et al.* "Defining the clinical course of multiple sclerosis: Results of an international survey", *Neurology*, April 1996, pp. 907-911, Vol. 46.	
	R11	LUCCHINETTI, C. *et al.* "Multiple sclerosis: recent developments in neuropathology, pathogenesis, magnetic resonance imaging studies and treatment", *Current Opinion in Neurology*, 2001, pp. 259-269, Vol. 14.	
	R12	MATTSON, D. "Update on the diagnosis of multiple sclerosis", *Expert Review of Neurotherapeutics*, May 2002, pp. 319-327, Vol. 2, No. 3.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B./

PTO/SB/08B (08-03)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 3 of 3

Complete if Known	
Application Number	
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Group Art Unit	
Examiner Name	K. Ballard
Attorney Docket Number	SER-125

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R13	MCDONALD, W. *et al.* "Recommended Diagnostic Criteria for Multiple Sclerosis: Guidlines from the International Panel on the Diagnosis of Multiple Sclerosis", *Annals of Neurology*, July 2001, pp. 121-127, Vol. 50, No. 1.	
	R14	MILLER, R. *et al.* "Therapeutic advances in ALS", *Neurology*, 1996, pp. S217, Vol. 47, Suppl. 4.	
	R15	NOSEWORTHY, J. *et al.* "Multiple Sclerosis", *The New England Journal of Medicine*, September 28, 2000, pp. 938-952, Vol. 343, No. 13.	
	R16	POSER, C. *et al.* "New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocols", *Annals of Neurology*, March 1983, pp. 227-231, Vol. 13, No. 3.	
	R17	RICE, G. *et al.* "Cladribine and progressive MS: Clinical and MRI outcomes of a multicenter controlled trial", *Neurology*, March 2000, pp. 1145-1155, Vol. 54.	
	R18	ROMINE, J. *et al.* "A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis", *Proceedings of the Association of American Physicians*, *January*/February 1999, pp. 35-44, Vol. 111, No. 1.	
	R19	SCHUMACHER, G. *et al.* "Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis", *Annals New York Academy of Sciences*, March 31, 1965, pp. 552-568, Vol. 122.	
	R20	SELBY, R. *et al.* "Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis", *Can. J. Neurol. Sci.*, 1998, pp. 295-299, Vol. 25.	
	R21	SIPE, J. *et al.* "A neurologic rating scale (NRS) for use in multiple sclerosis", *Neurology*, October 1984, pp. 1368-1372, Vol. 34.	
	R22	STELMASIAK, Z. *et al.* "A pilot trial of cladribine (2-chlorodeoxyadenosine) in remitting-relapsing multiple sclerosis", *Med. Sci Monit.*, 1998, pp. 4-8, Vol. 4, No. 1.	
	R23		
	R24		

Examiner Signature	/Kimberly Ballard/	Date Considered	07/28/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

This collection of information is required by 37 CFR 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /K.B./

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      (FILE 'HOME' ENTERED AT 19:58:17 ON 28 JUL 2009)

      FILE 'ZCAPLUS' ENTERED AT 19:58:37 ON 28 JUL 2009
                E CLADRIBINE/CT
                E E3+ALL

      FILE 'CAPLUS' ENTERED AT 19:59:29 ON 28 JUL 2009
                E US-2007722018/APPS

      FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 20:00:36 ON 28 JUL 2009
L1          7700 S CLADRIBINE OR 2-CHLORODEOXYADENOSINE OR 2-CHLORO-2-DEOXYADENO
L2        138027 S MULTIPLE(A)SCLEROSIS
L3           257 S L1(2P)L2
L4            88 S L3 AND ORAL?
L5            53 DUP REM L4 (35 DUPLICATES REMOVED)
L6           896 S DE-LUCA G/AU
L7             0 S L6 AND L1
L8            19 S L6 AND L2
L9            10 DUP REM L8 (9 DUPLICATES REMOVED)
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I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on December 18, 2009.

Frank C. Eisenschenk, Ph.D., Patent Attorney

AMENDMENT UNDER 37 C.F.R. § 1.111
Patent Application
Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

AMENDMENT UNDER 37 C.F.R. § 1.111

Sir:

Applicants request that the period for response be extended two months through and including January 4, 2010, the fees for which have been paid at the time this Amendment was filed.

In response to the Office Action dated August 3, 2009, please amend the above-identified patent application as follows:

J:\SER\125\Amd-Resp\Amd.doc/DNB/sl

In the Claims

1-17 (canceled).

18 (currently amended). A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine, wherein the formulation is to be orally administered following the sequential steps below:

(i) an induction period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period of between about 8 and about 10 months wherein no cladribine formulation is administered;

(iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine formulation is administered.

19 (currently amended). The method according to claim 18, wherein the induction period lasts up to about 4 months~~, or up to 3 months, or up to 2 months~~.

20 (currently amended). The method according to claim 19, wherein the induction period lasts ~~up to~~ about 2 months.

21 (currently amended). The method according to ~~claim 18~~ claim 19, wherein the induction period lasts ~~up to 2 months~~ about 3 months.

22 (currently amended). The method according to ~~claim 18~~claim 19, wherein the induction period lasts ~~up to~~ about 4 months.

23 (currently amended). The method according to claim 19, wherein the induction period lasts up to about 3 months~~4 months~~.

24 (currently amended). The method according to claim 18, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

25 (currently amended). The method according to claim 18, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

26 (canceled).

27 (currently amended). The method according to claim 18, wherein the cladribine-free (iv) period lasts ~~up to~~ about 10 months.

28 (currently amended). The method according to claim 18, wherein the maintenance period lasts ~~up to~~ about 4 months~~, or up to 3 months or up to 2 months~~.

29 (currently amended). The method according to claim 18, wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

30 (currently amended). The method according to claim 18, wherein the formulation is to be orally administered following the sequential steps below:

(i) an induction period wherein said cladribine formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period of between about 8 and about 10 months wherein no cladribine formulation is administered;

(iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine formulation is administered;

wherein the induction period lasts up to 4 months~~, or up to 3 months or up to 2 months~~; the cladribine-free period (ii) lasts up to 10 months~~, or up to 8 months or up to 10 months~~; the maintenance period (iii) lasts up to 2 months; the cladribine-free period (iv) lasts up to 10 months; the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated ~~performed~~ one, two or three times.

31 (currently amended). The method according to claim 30, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

32 (previously presented). The method according to claim 30, wherein the formulation is to be orally administered at a daily dose of 3 to 30 mg cladribine.

33 (currently amended). The method according to claim 32, wherein the ~~pharmaceutical~~ formulation is to be orally administered at a daily dose of 10 mg cladribine.

34 (currently amended). The method according to claim 18, wherein the ~~pharmaceutical~~ formulation is orally administered 1 to 7 days per month during the induction period.

35 (previously presented). The method according to claim 18, wherein the steps (iii) to (iv) are repeated at least one or two times.

36 (previously presented). The method according to claim 18, wherein said cladribine formulation is to be administered in combination with interferon-beta.

37 (previously presented). The method according to claim 30, wherein said cladribine formulation is to be administered in combination with interferon-beta.

38 (new). A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i);

(iv) a cladribine-free period wherein no cladribine is administered.

39 (new). The method according to claim 38, wherein the induction period lasts about 4 months.

40 (new). The method according to claim 38, wherein the induction period lasts about 2 months.

41 (new). The method according to claim 38, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

42 (new). The method according to claim 38, where the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

43 (new). The method according to claim 38, wherein the cladribine-free period (ii) lasts about 10 months.

44 (new). The method according to claim 38, wherein the cladribine-free (iv) period lasts 10 months.

45 (new). The method according to claim 38, wherein the maintenance period lasts about 2 months.

46 (new). The method according to claim 38, wherein the formulation is orally administered following the sequential steps below:

(i) an induction period wherein said formulation is administered orally and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period wherein no cladribine is administered;

(iii) a maintenance period wherein said formulation is administered orally and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i);

(iv) a cladribine-free period wherein no cladribine is administered.

wherein the maintenance period (iii) lasts about 2 months; the cladribine-free period (iv) lasts about 10 months; the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeatedly performed one, two or three times.

47 (new). The method according to claim 38, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

48 (new). The method according to claim 38, wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.

49 (new). The method according to claim 38, wherein the formulation is orally administered at a daily dose of 10 mg cladribine.

50 (new). The method according to claim 38, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

51 (new). The method according to claim 38, wherein the steps (iii) to (iv) are repeated at least one time.

52 (new). The method according to claim 38, wherein the steps (iii) to (iv) are repeated at least two times.

53 (new). The method according to claim 38, wherein the formulation is administered in combination with interferon-beta.

54 (new). A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg;

(iv) a cladribine-free period wherein no cladribine is administered.

55 (new). The method according to claim 54, wherein the induction period lasts about 4 months.

56 (new). The method according to claim 54, wherein the induction period lasts about 2 months.

57 (new). The method according to claim 54, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

58 (new). The method according to claim 54, where the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

59 (new). The method according to claim 54, wherein the cladribine-free period (ii) lasts about 10 months.

60 (new). The method according to claim 54, wherein the cladribine-free (iv) period lasts 10 months.

61 (new). The method according to claim 54, wherein the maintenance period lasts about 2 months.

62 (new). The method according to claim 54, wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.

63 (new). The method according to claim 54, wherein the formulation is orally administered at a daily dose of 10 mg cladribine.

64 (new). The method according to claim 54, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

65 (new). The method according to claim 54, wherein the steps (iii) to (iv) are repeated at least one or two times.

66 (new). The method according to claim 54, wherein the formulation is administered in combination with interferon-beta.

Remarks

Claims 18-37 are pending in the subject application. By this Amendment, Applicant has canceled claim 26, amended claims 18-25, 27-31, 33 and 34 and added new claims 38-66. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed (see, for example, page 7, line 15 through page 8, line 3; and pages 13-18 of the as-filed application). Entry and consideration of the amendments and new claims presented herein is respectfully requested. Accordingly, claims 18-25 and 27-66 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

The courtesy of an interview in this matter is requested at the time the Examiner considers this response.

Claim 30 is objected to because of informalities. By this Amendment, the repeated phrase "up to 10 months" has been deleted. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 18-37 are rejected under 35 U.S.C. § 103(a) as obvious over Bodor *et al.* (WO 2004/087101) and Beutler (U.S. Patent No. 5,506,213) in view of Bloom (U.S. Patent No. 4,964,848). The Office Action indicates that the Bodor *et al.* and Beutler references teach the use of cladribine for the treatment of multiple sclerosis. The Office Action argues, at pages 3-8:

> Specifically, Bodor discloses treatment of multiple sclerosis comprising administering to a patient in need thereof a therapeutically effect amount of a composition comprising cladribine, wherein the composition is formulated for oral administration. In particular, Bodor *et al.* teaches that for the treatment of multiple sclerosis, 10 mg of cladribine in solid dosage form is to be administered orally once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively, the patient may be treated with 10 mg of cladribine in the dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment. Further, Bodor *et al.* discloses that one of skill in the art will appreciate that the therapeutically effective amount of cladribine administered may be lowered or increased by fine tuning and/or by administering cladribine with another active ingredient.
>
> Hence, the teachings of Bodor *et al.* address the following recited limitations of the instant claims: an induction period lasting up to 4 months, or up to 3 months, or up to 2 months; the cladribine-free period lasts up to 10 months; the maintenance period lasts up to 4 months, or up to 3 months, or up to 2 months; the formulation is

to be orally administered at a daily dose of 3 to 30 mg cladribine or at a daily dose of 10 mg cladribine; and the pharmaceutical formulation is administered 1 to 7 days per month during the induction period.

Finally, regarding claims 36 and 37, Bodor *et al.* disclose administration of cladribine in conjunction with the administration of one or more additional active ingredients. For example, in the treatment of multiple sclerosis, Bodor *et al.* teach co-administration of interferon beta.

With regard to the purported teachings of Bodor *et al.*, Applicant notes that the reference is silent with respect to the administration of cladribine therapy after the cladribine-free period of between about 8 and 10 months. Thus, Bodor *et al.* fails to teach a cladribine-free period of between about 8 and 10 months followed by a "maintenance period" during which a cladribine formulation is administered such that the total dose administered in the "maintenance period" is lower than the total dose first administered to the patient which is then followed by another cladribine-free period.

The Office Action further argues:

In accord with the teachings of Bodor *et al.*, Beutler discloses a method of treating multiple sclerosis by administration of 2-chloro-2'-deoxyadenosine (a.k.a. cladribine), wherein oral administration is a preferred mode of administration. Beutler teaches that for oral administration, a therapeutically effective daily dose can range from about 0.04 mg/kg to about 1.0 mg/kg/day. Typical administration lasts for a time period of about 5 to about 14 days, with a 7-day time course being usual. Courses (cycles) of administration can also be repeated at monthly intervals. Oral unit dosages can be administered at intervals of one to several days to provide the therapeutically effective dose. Thus, for an average adult human weighing 150 lbs (68 kg), according to the claimed invention, if the total dose reached at the end of the induction period is 3.5 mg/kg and the total dose reached at the end of the maintenance period is 1.7 mg/kg, for example, this would amount to 238 mg and 115.6 mg cladribine, respectively. According to Beutler, a 68 kg adult receiving oral cladribine therapy for 7 days, for example, could receive a total dose of between 19.04 and 476 mg cladribine, which encompasses the instantly recited doses of claims 18, 24,25, and 29-31. Thus, Beutler notes, *in vivo* administration of the above dosages over a time period of about 5 to about 14 days or at weekly or day intervals provides an amount sufficient to kill at least 50 percent of the originally present monocytes (which acts to down-regulate the autoimmune aspect of MS). Beutler further teaches that the daily administration course can be repeated periodically over a period of several months, e.g. about three to about nine months. In usual practice, this means that treatments are administered over a period of about 5-7 days and are repeated at about 3 to about 4 week intervals for several months, e.g. about 3 to about 9 months. Therefore, for a 7 day administration period (*i.e.*, the induction period), the

> total dose of cladribine reached at the end of the 7 days would be in the range of 0.28 to 7.0 mg/kg, which would encompass the instantly recited range of 1.7 to 3.5 mg/kg. And in addition to addressing presently claimed limitations regarding the frequency of the administration cycles, Beutler's disclosure also addresses instantly recited limitations of claims 30 and 35, which state that the maintenance (iii) step and cladribine-free period (iv) step are repeated at least one, two or three times.

In this regard, Applicant notes that Beutler fails to teach any period of time that corresponds to a "cladribine-free period" as recited in the instant claims. Rather, Beutler teaches methods of treating multiple sclerosis comprising the administration of adenosine compounds, such as cladribine, that is repeated periodically, such as weekly or monthly over a period of several months to about one year (column 9, line 61 through column 10, line 7). In column 11 (at lines 1-15), Beutler discusses the typical cladribine administration cycles. In this passage, the typical administration period is about 5 to about 14 days (with a seven day time course typical) followed by a period during which cladribine is not administered. Where the treatment cycle is monthly, the "cladribine-free" period ranges from about 23-26 days (depending on the month for a 5 day administration period) to as little as 14-17 days (depending on the month for a 14 day administration period). Applicant submits that no passage of Beutler discloses or contemplates cladribine-free periods that range from about 8 to about 10 months.

The Office Action further argues:

> Taken together, the combined teachings of Bodor *et al.* and Beutler provide for method of treating multiple sclerosis comprising oral administration of cladribine, wherein a typical treatment course comprises the daily administration of cladribine for 1-7 days (i.e., induction phase) followed by a cladribine-free period and then another course of daily cladribine for 1-7 days in a subsequent treatment such as the second month i.e., maintenance phase), followed by up to 10 months of no treatment, wherein a weekly treatment course can be repeated periodically for several months. However, neither of the above references teach that the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase.

Applicant respectfully submits that the combined teachings of Bodor *et al.* and Beutler do not give rise to the method of treating multiple sclerosis as asserted in the Office Action. For example, there is no teaching in Bodor *et al.* regarding repeated treatment cycles comprising the administration of

cladribine after the 10 month cladribine free period and the Office Action points to no such teachings. While Beutler discloses multiple treatment "cycles", the teachings of that reference relate to the repeated weekly or monthly administration of cladribine over a period of 5 to 14 days within each "cycle".

The Office Action also notes other deficiencies in the teachings of Bodor *et al.* and Beutler. Notably, that "neither of the above references teach that the total dose of cladribine reached at the end of the maintenance phase is lower than the total dose reached at the end of the induction phase" (Office Action at the paragraph bridging pages 6-7). In an effort to cure this deficiency, the Office Action argues (citing to the teachings of Bloom at page 7 of the Office Action):

> Bloom discusses the treatment of multiple sclerosis and other autoimmune diseases, wherein effective treatment requires an intense induction phase lasting from about five to seven weeks during which time lymphocytes are continuously depleted from circulation to a level of less than 500 cells/μl, followed by a maintenance phase in a lower intensity treatment regimen is employed to hold the overall blood lymphocyte count to less than 500 cell/μl. While the initial induction phase of treatment is accomplished here by lymphocytapheresis and the maintenance phase is accomplished with the use of immunosuppressive or immunomodulatory agents other than cladribine, the principle of Bloom's teachings remains the same: effective treatment of multiple sclerosis requires an intense induction phase with substantial depletion of blood lymphocytes followed by a more moderate maintenance phase to hold the cell numbers down. Even with respect to the immunomodulatory agents employed in the maintenance phase, Bloom teaches that treatment dosages are lowered with each successive use of the drug (see, for example, column 4, lines 39-49 regarding the use of azathioprine (AZA) and prednisone).

Applicant respectfully disputes the alleged teachings of Bloom proffered in the Office Action. For example, the Office Action argues (at page 7) that Bloom teaches an induction period followed by a maintenance phase where "a lower intensity treatment regimen is employed to hold the overall blood lymphocyte count to less than 500 cell/μl. While the initial induction phase of treatment is accomplished here by lymphocytapheresis and the maintenance phase is accomplished with the use of immunosuppressive or immunomodulatory agents other than cladribine, the principle of Bloom's teachings remains the same: effective treatment of multiple sclerosis requires an intense induction phase with substantial depletion of blood lymphocytes followed by a more moderate maintenance phase to hold the cell numbers down". Such is not, in fact, the case.

As noted at column 4, lines 18-52 of Bloom, both lymphocytapheresis and a chemotherapeutic protocol are administered to an individual to hold lymphocyte numbers down to the desired levels (less than 500 cells/μL). It is unclear how this combined therapeutic regimen, including a combination of immunosuppressive drugs (AZA and prednisone) added to lymphocytapheresis can be construed as "a more moderate maintenance phase" or a "lower intensity treatment regimen". If anything, this combination protocol taught in Bloom would have been considered a more intense treatment regimen since both lymphocytapheresis and immunosuppression via AZA and prednisone were being employed on the subject.

Applicant further notes that the alleged rationale for combining Bloom with either Bodor *et al.* and/or Beutler, namely, "the principle of Bloom's teachings remains the same: effective treatment of multiple sclerosis requires an intense induction phase with substantial depletion of blood lymphocytes followed by a more moderate maintenance phase to hold the cell numbers down" would not be logical in view of the teachings of Beutler, who indicates that the level of circulating monocytes returns to pretreatment levels about two weeks after treatment with cladribine is stopped (see column 11, lines 22-24). As such, the teachings of Beutler suggests that it would not have been possible to "hold the cell numbers down" since the levels of circulating monocytes return to pretreatment levels about two weeks after cladribine treatment is stopped. Thus, Applicant submits that one skilled in the art would not have had a reasonable expectation of success in holding cell numbers down in view of the express teachings of Beutler where a treatment protocol such as that claimed in this application was followed. Indeed, the teachings of Beutler indicate to one skilled in the art that a cladribine-free period that exceeded more than two weeks was undesirable since total monocyte numbers would rebound to pretreatment levels about two weeks after cladribine administration ceased.

Turning to the argument that "[e]ven with respect to the immunomodulatory agents employed in the maintenance phase, Bloom teaches that treatment dosages are lowered with each successive use of the drug (see, for example, column 4, lines 39-49 regarding the use of azathioprine (AZA) and prednisone)". Applicant submits that this is an overstatement of the teachings of the reference. While it is true that the dosage of AZA and prednisone are lowered during the course of administration, the AZA dose is lowered from 5 mg/kg/day to 2.5 mg/kg/day over the span of five

(5) days where it is held constant for the course of treatment (at 2.5 mg/kg). Likewise, prednisone is reduced from 60 mg/kg/day to 15 mg/kg/day over the span of 10 weeks and held constant at that dosage (15 mg/kg/day) for at least one year. Thus, it is clear that Bloom does not teach lowering treatment dosages with each successive use of the drug, rather Bloom teaches the tapering the dosage of each drug to maintenance dosages that are maintained throughout the treatment protocol.

The Office Action further argues that:

> Thus, as evidenced by the prior art, the skilled artisan would have known that effective treatment of multiple sclerosis involves the removal of the majority (e.g., up to 90%; see Beutler, column 11) of activated lymphocytes from the patient in an initial phase of the treatment, followed by a maintenance phase in which the numbers of lymphocytes are maintained at a reduced level. The artisan would have also been aware that cladribine is useful for the treatment of multiple sclerosis, as cladribine is an immunosuppressive agent that functions by killing activated lymphocytes (and in particular, monocytes, which are presumably activated against self-antigens). Particularly in view of the chronic nature of multiple sclerosis, in order to reduce the severity or duration of future relapses (or to prevent them altogether) the artisan would have been aware that in order for long-term treatment to be successful, it must be sustainable and well-tolerated by the patient. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat multiple sclerosis with oral cladribine according to a cyclic treatment regimen, wherein treatment involves an induction phase and a maintenance phase, and wherein the total dosage administered in the maintenance phase is less than the total dosage administered in the induction phase. Additionally, even though cladribine therapy is generally well-tolerated with a low incidence of adverse effects (see, for example, Examples 1 and 2 in the Beutler patent), in order to reduce overall treatment costs associated with cladribine therapy and further lessen the risk of negative side effects, the artisan would have been motivated to use a lower dose in the maintenance phase that is still sufficient to sustain a therapeutically-effective immunosuppressive state.

As noted above, it would not have been obvious to one of ordinary skill in the art at the time the invention was made that effective treatment of multiple sclerosis involved the removal of the majority of activated lymphocytes from the patient in an initial phase of the treatment, followed by a maintenance phase in which the numbers of lymphocytes are maintained at a reduced level. Indeed, the express teachings of Beutler indicate that total monocyte numbers rebound to pretreatment levels about two weeks after cladribine administration is stopped (column 11, lines 20-24). Thus, one skilled in the art would not have had a reasonable expectation of success in maintaining lower

lymphocyte numbers in view of the express teachings of Beutler where a treatment protocol such as that claimed in this application was administered.

One of the final arguments set forth in the Office Action argues:

> Regardless, each of the recited doses, treatment durations, and frequencies are clearly result effective parameters that a person of ordinary skill in the art would routinely optimize (see M.P.E.P § 2144.05). Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. Indeed, both Bodor *et al.* and Beutler assert that it is within the level and skill of the artisan to fine-tune cladribine dosages and treatment protocols in order to achieve a desired therapeutic effect. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization would have been obvious at the time of applicant's invention. Furthermore, as was noted by the United States Supreme Court, if a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one method (e.g., Bloom's method of high dose, no dose, low dose), and a person of ordinary skill would recognize that it would improve similar methods (e.g., Bodor *et al.* or Beutler) in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *KSR,* 127 S. Ct. at 1740. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product is not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show it was obvious under 35 U.S.C. 103." *KSR Int'I Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 1742, 82USPQ2d 1385, 1396 (2007).

First, Applicant notes that the Court of Customs and Patent Appeals has held that a particular parameter must first be recognized as a result-effective variable, *i.e.*, a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation (*see In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977)). Applicant respectfully submits that the Office Action fails to provide any evidence that a dosing regimen, such as that claimed herein, was recognized to be a "result effective variable" that achieved a recognized result. While the Office Action argues that "both Bodor *et al.* and Beutler assert that it is within the level and skill of the artisan to fine-tune cladribine dosages and treatment protocols in order to achieve a desired therapeutic effect", this is far from a teaching that variations in the timing of cladribine administration would have a desired therapeutic effect or could be optimized. At best,

the teachings in each of those references might suggest or teach that the amount of cladribine administered to an individual patient should be "fine-tuned" to achieve a desired therapeutic effect. Applicants further submit that there is no evidence of record that suggests that the claimed dosing regimen could be derived by "fine-tuning" of dosing teachings of Bodor *et al.* and/or Beutler.

Applicant further submits that reliance on Bloom for the purported teaching that "if a technique has been used to improve one method (*e.g.*, Bloom's method of high dose, no dose, low dose), and a person of ordinary skill would recognize that it would improve similar methods (*e.g.*, Bodor *et al.* or Beutler) in the same way, using the technique is obvious unless its actual application is beyond his or her skill." Applicant submits that, as discussed above, Bloom fails to teach a "method of high dose, no dose, low dose" treatment. As noted above, Bloom's maintenance phase, if anything, is a higher intensity therapeutic regimen that utilized immunosuppression via **AZA and prednisone in combination with lymphocytapheresis** to maintain blood lymphocyte levels at the desired levels of less than 500 cells/μL. Furthermore, one skilled in the art would not have had a reasonable expectation of success in keeping blood lymphocyte levels at fewer than 500 cells/μL since Beutler expressly teaches circulating monocyte levels rebound to pretreatment levels about two weeks after cladribine treatment is stopped (column 11, lines 21-24). Thus, one skilled in the art would not expect to be able to maintain monocyte levels at the required levels where a cladribine-free period exceeded about two weeks.

As the Patent Office is aware, all the claim limitations must be taught or suggested by the prior art in order to establish a *prima facie* case of obviousness. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). The Examiner is required to explicitly demonstrate that "there was an apparent reason to combine the known elements in the fashion claimed" by the applicant, "other than the hindsight gleaned from the invention itself." *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1143 (Fed. Cir. 1985), *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 41 (2007). In addition, a reasonable expectation of success is required to establish a *prima facie* case of obviousness (*see* M.P.E.P. § 2143.02)

Applicant also respectfully submits that Bloom is non-analogous art. As the Patent Office is aware, the Patent Office's reviewing court has found that the classification of references is some evidence of "nonanalogy" or "analogy" with respect to the use of a reference in an obviousness rejection. In this regard, Applicant notes that Bloom is not classified in the same area as the instant invention. For example, the instant application is classified in Class 424, subclass 085.600 (Drug, Bio-Affecting And Body Treating Compositions) whereas the invention of Bloom is classified in the surgery (Class 604). Applicant submits that one skilled in the art would not have looked to patents issued into the surgery class for method of treating multiple sclerosis using drugs, such as cladribine. Additionally, Applicant also submits that one skilled in the art, seeking to treat multiple sclerosis using a drug regimen, would not have looked to the surgical arts and methods that extracted blood from a subject and then replaced or returned that blood to the body of the subject being treated (the inventions found in Class 604, subclasses 4-6; see attached classification index).

Applicant respectfully asserts that the claimed invention is not obvious over the cited references and that a *prima facie* case of obviousness has not been established because each of the limitations of the claimed invention has not been taught or suggested by the combination of references. Additionally, as discussed above, there is no apparent reason to combine the cited references absent the teachings of Applicant's specification and one of ordinary skill in the art would not have had a reasonable expectation of success in arriving at the claimed treatment protocol in view of the cited combination of references (particularly in view of the express teachings of Beutler). Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

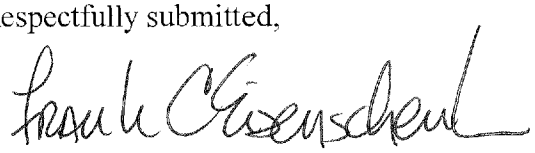
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicant's agreement with or acquiescence in the Examiner's position. Applicant expressly reserves the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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FCE/sl
Attachment: Classification index

This Class 604 is considered to be an integral part of Class 128 (see the Class 128 schedule for the position of this Class in schedule hierarchy). This Class retains all pertinent definitions and class lines of Class 128.

890.1 **CONTROLLED RELEASE THERAPEUTIC DEVICE OR SYSTEM**

891.1 .Implanted dynamic device or system

892.1 .Osmotic or diffusion pumped device or system

1 **SWAB INCLUDING HANDLE (E.G., STICK, ETC.) WITH ABSORBENT MATERIAL AT END THEREOF**

2 .Body treating material fed to absorbent material

3 ..Means broken, cut, pierced, or torn to permit flow of material

4.01 **BLOOD DRAWN AND REPLACED OR TREATED AND RETURNED TO BODY**

5.01 .Constituent removed from blood and remainder returned to body

5.02 ..Pathogenic component removed

5.03 ..Lipidic material removed

5.04 ..Toxic material removed

6.01 ..Component of blood removed (i.e., pheresis)

6.02 ...Erythrocyte

6.03 ...Leukocyte

6.04 ...Plasma

6.05 ...Single needle

6.06 ...Arterial and venous needles

6.07 ..Anticoagulant added

6.08 ..Infrared, visible light, ultraviolet, x-ray or electrical energy applied into blood

6.09 ..Filter means

6.1 ..Valve means

6.11 ..Pumping means

6.12 ...Injector or aspirator syringe supported only by person during use

6.13 ..Heating or cooling means

6.14 ..Oxygenating means

6.15 .Blood collection container

6.16 .Body inserted tubular conduit structure

7 **BLOOD TRANSFERRED BETWEEN DIFFERENT BODIES ALONG CONTINUOUS FLOW PATH (E.G., TRANSFUSION, ETC.)**

8 **DEVICES TRANSFERRING FLUIDS FROM WITHIN ONE AREA OF BODY TO ANOTHER (E.G., SHUNTS, ETC.)**

9 .With flow control means (e.g., check valves, hydrocephalus pumps, etc.)

10 ..With antisiphon means

11 **MEANS FOR INSERTING FIBROUS OR FORAMINOUS RESIDENT PACKING, RECEPTOR, OR MEDICAMENT CARRIER INTO BODY ORIFICE**

12 .With lubricating means

13 .With means for ejecting continuous length insert (e.g., gauze packing)

14 .Distal portion of inserting means deformed, expanded, or ruptured to permit passage of insert therefrom

15 .With slidable ejector (e.g., plunger or ram, etc.) inside tubular inserting means

16 ..Ejector moved into operating position from stored location inside or alongside inserting means

17 ...Ejector pivoted or swung into operating position

18 ..Tubular inserting means releasably interlocked with ejector

19 **MEANS FOR INTRODUCING OR REMOVING MATERIAL FROM BODY FOR THERAPEUTIC PURPOSES (E.G., MEDICATING, IRRIGATING, ASPIRATING, ETC.)**

20 .Infrared, visible light, ultraviolet, X-ray or electrical energy applied to body (e.g., iontophoresis, etc.)

21 ..With tubular injection means inserted into body

22 .With means for cutting, scarifying, or vibrating (e.g., ultrasonic, etc.) tissue

23 .Gas application

Class 600 is an integral part of this Class (Class 128), as shown by the position of this box, and follows the schedule hierarchy of this Class, retaining all pertinent definitions and Class lines of this class.

Class 601 is an integral part of this Class (Class 128), as shown by the position of this box, and follows the schedule hierarchy of this Class, retaining all pertinent definitions and Class lines of this class.

Class 602 is an integral part of this Class (Class 128), as shown by the position of this box, and follows the schedule hierarchy of this Class, retaining all pertinent definitions and Class lines of this class.

95.1 **TRUSS**
96.1 .Abdominal
97.1 .Head
98.1 .Perineal
99.1 .Support
100.1 ..Belt wholly flexible
101.1 ...Elastic in part
102.1 ..Belt and frame
103.1 ..Frame hinged
104.1 ..Frame wholly metallic
105.1 ..Frame with auxiliary straps
106.1 ..Pad carrier
107.1 ...Detachable
108.1 ...Pivoted
109.1 ...Resilient
110.1 ....Clamped
111.1 ...Resilient
112.1 .Pad
113.1 ..Composition
114.1 ..Medicating
115.1 ..Rigid
116.1 ..Adjustable center
117.1 ..Resilient
118.1 ...Inflated
119.1 ...Spring
120.1 ...Stuffed
121.1 ..Connections
122.1 ...Ball and socket
123.1 ...Hinged
124.1 ...Clamped
125.1 ...Resilient
126.1 ....Spring only
830 **FEMALE REPRODUCTORY TRACT SHIELDS, SUPPORTS, OR BIRTH CONTROL DEVICES (E.G., PESSARIES, CONTRACEPTIVE DEVICES)**
831 .Fallopian occluders
832 .With contraceptive, spermacidal, or antifertility agent
833 ..Intrauterine
834 .Pessaries
835 ..External supporters
836 ..Inflatable
837 ..Diaphragm
838 ...Inserters and removers
839 ..Intrauterine
840 ...Inserters and removers
841 ...With cervical cap
842 **MALE REPRODUCTORY TRACT SHIELDS OR BIRTH CONTROL DEVICES (E.G., PROPHYLACTICS, VAS DEFERENS VALVES, ETC.)**
843 .Vas occluders (implants, etc.)
844 .Condoms
845 **BODY RESTS, SUPPORTS OR POSITIONERS FOR THERAPEUTIC PURPOSE (E.G., SEXUAL, POSTURAL, HEAD, ETC.)**
846 **BODY PROTECTING OR RESTRAINING DEVICES FOR PATIENTS OR INFANTS (E.G., SHIELDS, IMMOBILIZERS)**
847 .With fluid supply
848 .Antisnoring device
849 .Drapes
850 ..Incision or cavity inserted
851 ..With handle or applicator means
852 ..With surgical implement retaining means
853 ..Fenestrated
854 ...With cover (flap)
855 ..Folded or stacked
856 ..Tubular
857 .Head or face protector (e.g., lips, ears, etc.)
858 ..Eye or nose protectors
859 ..Oral cavity protectors
860 ...Tongue
861 ...Teeth protectors (e.g., mouthpieces)
862 ....Thermoplastic or thermosetting type
863 ..Breath or contaminated air deflectors

864 ..Aural protectors (e.g., ear)
865 ...Inflatable or expandable
866 ...External ear or head mounting means
867 ...With noise or pressure attenuating means (e.g., dampening, filtering, etc.)
868 ....Valve means (e.g., diaphragm)
869 .Restrainers and immobilizers (e.g., strait jackets, etc.)
870 ..Body type (e.g., backboards)
871 ...Antisupination
872 ...Crib blankets, sheets, and covers
873 ...Garment type (e.g., sleeping bags)
874 ....Vest or shirt type for upper torso
875 .....Harness
876 ...Belt or strap
877 ..Intravenous limb restrainers/ supports (e.g., armboards, etc.)
878 ..Arm or hand
879 ...Hand
880 ....Thumb/finger (e.g., anti-thumb sucking, etc.)
881 ...Elbow
882 ..Leg or foot
883 ..Sexual restraints
884 ...Intravaginal (e.g., antirape devices)
885 ..Incontinent type
886 ...With detector or alarm
887 .Nonabsorbent body opening occluders, seals, or supporters (e.g., surgical or natural orifice occluders)
888 .Wound shields (e.g., vaccination)
889 .Chafing shields (e.g., decubitus pads, etc.)
890 ..Nipple
891 ..Crotch or thigh
892 ..Joint or limb (e.g., foot, elbow, heel, knee, etc.)
893 ...Foot/toe (e.g., corn, bunion, etc.)
894 ....Padded or cushioned
200.11 **MEANS FOR PASSING RESPIRATORY GAS THROUGH BODY OF LIQUID BEFORE INHALATION**
200.12 .Pocket type
200.13 .Plural orifice means passing gas into liquid
200.14 **LIQUID MEDICAMENT ATOMIZER OR SPRAYER**
200.15 .With tongue depressor
200.16 .Ultrasonic
200.17 .Rotating
200.18 .Spray impinged against baffle in or adjacent flow conduit
200.19 .Means for selectively dispensing different fluids
200.21 .Gas stream aspirating medicament from reservoir
200.22 ..Gas flow induced by expansion chamber device (e.g., piston/ cylinder ram, squeeze bulb, etc.)
200.23 .Pre-pressurized container holding medicament
200.24 **RESPIRATORY METHOD OR DEVICE**
200.25 .Artificial gill, or means for separating entrained air from liquid stream
200.26 .Means placed in body opening to facilitate insertion of breathing tube
200.27 .Gas stream directed away from face mask to penetrate contaminated atmosphere
200.28 .Body or head supported means, other than face mask or hood, with gas stream to screen face or penetrate contaminated atmosphere
200.29 .Underwater exhalation dispersing means
201.11 .Draw-type snorkel
201.12 .Corrective or magnifying lens combined with face mask having eyepiece or transparent viewing portion
201.13 .Inhaled gas heated or humidified by exhaled gas
201.14 .Viewing strip slidable relative to mask
201.15 .Means for keeping viewing member (e.g., eyeglass, transparent face shield, etc.) clear
201.16 ..Wiper
201.17 ..Mask with porous lower filtering portion and impervious upper portion shielding user's eyeglasses from exhaled breath

201.18 .Means for preventing nasal inhalation
201.19 .Means for transmitting, or facilitating, voice communication from face mask, hood, or helmet
201.21 .Using liquified oxygen
201.22 .Including body or head supported means covering user's scalp
201.23 ..And nose and mouth also covered
201.24 ...Face mask, visor, or like face-covering means hinged to scalp covering means
201.25 ...Means for removing substance from respiratory gas
201.26 ...Including means inserted in mouth
201.27 ...Diving or swimming apparatus
201.28 ...Having valve, or valve control, structure
201.29 ...Garment associated with head cover
202.11 ....Flight suit
202.12 .Hypobaric body chamber
202.13 .Combined with or convertible to a nonrespiratory device, or having nonrespiratory function other than hyperbaric treatment
202.14 ..Having buoyancy chamber
202.15 ..Having means for facilitating ingestion of food or drink
202.16 ..Means effecting nonrespiratory medical treatment
202.17 ...Device usable either as inhaler or means for rubbing medicament on body surface
202.18 ..Pillow or other support exclusively for head
202.19 ..Garment
202.21 .Smoking device simulator
202.22 .Means for indicating improper condition of apparatus
202.23 .Means for preventing electric shock or arcing
202.24 .Means for protecting user from pressure wave or flame resulting from gas ignition
202.25 .Ozone or ion generation
202.26 .Gas produced by electrolysis or chemical reaction
202.27 .Means for quickly connecting or disconnecting apparatus components
202.28 .Means using rescuer's breath for supplying respiratory gas to another person
202.29 ..Movable wall separating breath of rescuer and victim
203.11 ..Valved
203.12 .Means for mixing treating agent with respiratory gas
203.13 ..Means for supplying anesthetic under patient's control
203.14 ..Control means responsive to condition other than user's airway pressure
203.15 ..Particulate treating agent carried by breathed gas
203.16 ..Means for mixing respiratory gas with water vapor and another treating agent
203.17 ...Electrically heated means producing water vapor
203.18 ..Means for mixing treating agent with oral exhalation and directing mixture into nasal passage
203.19 ..Means for controlling gravity flow of treating agent from holder
203.21 ..Means broken or pierced to supply treating agent
203.22 ..Means for supplying, or permitting inhalation of, separate streams of treating agent/respiratory gas mixture through nasal passages
203.23 ..Pocket-type draw tube having discharge aperture for air/treating agent mixture at end thereof
203.24 ...With gas flow control means other than pivotal or removable closure
203.25 ..Means for varying treating agent/respiratory gas ratio
203.26 ..Means for heating treating agent, respiratory gas, or mixture thereof
203.27 ...Electric
203.28 ..Including expandable bag, bellows, or squeeze bulb
203.29 ..Including face mask covering nose and mouth
204.11 ..Treating agent holder solely supported by head
204.12 ...Holder solely supported by nose

204.13 ..Treating agent evaporated from extended surface absorbent (e.g., sponge, fibrous wick, screen, etc.)
204.14 ..Respiratory gas passed over surface of liquid treating agent in reservoir
204.15 .Means for cooling respiratory gas or respiration device
204.16 ..Substance removed from respiratory gas by cooling
204.17 .Means for heating respiratory gas or respiration device
204.18 .Means for supplying respiratory gas under positive pressure
204.19 ..Permanent magnet included in gas flow control means
204.21 ..Electric control means
204.22 ...Means for sensing partial pressure, or amount, of component in gas mixture
204.23 ...Means for sensing condition of user's body
204.24 ..Fluidic control device utilizing Coanda effect or jet impingement to alter fluid flow
204.25 ..Gas stream passed through jet nozzle or venturi passage
204.26 ..Gas supply means responsive to breathing
204.27 ...Snap action toggle included in control mechanism
204.28 ...Bag or bellows included in control mechanism
204.29 ..Control means responsive to variation in ambient pressure
205.11 ..Means for varying air/oxygen ratio
205.12 ..Means for removing substance from respiratory gas
205.13 ..Respiratory gas supplied from expandable bag, bellows, or squeeze bulb
205.14 ...Means for adjusting gas volume delivered to user from bag, bellows, or bulb during inflation-deflation cycle
205.15 ...Held in pressurizable housing
205.16 ...Biased to contracted or expanded position by mechanical means (e.g., weight, spring, etc.)
205.17 ...Rebreathing bag or bellows
205.18 ..Gas supplied by piston pump
205.19 ..Suction means for assisting exhalation
205.21 ..Means broken or pierced to supply gas
205.22 ..Gas container supported on body
205.23 ..Indicator structure
205.24 ..Valve, or valve control, structure
205.25 ..Face mask covering a breathing passage
205.26 ..Atmosphere enclosure (e.g., oxygen tent, hyperbaric chamber for pressurizing whole body, etc.)
205.27 .Means for removing substance from respiratory gas
205.28 ..Carbon dioxide
205.29 ..Particulate filtering
206.11 ...Including means inserted in nasal passage
206.12 ...Face mask covering a breathing passage
206.13 ....Mask attached to ear
206.14 ....Mask adhesively attached to face
206.15 ....With gas flow control valve
206.16 ....With frame, shaping means, reinforcement, or filter formed of wire
206.17 ....With separate filter encircling element, or housing, securing filter on mask
206.18 ....Covering nose only
206.19 ....Body of mask, other than viewing means, formed of porous filter material (e.g., surgical mask formed entirely of cloth, etc.)
206.21 .Face mask covering a breathing passage
206.22 ..Means for handling liquid (e.g., saliva, breath condensation, etc.) accumulated in mask
206.23 ..Mask/eyepiece sealing structure
206.24 ..Mask/face sealing structure
206.25 ...Adhesive
206.26 ...Closed air-filled passage adjacent mask edge (e.g., tubular bead, etc.)
206.27 ..Means holding mask readily accessible for use
206.28 ..Covering nose and mouth

206.29 ...Including means inserted in mouth
207.11 ...Structure of means securing mask to head
207.12 ...Valve for controlling gas flow
207.13 ..Covering nose only
207.14 .Respiratory gas supply means enters mouth or tracheotomy incision
207.15 ..Breathing passage occluder
207.16 ..Valve for controlling gas flow
207.17 ..Holding strap extending circumferentially of head or neck
207.18 .Respiratory gas supply means enters nasal passage
207.29 **DEVICE FOR CREATING A TRACHEOTOMY INCISION**

Class 604 is an integral part of this Class (Class 128), as shown by the position of this box, and follows the schedule hierarchy of this Class, retaining all pertinent definitions and Class lines of this class.

Class 606 is an integral part of this Class (Class 128), as shown by the position of this box, and follows the schedule hierarchy of this Class, retaining all pertinent definitions and Class lines of this class.

Class 607 is an integral part of this Class (Class 128), as shown by the position of this box, and follows the schedule hierarchy of this Class, retaining all pertinent definitions and Class lines of this class.

903 **RADIO TELEMETRY**
904 **TELEPHONE TELEMETRY**
905 **FEEDBACK TO PATIENT OF BIOLOGICAL SIGNAL OTHER THAN BRAIN ELECTRIC SIGNAL**
906 **MULTIPHASIC DIAGNOSTIC CLINIC**
907 **ACUPUNCTURE**
908 **PATIENT PROTECTION FROM ELECTRIC SHOCK**
909 **BREATHING APPARATUS WITH MEANS FOR PREVENTING PATIENT CROSS-CONTAMINATION**
910 **ANESTHESIA GAS SCAVENGING SYSTEM**
911 **UNILIMB INHALATION-EXHALATION BREATHING TUBES**
912 **CONNECTIONS AND CLOSURES FOR TUBES DELIVERING FLUIDS TO OR FROM THE BODY**
913 **BREATHABLE LIQUIDS**
914 **REBREATHING APPARATUS FOR INCREASING CARBON DIOXIDE CONTENT IN INHALED GAS**
915 **ULTRASOUND MAMMOGRAPHY**
916 **ULTRASOUND 3-D IMAGING**
917 **BODY FLUID, DEVICES FOR PROTECTION THEREFROM (E.G., AIDS, HEPATITUS, ETC.)**
918 .Condoms and shields
919 .Syringe, means to protect user
920 **COMPUTER ASSISTED MEDICAL DIAGNOSTICS**
921 .Diet management
922 .Including image analysis
923 .By comparison of patient data to other data
924 ..Using artificial intelligence
925 .Neural network

897 **MISCELLANEOUS**
898 .Methods
899 .Devices placed entirely within body and means used therewith (e.g., magnetic implant locator)

CROSS-REFERENCE ART COLLECTIONS

900 **BLOOD PRESSURE RECORDER**
901 **SUPPRESSION OF NOISE IN ELECTRIC SIGNAL**
902 **BIOLOGICAL SIGNAL AMPLIFIER**

FOREIGN ART COLLECTIONS

FOR 000 **CLASS-RELATED FOREIGN DOCUMENTS**

DIGESTS

DIG 1 **MOTORIZED SYRINGE**
DIG 3 **HEART-LUNG**
DIG 6 **INTRAVENOUS INJECTION SUPPORT**
DIG 7 **SERVO-SYSTEMS**
DIG 8 **COLLAGEN**
DIG 10 **FLUID AMPLIFIERS**

DIG 12 **PRESSURE INFUSION**
DIG 13 **INFUSION MONITORING**
DIG 14 **TEFLON**
DIG 15 **HOOK AND LOOP TYPE FASTENER**
DIG 18 **HEAT SHRINKABLE FILM**
DIG 19 **CLAVICLE SPLINT**
DIG 20 **INFLATABLE SPLINT**
DIG 21 **SILICONE**
DIG 22 **BLOOD COAGULATION**
DIG 23 **CERVICAL COLLARS**
DIG 24 **MEDICAL-SURGICAL BAGS**
DIG 25 **ARTIFICIAL SPHINETERS AND DEVICES FOR CONTROLLING URINARY INCONTINENCES**
DIG 26 **CANNULA SUPPORTERS**
DIG 27 **CRYOGENIC**

Electronic Patent Application Fee Transmittal

Application Number:	11722018
Filing Date:	18-Jun-2007
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Attorney Docket Number:	SER-125

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	1615	28	52	1456
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 2 months with $0 paid	1252	1	490	490
Miscellaneous:				
			Total in USD ($)	**1946**

Electronic Acknowledgement Receipt

EFS ID:	6668020
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER-125
Receipt Date:	18-DEC-2009
Filing Date:	18-JUN-2007
Time Stamp:	13:50:53
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1946
RAM confirmation Number	10922
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amd.pdf	2202869 205a2f67e512a338859e04a1b60d960cde106669	yes	26

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	26

Warnings:

Information:

2	Fee Worksheet (PTO-875)	fee-info.pdf	32469 10c9a9801379 71c78aef366f3331f72c686d7de5	no	2

Warnings:

Information:

Total Files Size (in bytes):	2235338

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/722,018	06/18/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/18/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 48	Minus	** 20	= 28	X $ =		OR	X $52=	1456
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	1456

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/ANGELA D. JOHNSON/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 15, 2010.

Frank C. Eisenschenk, Ph.D., Patent Attorney

PETITION TO ADD INVENTORS
UNDER 37 C.F.R. §1.48(a)
Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR §1.48(a)

Sir:

It is respectfully petitioned that the inventorship of the above-identified application be corrected to add Arnaud Ythier, Alain Munafo and Maria Lopez-Bresnahan as inventors. Authority for this petition and the correction of inventorship is found in 37 C.F.R. §1.48(a), reproduced below.

37 C.F.R. § 1.48 Correction of inventorship in a patent application, other than a reissue application

(a) If the inventive entity is set forth in error in an executed § 1.63 oath or declaration in a nonprovisional application, and such error arose without any deceptive intention on the part of the person named as an inventor in error or on the part of the person who through error was not named as an inventor, the inventorship of the nonprovisional application may be amended to name only the actual inventor or inventors. If the nonprovisional application is involved in an interference, the amendment must comply with the requirements of this section and must be accompanied by a motion under § 1.634. Amendment of the inventorship requires:

(1) A request to correct the inventorship that sets forth the desired inventorship change;

(2) A statement from each person being added as an inventor and from each person being deleted as an inventor that the error in inventorship occurred without deceptive intention on his or her part;

(3) An oath or declaration by the actual inventor or inventors as required by § 1.63 or as permitted by §§ 1.42, 1.43 or § 1.47;

(4) The processing fee set forth in § 1.17(i); and

(5) If an assignment has been executed by any of the original named inventors, the written consent of the assignee (see § 3.73(b) of this chapter).

Arnaud Ythier, Alain Munafo and Maria Lopez-Bresnahan were unintentionally, and without deceptive intent, not originally included on the application as co-inventors.

Accompanying this petition are:

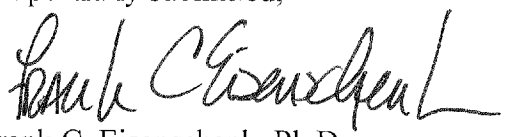
(1) A statement from the individuals being added as inventors that the error in inventorship occurred without deceptive intention on his/her part;

(2) A declaration under § 1.63 by the actual inventors; and

(3) The fee set forth in § 1.17(i).

The fee of $130.00 was paid at the time this Petition was filed. The Commissioner is also authorized to charge any additional fees that may be required by this paper to Deposit Account No. 19-0065.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: (352) 375-8100
Fax No. : (352) 372-5800
Address : P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl
Attachments: as stated above

J:\SER\125\ADD INVENTOR\PET-ADD-INVENTOR.DOC/DNB/sl

Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 C.F.R. §1.48(a)(2)

Sir:

As required by 37 C.F.R. §1.48(a)(2), the undersigned submits this paper to accompany the petition to correct inventorship filed on this same date and hereby states that the inventorship error excluding me, Arnaud Ythier, as a co-inventor on U.S. Serial No. 11/722,018 occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Name: Arnaud Ythier

July 15th 2009
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 C.F.R. §1.48(a)(2)

Sir:

As required by 37 C.F.R. §1.48(a)(2), the undersigned submits this paper to accompany the petition to correct inventorship filed on this same date and hereby states that the inventorship error excluding me, Alain Munafo, as a co-inventor on U.S. Serial No. 11/722,018 occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Name: Alain Munafo

July 7, 2009
Date

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Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 C.F.R. §1.48(a)(2)

Sir:

As required by 37 C.F.R. §1.48(a)(2), the undersigned submits this paper to accompany the petition to correct inventorship filed on this same date and hereby states that the inventorship error excluding me, Maria Lopez-Bresnahan, as a co-inventor on U.S. Serial No. 11/722,018 occurred without any deceptive intent on my part.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

Name: Maria Lopez-Bresnahan

Date 3/11/10

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CONSENT UNDER 37 C.F.R. §1.48(a)(5)

Sir:

As required by 37 C.F.R. §1.48(a)(5), the undersigned, on behalf of Merck Serono SA, submits this paper and a certificate under 37 C.F.R. § 3.73(b) to accompany the petition to correct the inventorship for the above-referenced patent application. I hereby state that the assignee of record, Merck Serono SA, for Serial No. 11/722,018, agrees to the change of inventorship to add Arnaud Ythier, Alain Munafo and Maria Lopez-Bresnahan as co-inventors in the subject application as requested by the accompanying petition.

CERTIFICATE UNDER 37 CFR §3.73(b)

Merck Serono SA certifies that it is the assignee of the entire right, title, and interest in the patent application identified above by virtue of assignment from Giampiero De Luca to Laboratoires Serono, recorded in the United States Patent Office at REEL/FRAME 019685/0061 on August 13, 2007, and a Change of Name from Laboratoires Serono S.A. to Merck Serono, recorded in the United States Patent Office at REEL/FRAME 023000/0862 on July 24, 2009, and an assignment from Arnaud Ythier, Alain Munafo and Maria Lopez-Bresnahan to Merck Serono SA, a copy of which is attached.

J:\SER\125\Add Inventor\MerckSerono-Statement.doc/DNB/sl

As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owners to Merck Serono SA was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

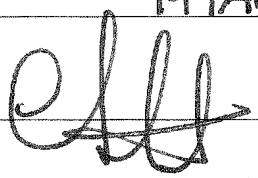
The undersigned has reviewed all of the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee named above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or of any patent issuing thereon.

MERCK SERONO SA

Date: 19 August 2009

Signature: 

Name: Giampiero De Luca

Title: Authorized Representative

C:\DOCUME~1\m141231\LOCALS~1\Temp\notes6030C8\MerckSerono-Statement.doc/DNB/sl

ASSIGNMENT

WHEREAS, we, the undersigned, residing at the indicated addresses given below, have invented certain new and useful improvements in **CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS**, for which an application for United States Letters Patent was filed June 18, 2007, as Serial No. 11/722,018.

WHEREAS, MERCK SERONO S.A., a corporation of the country of Switzerland, having a place of business at Centre Industriel, 1267 Coinsins, Vaud, Switzerland, is desirous of acquiring the entire right, title, and interest in and to said invention and in and to any Letters Patent which may be granted therefor in the United States and in any and all foreign countries;

NOW, THEREFORE, in view of MERCK SERONO S.A.'s review and evaluation of our patent disclosure and other valuable consideration, receipt of which is hereby acknowledged, I, the undersigned, have sold, assigned, and transferred, and by these presents do sell, assign, and transfer, unto said MERCK SERONO S.A., its successors and assigns, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title, and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, and extensions thereof.

We hereby authorize and request the Patent Office Officials in the United States and in any and all foreign countries to issue any and all of said Letters Patent, when granted, to MERCK SERONO S.A., as the assignees of the entire right, title, and interest in and to the same, for the sole use and behoof of MERCK SERONO S.A., its successors and assigns.

FURTHER, we agree that we will communicate to MERCK SERONO S.A., or its representatives, any facts known to us respecting said invention; testify in any legal proceedings; sign all lawful papers; execute all divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to MERCK SERONO S.A.; make all rightful oaths; and generally do everything possible to aid MERCK SERONO S.A., its successors and assigns, to obtain and enforce proper protection for said invention in the United States and in any and all foreign countries.

IN TESTIMONY WHEREOF, I have hereunto set my hand this 15th day of July, 2009.

Signed _____

Arnaud Ythier
Route de Vireloup 88
1239 Collex-Bossy
Switzerland

WITNESS:

Signature: _____

Printed Name: CAROL JASCI

Date: 15.7.2009

IN TESTIMONY WHEREOF, I have hereunto set my hand this 07 day of July, 2009.

Signed Alain Munafo

Alain Munafo
Rue des Pressoirs 6
1180 Tartegnin
Switzerland

WITNESS:

Signature:

Printed Name: CECE FORSSMANN

Date: July 7th, 2009

IN TESTIMONY WHEREOF, I have hereunto set my hand this 11th day of March, 2010.

Signed _____

Maria Lopez-Bresnahan
145 South Great Road
Lincoln, MA 01773

WITNESS:

Signature: _____

Printed Name: Victoria Bresnahan

Date: 11- March - 2010

Application Information

Application Number::	11/722,018
Filing date::	06/18/2008
Application Type::	Regular (National Stage)
Subject Matter::	Utility
Suggested Classification::	None
Suggested Group Art Unit::	None
CD-ROM or CD-R?::	None
Number of CD disks::	None
Number of copies of CDs::	None
Sequence submission?::	No
Computer Readable Form?::	No
Number of Copies of CRF::	None
Title::	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
Attorney Docket Number::	SER.125
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	None
Total Drawing Sheets::	None
Small Entity?::	No
Petition included?::	No
Petition Type::	N/A
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Italy
Status::	Unknown
Inventor One Given Name::	Giampiero
Family Name::	DE LUCA
City of Residence::	Conches/Geneva
Country of Residence::	Switzerland
Street of Mailing Address::	Chemin des Conches 15B
City of Mailing Address::	Conches/Geneva
Country of Mailing Address::	Switzerland
Postal or Zip Code of Mailing Address::	CH-1231

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	CH and FR
Status::	Unknown
Inventor Two Given Name::	Arnaud
Family Name::	YTHIER
City of Residence::	Collex-Bossy
Country of Residence::	Switzerland
Street of Mailing Address::	Route de Vireloup 88
City of Mailing Address::	Collex-Bossy
Country of Mailing Address::	Switzerland
Postal or Zip Code of Mailing Address::	1239

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	CH
Status::	Unknown
Inventor Three Given Name::	Alain
Family Name::	MUNAFO
City of Residence::	Tartegnin
Country of Residence::	Switzerland
Street of Mailing Address::	Rue des Pressoirs 6
City of Mailing Address::	Tartegnin
Country of Mailing Address::	Switzerland
Postal or Zip Code of Mailing Address::	1180

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Unknown
Inventor Four Given Name::	Maria
Family Name::	LOPEZ-BRESNAHAN
City of Residence::	Lincoln
State or Province of Residence::	MA
Street of Mailing Address::	145 South Great Road
City of Mailing Address::	Lincoln
State or Province of mailing address::	MA
Postal or Zip Code of Mailing Address::	01773

Representative Information

Representative Customer Number::	000023557

Correspondence Information

Correspondence Customer Number::	000023557
Telephone Number One::	(352) 375-8100
Telephone Number Two::	
Fax Number::	(352) 372-5800
Electronic Mail Address::	fce@slspatents.com

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This application is a	National Stage of	PCT/EP2005/056954	December 20, 2005
PCT/EP2005/056954	An application claiming the benefit under 35 USC 119(e) of	60/638,669	December 22, 2004

Foreign Priority Information

Country::	Application Number::	Filing Date::	Priority Claimed::
EP	04106909.7	December 22, 2004	Yes

Assignee Information

Assignee Name::	~~Laboratoires Serono S.A.~~ Merck Serono S.A.
Street of Mailing Address::	~~Zone Industrielle de l'Ouriettaz~~ Centre Industriel
City of Mailing Address::	~~Aubonne~~ Coinsins, Vaude
Country of Mailing Address::	Switzerland
Postal or Zip Code of Mailing Address::	~~CH-1170~~ 1267

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CLABRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☑ Application No. PCT/EP2005/056954, filed on DECEMBER 20, 2005,

☑ as amended on JUNE 18, 2007 (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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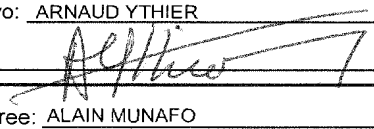
All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature:  Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

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Title of Invention	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

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This declaration is directed to:

☐ The attached application, or

☑ Application No. PCT/EP2005/056954, filed on DECEMBER 20, 2005,

☑ as amended on JUNE 18, 2007 (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

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FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

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I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

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FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/722,018
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Title	Clabribind Regimen for ...
Art Unit	1614
Examiner Name	
Attorney Docket Number	SER.125

I hereby revoke all previous powers of attorney given in the above-identified application.

☒ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: 23557

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☒ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	15th July 2009
Name	ARNAUD YTHIER	Telephone	
Title and Company			

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/722,018
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Title	Clabribind Regimen for ...
Art Unit	1614
Examiner Name	
Attorney Docket Number	SER.125

I hereby revoke all previous powers of attorney given in the above-identified application.

☒ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

23557

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☒ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Applicant or Assignee of Record

Signature	Alain Munafo	Date	July 7, 2009
Name	ALAIN MUNAFO	Telephone	+ 41 22 414 3833
Title and Company	Merck Serono S.A. Geneva		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	11/722,018
Filing Date	June 18, 2007
First Named Inventor	Giampiero de Luca
Title	Clabribind Regimen for ...
Art Unit	1614
Examiner Name	
Attorney Docket Number	SER.125

I hereby revoke all previous powers of attorney given in the above-identified application.

☒ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

23557

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☒ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	11-March-2010
Name	MARIA LOPEZ-BRESNAHAN	Telephone	
Title and Company			

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Patent Application Fee Transmittal

Application Number:	11722018
Filing Date:	18-Jun-2007
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Attorney Docket Number:	SER-125

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Petition fee- 37 CFR 1.17(h) (Group III)	1464	1	130	130
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	7206759
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER-125
Receipt Date:	15-MAR-2010
Filing Date:	18-JUN-2007
Time Stamp:	12:41:29
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$130
RAM confirmation Number	9250
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees) Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees) Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	Comm.pdf	93741 edda5c2a3413921285d2ca539ec7035c8600cdda	no	2
Warnings:					
Information:					
2	Petition for review by the Technology Center SPRE.	Petition.pdf	668293 13fcd3f5a28364e5b4183fca2998a7b9723cbb3d	no	11
Warnings:					
Information:					
3	Application Data Sheet	ADS-supp.pdf	242033 bfa9511b378c1352bf39bd1a30a15c09569e69b8	no	5
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
4	Oath or Declaration filed	executed-Dec-POA.pdf	1113099 9ae6df822a683499fc429ff6b7224cba986048ec	no	7
Warnings:					
Information:					
5	Fee Worksheet (PTO-875)	fee-info.pdf	30394 3fe8ba2da71ba6a58daf218b535364e557e3cd6d	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2147560		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 15, 2010.

Frank C. Eisenschenk, Ph.D., Patent Attorney

COMMUNICATION
Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

COMMUNICATION UNDER 37 CFR §1.48(a)

Sir:

Attached herewith are the following documents:

1) Petition Under 37 CFR §1.48(a);
2) Statement under 37 CFR §1.48(a)(2) submitted by added inventor Arnaud Ythier;
3) Statement under 37 CFR §1.48(a)(2) submitted by added inventor Alain Munafo;
4) Statement under 37 CFR §1.48(a)(2) submitted by added inventor Maria Lopez-Bresnahan;
5) Executed Declaration (37 CFR §1.63) form signed by all inventors;
6) Power of Attorney signed by Arnaud Ythier;
7) Power of Attorney signed by Alain Munafo;
8) Power of Attorney signed by Maria Lopez-Bresnahan;
9) Consent and Certificate Under 37 CFR §3.73(b); and
10) Supplemental Application Data Sheet.

J:\SER\125\Add Inventor\Comm.doc/DNB/sl

The Commissioner is authorized to charge any fees that may be required by this paper to Deposit Account No. 19-0065.

Respectfully submitted,

Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/sl
Attachments: as stated above

J:\SER\125\Add Inventor\Comm.doc/DNB/sl

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23557 7590 03/22/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/22/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	06/18/2007	Giampiero De Luca	SER-125	5532

TITLE OF INVENTION: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/22/2010

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23557 7590 03/22/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	06/18/2007	Giampiero De Luca	SER-125	5532

TITLE OF INVENTION: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/22/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
BALLARD, KIMBERLY	1649	514-046000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	06/18/2007	Giampiero De Luca	SER-125	5532

23557 7590 03/22/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/22/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)

(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 301 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 301 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	11/722,018	DE LUCA, GIAMPIERO	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the response filed 18 December 2009*.

2. ☒ The allowed claim(s) is/are *18-25 and 27-66*.

3. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20100311* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	11/722,018	DE LUCA, GIAMPIERO	
	Examiner	Art Unit	
	Kimberly Ballard	1649	

All Participants:

(1) *Kimberly Ballard*.

(2) *Chris Eisenschenk*.

Status of Application: *pending*

(3) _____.

(4) _____.

Date of Interview: *10 March 2010*

Time: *2 PM*

Type of Interview:
☒ Telephonic
☐ Video Conference
☐ Personal (Copy given to: ☐ Applicant ☐ Applicant's representative)

Exhibit Shown or Demonstrated: ☐ Yes ☒ No
If Yes, provide a brief description: .

Part I.

Rejection(s) discussed:

Claims discussed:
46

Prior art documents discussed:

Part II.

SUBSTANCE OF INTERVIEW DESCRIBING THE GENERAL NATURE OF WHAT WAS DISCUSSED:
Discussed minor examiner's amendments to claims. Discussed co-pending junior application with similar subject matter.

Part III.

☒ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview directly resulted in the allowance of the application. The examiner will provide a written summary of the substance of the interview in the Notice of Allowability.

☐ It is not necessary for applicant to provide a separate record of the substance of the interview, since the interview did not result in resolution of all issues. A brief summary by the examiner appears in Part II above.

/Kimberly Ballard/
Examiner, Art Unit 1649

(Applicant/Applicant's Representative Signature – if appropriate)

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Chris Eisenschenk on March 10, 2010.

The application has been amended as follows:

IN THE CLAIMS

In claim 46, line 10 of the claim (step iv), replace the period "." at the end of the line with a semicolon -- ; -- .

Examiner's Notes

The art made of record and not relied upon is considered pertinent to applicant's disclosure: US 2010/0021429 by Brentzel et al. (published 01/28/2010; filed 05/23/2007). This patent application currently has the same assignee (Merck Serono SA) and has similar claimed subject matter, but is considered junior to the instant application.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard
Art Unit 1649

/Elizabeth C. Kemmerer/
Elizabeth C. Kemmerer, Ph.D.
Primary Examiner, Art Unit 1646

Notice of References Cited	Application/Control No. 11/722,018	Applicant(s)/Patent Under Reexamination DE LUCA, GIAMPIERO	
	Examiner Kimberly Ballard	Art Unit 1649	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2010/0021429	01-2010	Brentzel et al.	424/85.6
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L7	453	(cladribine leustatin (2-chlorodeoxyadenosine) (2-chloro-2'deoxyadenosine)).clm.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2010/03/08 15:16
L8	67201	multiple adj sclerosis	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2010/03/08 15:16
L9	101	l7 and L8	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2010/03/08 15:16

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L5	0	De-luca-gia$.in.	USPAT; UPAD	OR	ON	2010/03/08 15:05
L6	69	(cladribine leustatin (2-chlorodeoxyadenosine) (2-chloro-2'deoxyadenosine)).clm.	USPAT; UPAD	OR	ON	2010/03/08 15:06

3/8/2010 3:27:55 PM
C:\Documents and Settings\kballard\My Documents\EAST\Workspaces\11.722018.wsp

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     (FILE 'HOME' ENTERED AT 15:32:38 ON 08 MAR 2010)

     FILE 'CAPLUS' ENTERED AT 15:32:55 ON 08 MAR 2010
                E US2007-722018/APPS
L1              1 S E3

     FILE 'STNGUIDE' ENTERED AT 15:33:26 ON 08 MAR 2010

     FILE 'REGISTRY' ENTERED AT 15:34:07 ON 08 MAR 2010
L2              1 S 4291-63-8/RN
                SET NOTICE 1 DISPLAY
                SET NOTICE LOGIN DISPLAY

     FILE 'MEDLINE, BIOSIS, CAPLUS, EMBASE' ENTERED AT 15:34:51 ON 08 MAR 2010
L3         145708 S MULTIPLE(A)SCLEROSIS
L4            638 S L2 AND L3
L5              0 S L4 AND ((INDUCTION OR MAINTENANCE)(S)(PHASE OR PERIOD))
L6         369890 S (INDUCTION OR MAINTENANCE OR TREATMENT)(S)(PHASE OR PERIOD)
L7             41 S L4 AND L6
L8             25 DUP REM L7 (16 DUPLICATES REMOVED)
L9            906 S DE LUCA G/AU
L10            19 S L9 AND L3
L11            10 DUP REM L10 (9 DUPLICATES REMOVED)
```

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11722018	DE LUCA, GIAMPIERO
	Examiner	**Art Unit**
	Kimberly A. Ballard	1649

ORIGINAL		INTERNATIONAL CLASSIFICATION									
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED				
514	46	A	6	1	K	31 / 52 (2006.01.01)	A	6	1	K	9 / 00 (2006.01.01)
CROSS REFERENCE(S)		A	6	1	K	31 / 7076 (2006.01.01)					
		A	6	1	K	38 / 21 (2006.01.01)					

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
424	85.6				

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/Kimberly A. Ballard/ Examiner.Art Unit 1649 (Assistant Examiner)	03/11/2010 (Date)	**Total Claims Allowed:** 48
/Elizabeth C. Kemmerer/ Primary Examiner.Art Unit 1646 (Primary Examiner)	03/12/2010 (Date)	O.G. Print Claim(s) 1 O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11722018	DE LUCA, GIAMPIERO
	Examiner	Art Unit
	Kimberly Ballard	1649

SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
Inventor search (PALM, EAST, NPL) - updated search	03/08/2010	KAB
EAST (USPAT, USOCR, PGPUB, DERWENT, FPRS, EPO, JPO) - updated search	03/08/2010	KAB
STN (MEDLINE, BIOSIS, CAPLUS, EMBASE) - updated search	03/08/2010	KAB
Patentability conference with Elizabeth Kemmerer (primary examiner) and Jeffrey Stucker (SPE)	03/10/2010	KAB

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
	See EAST search results	03/08/2010	KAB

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United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	06/18/2007	Giampiero De Luca	SER.125	5532

23557 7590 03/25/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER	
BALLARD, KIMBERLY	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
03/25/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

euspto@slspatents.com

UNITED STATES DEPARTMENT OF COMMERCE
U.S. Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
11722018	6/18/2007	DE LUCA, GIAMPIERO	SER-125

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

EXAMINER
Kimberly Ballard

ART UNIT	PAPER
1649	20100316

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

In view of the papers filed March 15, 2010, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by addition of Arnaud Ythier, Alain Munafo, and Maria Lopez-Bresnahan.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Ballard whose telephone number is 571-272-2150. The examiner can normally be reached on Monday-Friday 8:30 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646

PTO-90C (Rev.04-03)

Granted. /KAB/ 03/16/2010

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on March 15, 2010.

Frank C. Eisenschenk, Ph.D., Patent Attorney

PETITION TO ADD INVENTORS
UNDER 37 C.F.R. §1.48(a)
Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner	:	Kimberly Ballard
Art Unit	:	1649
Applicant	:	Giampiero De Luca
Serial No.	:	11/722,018
Filed	:	June 18, 2007
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PETITION UNDER 37 CFR §1.48(a)

Sir:

It is respectfully petitioned that the inventorship of the above-identified application be corrected to add Arnaud Ythier, Alain Munafo and Maria Lopez-Bresnahan as inventors. Authority for this petition and the correction of inventorship is found in 37 C.F.R. §1.48(a), reproduced below.

37 C.F.R. § 1.48 Correction of inventorship in a patent application, other than a reissue application

(a) If the inventive entity is set forth in error in an executed § 1.63 oath or declaration in a nonprovisional application, and such error arose without any deceptive intention on the part of the person named as an inventor in error or on the part of the person who through error was not named as an inventor, the inventorship of the nonprovisional application may be amended to name only the actual inventor or inventors. If the nonprovisional application is involved in an interference, the amendment must comply with the requirements of this section and must be accompanied by a motion under § 1.634. Amendment of the inventorship requires:

(1) A request to correct the inventorship that sets forth the desired inventorship change;

Please see petition under 37 CFR 1.48a received 15 March 2010 for addition of new inventors. /KAB/ 03/16/2010

PTO/SB/01A (09-04)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	CLABRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☑ Application No. PCT/EP2005/056954, filed on DECEMBER 20, 2005,

☑ as amended on JUNE 18, 2007 (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: GIAMPIERO DE LUCA

Signature: _____ Citizen of: SWITZERLAND

Inventor two: ARNAUD YTHIER

Signature: _____ Citizen of: SWITZERLAND and FRANCE

Inventor three: ALAIN MUNAFO

Signature: _____ Citizen of: SWITZERLAND

Inventor four: MARIA LOPEZ-BRESNAHAN

Signature: _____ Citizen of: UNITED STATES

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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BIB DATA SHEET

CONFIRMATION NO. 5532

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/722,018	06/18/2007	514	1649	SER-125

APPLICANTS

Giampiero De Luca, Conches, SWITZERLAND; Arnaud Ythier, Collex-Bossy, SWITZERLAND; Alain Munafo, Tartegnin, SWITZERLAND; Maria Lopez-Bresnahan, Lincoln, MA.

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2005/056954 12/20/2005
which claims benefit of 60/638,669 12/22/2004

/KAB/ 03/16/2010

**** FOREIGN APPLICATIONS ***************************

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

12/10/2008

Foreign Priority claimed	35 USC 119(a-d) conditions met	Verified and Acknowledged	Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
☑ Yes ☐ No	☑ Yes ☐ No	/KIMBERLY BALLARD/ Examiner's Signature	☐ Initials	SWITZERLAND	0	20	1

ADDRESS

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES

TITLE

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

FILING FEE RECEIVED		
2356	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

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Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
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or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23557 7590 03/22/2010

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A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
Ph: (352)375-8100 Fax: (352)372-5800

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

N/A - Filed EFS	(Depositor's name)
	(Signature)
	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	06/18/2007	Giampiero De Luca	SER-125	5532

TITLE OF INVENTION: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	06/22/2010

EXAMINER	ART UNIT	CLASS-SUBCLASS
BALLARD, KIMBERLY	1649	514-046000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 SALIWANCHIK, LLOYD & SALIWANCHIK
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: MERCK SERONO S.A.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): COINSINS, VAUD, SWITZERLAND

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Frank C Eisenschenk Date March 25, 2010

Typed or printed name FRANK C. EISENSCHENK, PH.D. Registration No. 45,332

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	11722018
Filing Date:	18-Jun-2007
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Attorney Docket Number:	SER.125

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**1810**

Electronic Acknowledgement Receipt

EFS ID:	7283753
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125
Receipt Date:	25-MAR-2010
Filing Date:	18-JUN-2007
Time Stamp:	13:20:02
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1810
RAM confirmation Number	9736
Deposit Account	190065
Authorized User	EISENSCHENK,FRANK C.

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IssueFee.pdf	209402 c75551bf9ca7598464e3cb696dd4da3af272af93	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	31967 2428e741ea520d0e40306892233567273b47befd	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	241369		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 5532

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/722,018	06/18/2007 RULE	514	1649	SER.125

APPLICANTS

Giampiero De Luca, Conches, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

BW 3-30-10

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2005/056954 12/20/2005 which claims benefit of 60/638,669 12/22/2004

**** FOREIGN APPLICATIONS *********************

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 12/10/2008

		STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
Foreign Priority claimed	☒ yes ☐ no	SWITZERLAND	0	20	1
35 USC 119 (a-d) conditions met	☒ yes ☐ no ☐ Met after Allowance				
Verified and Acknowledged	Examiner's Signature Initials				

ADDRESS
23557

TITLE

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

FILING FEE RECEIVED	FEES: Authority has been given in Paper	
2656	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/722,018	06/18/2007	1649	2656	SER.125	20	1

CONFIRMATION NO. 5532

CORRECTED FILING RECEIPT

23557
SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614



Date Mailed: 03/31/2010

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Giampiero De Luca, Conches, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

Assignment For Published Patent Application

Laboratoires Serono S.A., Aubonne, SWITZERLAND

Power of Attorney: The patent practitioners associated with Customer Number 23557

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/EP2005/056954 12/20/2005
which claims benefit of 60/638,669 12/22/2004

Foreign Applications

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

If Required, Foreign Filing License Granted: 12/10/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/722,018**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
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Bib Data Sheet

CONFIRMATION NO. 5532

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/722,018	06/18/2007 RULE	514	1649	SER.125

APPLICANTS

Giampiero De Luca, Conches, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/EP2005/056954 12/20/2005 which claims benefit of 60/638,669 12/22/2004

**** FOREIGN APPLICATIONS *********************

EUROPEAN PATENT OFFICE (EPO) 04106909.7 12/22/2004

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 12/10/2008

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☐ no	SWITZERLAND	0	20	1

35 USC 119 (a-d) conditions met ☐ yes ☐ no ☐ Met after Allowance

Verified and Acknowledged _____ Examiner's Signature Initials

ADDRESS
23557

TITLE

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

FILING FEE RECEIVED	
2656	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

- ☐ All Fees
- ☐ 1.16 Fees (Filing)
- ☐ 1.17 Fees (Processing Ext. of time)
- ☐ 1.18 Fees (Issue)
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/722,018	05/11/2010	7713947	SER.125	5532

23557 7590 04/21/2010

SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 300 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Giampiero De Luca, Conches, SWITZERLAND;
Arnaud Ythier, Collex-Bossy, SWITZERLAND;
Alain Munafo, Tartegnin, SWITZERLAND;
Maria Lopez-Bresnahan, Lincoln, MA;

I hereby certify that this correspondence is being electronically filed in the United States Patent and Trademark Office on May 20, 2010.

Frank C. Eisenschenk, Ph.D., Patent Attorney

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 CFR 1.322
Docket No. SER.125

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan
Issued	:	May 11, 2010
Patent No.	:	7,713,947
Conf. No.	:	5532
For	:	Cladribine Regimen for Treating Multiple Sclerosis

Mail Stop Certificate of Corrections Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CERTIFICATE OF CORRECTION
UNDER 37 CFR 1.322 (OFFICE MISTAKE)

Sir:

A Certificate of Correction for the above-identified patent has been prepared and is attached hereto.

In the left-hand column below is the column and line number where errors occurred in the patent. In the right-hand column is the page and line number in the application where the correct information appears.

Patent Reads:	**Application Reads:**
Column 1, line 31:	Page 1, lines 14-15:
"Clinical is disability"	--Clinical disability--

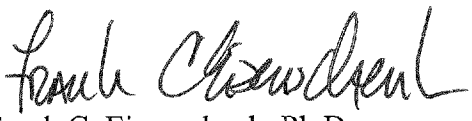
J:\SER\125\PTO-Misc\COC.Req.doc/DNB/jb

Column 7, line 32:	Page 12, lines 1-2:
"WFN-beta, WFN-beta"	--IFN-beta, IFN-beta--
Column 14, line 12:	Page 24, line 17:
"UI; (International unit)"	--UI (International unit)--.

A true and correct copy of pages 1, 12, and 24 of the specification as filed which support Applicants' assertion of the errors on the part of the Patent Office accompanies this Certificate of Correction.

Approval of the Certificate of Correction is respectfully requested.

Respectfully submitted,



Frank C. Eisenschenk, Ph.D.
Patent Attorney
Registration No. 45,332
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

FCE/jb
Attachments: Copy of pages 1, 12, and 24 of the specification
Certificate of Correction

J:\SER\125\PTO-Misc\COC.Req.doc/DNB/jb

Cladribine regimen for treating Multiple Sclerosis

Field of the Invention

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

Background of the Invention

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

In one embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.

IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.

Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebif® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in E. Coli, commercially available under the trademark Betaseron®, it may preferably be

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) are repeated at least one or two times.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be administered in combination with interferon-beta.

Examples

The following abbreviations refer respectively to the definitions below:

kg (kilogram), **µg** (microgram), **mg** (milligram), **AEs** (Adverse effects), CNS (Cnetral nervous system), **CSF** (Cerebrospinal fluid), **EDSS** (Expanded Disability Status Scale, **SNRS** (Scripps Neurologic Rating Scale), **IFN** (interferon), **i.v.** (intra-veinous), **MIU** (Million International units), **MS** (multiple sclerosis), **MRI** (Magnetic resonance imaging), **p.o.** (per os), **PPMS** (Primary progressive multiple sclerosis), **PRMS** (Progressive relapsing multiple sclerosis), **RRMS** (Relapsing-remitting multiple sclerosis), **SPMS** (Secondary progressive multiple sclerosis), **s.c.** (subcutaneous), **TIW** (Three times a week), **2-CdA** (2-chloro-2'deoxyadenosine or Cladribine), **UI** (International unit).

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

Example 1: Oral cladribine in the treatment of relapsing forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female.

Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,713,947 Page 1 of 1

APPLICATION NO.: 11/722,018

DATED : May 11, 2010

INVENTORS : Giampiero De Luca, Arnaud Ythier, Alain Munafo, Maria Lopez-Bresnahan

It is certified that errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 31, "Clinical is disability" should read --Clinical disability--.

Column 7,
Line 32, "WFN-beta, WFN-beta" should read --IFN-beta, IFN-beta--.

Column 14,
Line 12, "UI; (International unit)" should read --UI (International unit)--.

MAILING ADDRESS OF SENDER:
Saliwanchik, Lloyd & Saliwanchik
P.O. Box 142950
Gainesville, FL 32614-2950

Electronic Acknowledgement Receipt

EFS ID:	7651975
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Frank Christopher Eisenschenk/Jenny Bedner
Filer Authorized By:	Frank Christopher Eisenschenk
Attorney Docket Number:	SER.125
Receipt Date:	20-MAY-2010
Filing Date:	18-JUN-2007
Time Stamp:	13:47:51
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	COC-Req.pdf	396206 9e7eef3d84f79fc56e6fac80984f434c5e166404	no	6

Warnings:	
Information:	

Total Files Size (in bytes):	396206

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,713,947 B2
APPLICATION NO. : 11/722018
DATED : May 11, 2010
INVENTOR(S) : Giampiero De Luca et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 31, "Clinical is disability" should read --Clinical disability--.

Column 7,
Line 32, "WFN-beta, WFN-beta" should read --IFN-beta, IFN-beta--.

Column 14,
Line 12, "UI; (International unit)" should read --UI (International unit)--.

Signed and Sealed this

Fifteenth Day of June, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

This form is to be submitted with the Power of Attorney by Applicant Form to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form.

Application Number	11/722,018
Patent Number	7,713,947
Filing Date	June 18, 2007
Issue Date	May 11, 2010
First Named Inventor	Giampiero De Luca
Art Unit	1649
Examiner Name	BALLARD, KIMBERLY
Attorney Docket Number	000758US
Title	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Signature of Applicant or Patent Practitioner

Signature	/Kirsten Grueneberg/
Name	Dr. Kirsten Grueneberg
Reg. No.	47,297
Customer No.	151167

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

*Total of __1__ form(s) is/are submitted.

PTO/SB/81A (12-08)
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PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,713,947
Issue Date	May 11, 2010
First Named Inventor	Giampiero De Luca
Title	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
Attorney Docket No.	000758US

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

151167

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified patent to:

☒ The address associated with the above-identified Customer Number.

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OR

☐ Firm or Individual Name	
Address	
City	State / Zip
Country	
Telephone	Email

I am the:

☐ Inventor, having ownership of the patent.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____

SIGNATURE of Inventor or Patent Owner

Signature		Date	May 31, 2011
Name	Pietro VON BALMOOS	Telephone	
Title and Company	Authorized Representative, Merck Serono S.A.	Authorized Representative Merck Serono S.A.	

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☒ A total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Merck Serono S.A.

Application No./Patent No.: 7,713,947 Filed/Issue Date: May 11, 2010

Titled:
CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Merck Serono S.A., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel_____, Frame_____, or a copy* is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Giampiero DE LUCA To: LABORATOIRES SERONO S.A.

The document was recorded in the United States Patent and Trademark Office at
Reel 019685, Frame 0061, or a copy* is attached.

2. From: LABORATOIRES SERONO SA To: MERCK SERONO SA

The document was recorded in the United States Patent and Trademark Office at
Reel 023601, Frame 0156, or a copy* is attached.

3. From: Arnaud YTHIER; Alain MUNAFO; and Maria LOPEZ-BRESNAHAN To: MERCK SERONO S.A.

The document was recorded in the United States Patent and Trademark Office at
Reel 024080, Frame 0041, or a copy* is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ *As required by 37 CFR 3.73(b)(1)(i), if a copy/copies is/are attached, the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Kirsten Grueneberg/ May 21, 2019

Signature Date

Dr. Kirsten Grueneberg 47,297

Printed or Typed Name Title or Registration Number

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	36070091
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	23557
Filer:	Eric J.I. Myers/Malika Ash Shakur
Filer Authorized By:	Eric J.I. Myers
Attorney Docket Number:	SER.125
Receipt Date:	21-MAY-2019
Filing Date:	18-JUN-2007
Time Stamp:	12:46:30
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2019-05-21-POA-373-Stmt-as-filed.pdf	516944 87d826cb7901275f81b715972a46a76b6b985b1e	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	2
	Assignee showing of ownership per 37 CFR 3.73	3	3
Warnings:			
Information:			
	Total Files Size (in bytes):	516944	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Docket No. 000758US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT:	U.S. PAT. NO. 7,713,947
ISSUED:	MAY 11, 2010
APPLICATION:	11/722,018
FILED:	JUNE 18, 2007
INVENTORS:	DE LUCA ET AL.
EXPIRATION:	OCTOBER 16, 2026
TITLE:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

RECEIVED
MAY 24 2019
PATENT EXTENSION
OPLA

TRANSMITTAL LETTER

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

Enclosed are the following items for filing in connection with the above-referenced Patent and a Request for Extension of Patent Term under 35 U.S.C. §156:

1. Return Receipt Postcard, and
2. Three total copies (original plus two copies) of each of the following:

   This transmittal letter and certificate of mailing

   Fee Transmittal

   Application for Extension of Patent Term under 35 U.S.C. §156

   Exhibit A: U.S. Patent No. 7,713,947 ("the '947 patent")

   Exhibit B: Certificate of Correction of June 15, 2010 in the '947 patent

   Exhibit C: Assignment from inventor DE LUCA to LABORATORIES SERONO SA

Exhibit D: Assignment (Merger/Change of Name) from LABORATORIES SERONO SA to MERCK SERONO SA

Exhibit E: Assignment from inventors YTHIER, MUNAFO, and LOPEZ-BRESNAHAN to MERCK SERONO SA

Exhibit F: Letter from EMD Serono, Inc. of Billerica, MA, which is the Marketing Applicant for Mavenclad, authorizing Applicant Merck Serono SA to rely upon Marketing Applicant's activities

Exhibit G: Power of Attorney submitted May 21, 2019

Exhibit H: Mavenclad Label

Exhibit I: P.2.2 Drug Product information, submitted in NDA 22561 in May 2018, pages 20-32

Exhibit J: FDA Approval Letter for Mavenclad NDA 22561

Exhibit K: Email with Timestamp sent 4:42 pm on March 29, 2019 from Sandra Folkendt (FDA) to Tammy Sarnelli (Marketing Applicant)

Exhibit L: Leustatin (cladribine) NDA 020229: listing and label

Exhibit M: Maintenance Fee Statement (First Maintenance Fee Payment)

Exhibit N: Maintenance Fee Statement (Second Maintenance Fee Payment)

Exhibit O: Letter from FDA showing date of IND application 74634

Exhibit P: Letter signed October 13, 2009 from FDA to Marketing Applicant (receipt of NDA 22561)

Exhibit Q: Letter signed August 22, 2011 from FDA to Marketing Applicant (receipt of withdrawal of NDA 22561)

Exhibit R: Letter signed June 13, 2018 from FDA to Marketing Applicant (receipt of NDA 22561)

Exhibit S: Chronology of Major Communications between FDA and Marketing Applicant (for IND application 74634 and NDA 22561)

Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. 601920 under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. 601920.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

Customer Number
151167
Phone: (571) 458-7790
Fax: (571) 458-7789

Dr. Kirsten Grueneberg
Attorney of Record
Registration No. 47,297

Eric Myers
Registration No. 68,546

CERTIFICATE OF MAILING

I hereby certify that this correspondence (along with any paper referred to as being attached or enclosed) and fee is being deposited with the United States Postal Service with sufficient postage as Priority Mail Express® with label number EJ 028 863 791 US in an envelope addressed to:

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

on May 24, 2019.

Signature /Kirsten Grueneberg/
Dr. Kirsten Grueneberg
Reg. No. 47,297

FEE TRANSMITTAL		
	Patent Number	7,713,947
	Issue Date	May 11, 2010
	First Named Inventor	Giampiero De Luca
☐No fee required	Application Number	11/722,018
	Filing Date	June 18, 2007
☒Total payment $ 1120.00	Attorney Docket No.	000758US
	Title	Cladribine regimen for treating multiple sclerosis

☐Applicant asserts small entity status, 37 CFR 1.27
☐Applicant asserts micro entity status, 37 CFR 1.29 *(Form PTO/SB/15 or equivalent enclosed or already submitted)*
☐Track 1 Prioritized Examination

Claims Fees:

Total:	(- 20) ×	$100	$
Independent:	(- 3) ×	$460	$
☐Multiple dependency		$820	$
☐Late filing declaration		$160	$
☐Non-electronic filing fee		$400	$
☐Non-English translation		$140	$

Extension Fees under 37 CFR 1.136(a) and 1.17(a), see petition filed herewith, if applicable:

☐Within first month	$ 200	$
☐Within second month	$ 600	$
☐Within third month	$1400	$
☐Within fourth month	$2200	$
☐Within fifth month	$3000	$

☐Terminal Disclaimer	$ 160	$
☐RCE – 1st Request	$1300	$
☐RCE – 2nd or Subseq.	$1900	$
☐Notice of Appeal	$ 800	$
☐Appl'n Size (pp.-100)/50 ×	$ 400	$

Other:
☒Extension of term of patent under §156 (fee under 1.20(j)(1)) $1120.00

Payment in the amount of $ 1120.00 paid by:
☐Credit Card (online if electronically filed, or attached if paper filed)
☒Deposit Account No. **601920**.

☒ Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. **601920** under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. **601920**.

☒ If these papers are not considered timely, then Applicants hereby petition under 37 CFR 1.136 for any necessary extension of time, further authorizing any necessary extension of time fees to be charged to Deposit Account No. **601920**.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

Dr. Kirsten Gruneberg
Registration No. 47,297

Eric Myers
Registration No. 68,546

Customer Number
151167
Phone: (571) 458-7790
Fax: (571) 458-7789

Docket No. 000758US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT:	U.S. PAT. NO. 7,713,947
ISSUED:	MAY 11, 2010
APPLICATION:	11/722,018
FILED:	JUNE 18, 2007
INVENTORS:	DE LUCA ET AL.
EXPIRATION:	OCTOBER 16, 2026
TITLE:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

APPLICATION FOR EXTENSION OF TERM UNDER 35 USC §156
FOR U.S. PATENT NO. 7,713,947

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

Pursuant to 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791, Merck Serono SA of Coinsins, Switzerland ("Applicant") respectfully requests extension of the patent term of U.S. Patent No. 7,713,947 ("the '947 patent," Exhibit A, with Certificate of Correction, Exhibit B), issued on May 11, 2010, due to regulatory review.

Applicant is the owner and assignee of the entire right, title, and interest in the '947 patent. Inventor De Luca assigned his right, title, and interest to Laboratories Serono SA in an assignment executed on July 12, 2007 and recorded at reel/frame 019685/0061 (Exhibit C).[1] Laboratories Serono SA then changed to Merck Serono SA, assigning its interest to the same

[1] Other documents pertaining to corporate name changes were recorded, which had been executed prior to the assignment of Inventor De Luca to Laboratories Serono SA. Because they predate the assignment of any inventor, they are not relevant here. Additionally, further documents were recorded as set forth herein to document corporate name change, which further documents were executed after the assignment from Inventor De Luca to Laboratories Serono SA.

on December 12, 2008, as recorded at reel/frame 023601/0156 (Exhibit D). Remaining inventors Ythier, Munafo, and Lopez-Bresnahan then assigned their respective rights, titles, and interests to Merck Serono SA in assignments executed on July 15, 2009; July 7, 2009; and March 10, 2010, respectively, all of which are recorded at reel/frame 024080/0041 (Exhibit E).

The Approved Product relevant to this application is Mavenclad (cladribine) ("Mavenclad" or "Approved Product"). The Marketing Applicant for Mavenclad is EMD Serono, Inc. of Billerica, MA. A letter on behalf of the Marketing Applicant authorizing Applicant Merck Serono SA to rely upon the activities of the Marketing Applicant, its predecessors, and affiliates is attached hereto at Exhibit F.

Enclosed as Exhibit G is a copy of the Power of Attorney submitted in the '947 patent file on May 21, 2019, appointing the undersigned and other attorneys at the undersigned's law firm as agent to transact all business with the USPTO on behalf of Applicant in connection with the '947 patent.

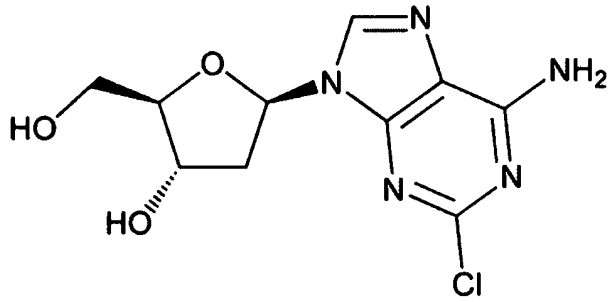
Applicant respectfully submits the following information in accordance with 35 U.S.C. §156 and 37 C.F.R. §§1.710-1.791. The following sections are numbered to correspond to the numbered subsections of 37 C.F.R. §1.740(a).

37 C.F.R. §1.740(a)(1): A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics

The Approved Product is Mavenclad. Mavenclad contains cladribine, hydroxypropyl betadex, magnesium stearate, and sorbitol. It is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults (Exhibit H, at pages 3 and 19-20).

Cladribine, a nucleoside metabolic inhibitor, is a white or almost white, non-hydroscopic, crystalline powder with the molecular formula $C_{10}H_{12}ClN_5O_3$ and molecular

weight 285.69. It differs in structure from the naturally occurring nucleoside, deoxyadenosine, by the substitution of chlorine for hydrogen in the 2-position of the purine ring. The chemical name of cladribine is 2-chloro-2′-deoxy-adenosine. The structural formula is shown below:



(Exhibit H, at pages 19-20).

Hydroxypropyl betadex (hydroxypropyl beta-cyclodextrin) forms complexes with various compounds. (Exhibit H at page 23). In several formulations in the Pharmacokinetic Studies and Clinical Trials leading to approval of Mavenclad, and in the commercial product of Mavenclad, the cladribine and cyclodextrin were and are present in the form of a complex. (Exhibit I, P.2.2 Drug Product information, submitted in NDA 22561 in May 2018, pages 20-32).

The Approved Product is available as 10 mg uncoated tablets. The tablets are white, round, biconvex, and engraved with a "C" on one side and "10" on the other side. The tablets are packaged in a blister. (Exhibit H, at pages 6-7).

37 C.F.R. §1.740(a)(2): A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred

Regulatory review of the Approved Product occurred under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. §355(b)).

37 C.F.R. §1.740(a)(3): An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred

The Approved Product received permission for commercial marketing or use under Section 505(b)(1) of the FDCA (21 U.S.C. §355(b)) on April 1, 2019.

35 U.S.C. §156(d)(1) states that "For purposes of determining the date on which a product receives permission under the second sentence of this paragraph, if such permission is transmitted after 4:30 P.M., Eastern Time, on a business day, or is transmitted on a day that is not a business day, the product shall be deemed to receive such permission on the next business day." (emphasis added). The Letter from the FDA to the Marketing Applicant granting permission for commercial marketing or use under Section 505(b)(1) of the FDCA (Exhibit J) was signed on Friday, March 29, 2019 at 4:27 pm. However, this letter was first transmitted to the Marketing Applicant on Friday, March 29, 2019 at 4:42 pm, as shown by the Timestamped Email from Sandra Folkendt (FDA) to Tammy Sarnello (Marketing Applicant). (Exhibit K). Accordingly, the Approved Product is deemed to have received permission on the next business day, which was Monday, April 1, 2019.

37 C.F.R. §1.740(a)(4): In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in the Approved Product is a cladribine-cyclodextrin complex. In several formulations in the Pharmacokinetic Studies and Clinical Trials leading to approval of Mavenclad, and in the commercial product of Mavenclad, the cladribine and cyclodextrin were and are present in the form of a complex. (Exhibit I, P.2.2 Drug Product information, submitted NDA 22561 in May 2018, pages 20-32).

A cladribine-cyclodextrin complex has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

While cladribine-containing formulations have previously been approved under Section 505(b) of the FDCA, including an earliest approval in 1993 under the name Leustatin for treatment of hairy cell leukemia, Applicant notes that such approval was not for a product containing a cladribine-cyclodextrin complex as the active ingredient. (Exhibit L, listing and label for Leustatin (cladribine) NDA 020229 without inclusion of cyclodextrin).

37 C.F.R. §1.740(a)(5): A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted

This application is being submitted within the sixty-day period permitted for submission pursuant to § 1.720(f). Specifically, the sixty-day period beginning on April 1, 2019 ends on May 30, 2019, which is therefore the date of the last day on which the present application could be submitted.

37 C.F.R. §1.740(a)(6): A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration

Applicant seeks extension for the following (see Exhibit A):

U.S. Patent No. 7,713,947

Names of Inventors: Giampiero De Luca, Arnaud Ythier, Alain Munafo, and Maria Lopez-Bresnahan

Date of Issue: May 11, 2010

Date of Expiration: October 16, 2026

As to the date of expiration, the '947 patent issued from U.S. Patent Application No. 11/722,018, filed on June 18, 2007, which was a national stage entry under 35 U.S.C. §371 of

PCT/EP2005/056954, filed on December 20, 2005.[2] The '947 patent is entitled to 300 days of Patent Term Adjustment, as indicated on the face of the patent itself. Thus, prior to the addition of the Patent Term Extension applied for herein, the term of the '947 patent extends twenty years plus 300 days from its international filing date. The '947 patent therefore expires on October 16, 2026.

37 C.F.R. §1.740(a)(7): A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings

A complete copy of the '947 patent is provided herewith as Exhibit A.

37 C.F.R. §1.740(a)(8): A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent

No terminal disclaimer or reexamination certificate has been issued. A certificate of correction, issued on June 15, 2010, is attached here as Exhibit B. Maintenance Fee Payment Statements are attached here: a statement for the payment of the first maintenance fee (Exhibit M) and a statement for the payment of the second maintenance fee (Exhibit N). The required maintenance fees which have been due, i.e. the first and second such fees, have been paid.

37 C.F.R. §1.740(a)(9): A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on ... (ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product ...

The '947 patent claims a method of treatment of multiple sclerosis (MS) by oral administration of the Approved Product. At least claims 1-3, 6, 7, 9, 11, 16, 36, 38, 39, and 41-46 read on administration of the Approved Product for an approved use thereof, as shown below:

[2] The '947 patent also contains earlier claims to priority under 35 U.S.C. §119, but "Priority under section 119, 365(a), 365(b), 386(a), or 386(b) shall not be taken into account in determining the term of a patent." (35 U.S.C. §154(a)(3)).

Claim 1	Mavenclad Label (Exhibit H)
A method of treating multiple sclerosis	"MAVENCLAD is ... indicated for the treatment of relapsing forms of multiple sclerosis (MS)"
comprising the oral administration of a formulation comprising cladribine	"MAVENCLAD® (cladribine) tablets, for oral use"
wherein the formulation is to be orally administered following the sequential steps below: (i) an induction period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)" "First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"
(ii) a cladribine-free period of between about 8 and about 10 months wherein no cladribine formulation is administered; (iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); and	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)" "Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle." "Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"
(iv) a cladribine-free period wherein no cladribine formulation is administered.	"Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years."

Claim 2	Mavenclad Label (Exhibit H)
The method according to claim 1,	See above
wherein the induction period lasts up to about 4 months.	"First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 3	Mavenclad Label (Exhibit H)
The method according to claim 2,	See above
wherein the induction period lasts about 2 months.	"First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 6	Mavenclad Label (Exhibit H)
The method according to claim 2,	See above
wherein the induction period lasts up to about 3 months.	"First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 7	Mavenclad Label (Exhibit H)
The method according to claim 1,	See above
wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)"

Claim 9	Mavenclad Label (Exhibit H)
The method according to claim 1,	See above
wherein the cladribine-free (iv) period lasts about 10 months.	"Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years."

Claim 11	Mavenclad Label (Exhibit H)
The method according to claim 1,	See above
wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)"

Claim 16	Mavenclad Label (Exhibit H)
The method according to claim 1,	See above
wherein the formulation is orally administered 1 to 7 days per month during the induction period.	"First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

(listing of claims continued on next page)

Claim 36	Mavenclad Label (Exhibit H)
A method of treating multiple sclerosis	"MAVENCLAD is ... indicated for the treatment of relapsing forms of multiple sclerosis (MS)"
comprising the oral administration of a formulation comprising cladribine	"MAVENCLAD® (cladribine) tablets, for oral use"
following the sequential steps below: (i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)" "First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"
(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered; (iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg;	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)" "Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle." "Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"
(iv) a cladribine-free period wherein no cladribine is administered.	"Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years."

Claim 38	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the induction period lasts about 2 months.	"First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 39	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.	"The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course)"

Claim 41	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the cladribine-free period (ii) lasts about 10 months.	"Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle."

Claim 42	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the cladribine-free (iv) period lasts 10 months.	"Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years."

Claim 43	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the maintenance period lasts about 2 months.	"Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle." "Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 44	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.	"10 mg Tablets" "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 45	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the formulation is orally administered at a daily dose of 10 mg cladribine.	"10 mg Tablets" "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

Claim 46	Mavenclad Label (Exhibit H)
The method according to claim 36,	See above
wherein the formulation is orally administered 1 to 7 days per month during the induction period.	"First Course/First Cycle: start any time." "First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle." "Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days"

* * *

37 C.F.R. §1.740(a)(10): A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C.156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

The '947 patent, for which extension of term is sought, claims the use of a human drug.

(A) The effective date of the investigational new drug (IND) application and the IND number;

Approval of the Approved Product resulted from the filing of investigational new drug (IND) application 74634, which has an effective date of April 12, 2006, thirty days after the IND application receipt date of March 13, 2006. (Exhibit O).

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

Approval of the Approved Product resulted from the filing of New Drug Application (NDA) number 22561. As noted in the letter granting approval of the NDA, NDA 22561 has an original submission date of September 30, 2009. (Exhibit J at page 1). Applicants also submit herewith the following three letters from the Food and Drug Administration to the Marketing Applicant, evidencing the timeline of the NDA: Letter signed October 13, 2009 (receipt of NDA 22561, Exhibit P), Letter signed August 22, 2011 (receipt of withdrawal of NDA 22561, Exhibit Q), and Letter signed June 13, 2018 (receipt of NDA 22561, Exhibit R).

(C) The date on which the NDA was approved or the Product License issued

The NDA was approved on March 29, 2019. (Exhibit J). However, the Approved Product is deemed to have received permission on the next business day, which was Monday, April 1, 2019.

35 U.S.C. §156(d)(1) states that "For purposes of determining the date on which a product receives permission under the second sentence of this paragraph, if such permission

is transmitted after 4:30 P.M., Eastern Time, on a business day, or is transmitted on a day that is not a business day, the product shall be deemed to receive such permission on the next business day." (emphasis added). The Letter from the FDA to the Marketing Applicant granting permission for commercial marketing or use under Section 505(b)(1) of the FDCA (Exhibit J) was signed on Friday, March 29, 2019 at 4:27 pm. However, this letter was first transmitted to the Marketing Applicant on Friday, March 29, 2019 at 4:42 pm, as shown by the Timestamped Email from Sandra Folkendt (FDA) to Tammy Sarnello (Marketing Applicant). (Exhibit K). Accordingly, the Approved Product is deemed to have received permission on the next business day, which was Monday, April 1, 2019.

* * *

37 C.F.R. §1.740(a)(11): A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities

The brief description of the significant activities undertaken by the Marketing Applicant during the applicable regulatory review period with respect to the Approved Product and the significant dates applicable to such activities is provided herewith in Exhibit S: the Chronology of Major Communications between FDA and Marketing Applicant for IND application 74634 and NDA 22561. Applicants also submit herewith the following three letters from the Food and Drug Administration to the Marketing Applicant, evidencing the timeline of the NDA: Letter signed October 13, 2009 (receipt of NDA 22561, Exhibit P), Letter signed August 22, 2011 (receipt of withdrawal of NDA 22561, Exhibit Q), and Letter signed June 13, 2018 (receipt of NDA 22561, Exhibit R).

* * *

37 C.F.R. §1.740(a)(12): A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined

In the opinion of the Applicant, the '947 patent is eligible for the extension of 1826 days sought, having satisfied the requirements of 35 U.S.C. §156 and 37 C.F.R. §1.720 as follows:

35 U.S.C. §156(a), 37 C.F.R. §1.720(a): [the] patent ... claims a product, a method of using a product, or a method of manufacturing a product

The '947 patent claims a method of using a product.

35 U.S.C. §156(a)(1) , 37 C.F.R. §1.720(g): the term of the patent has not expired before an application is submitted under subsection (d)(1) for its extension

As noted above, the '947 patent (prior to patent term extension) expires on October 16, 2026, and thus has not yet expired before the submission of this application.

35 U.S.C. §156(a)(2), 37 C.F.R. §1.720(b): the term of the patent has never been extended under 35 U.S.C. §156(e)(1)

The term of the '947 patent has never been extended under 35 U.S.C. §156(e)(1).

35 U.S.C. §156(a)(3), 37 C.F.R. §1.720(c): an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of 35 U.S.C. §156(d) and 37 C.F.R. §1.740

The present application for extension is submitted by the authorized attorney of the owner of record of the patent in accordance with the requirements of 35 U.S.C. §156(d) and 37 C.F.R. §1.740. (Exhibit G).

35 U.S.C. §156(a)(4), 37 C.F.R. §1.720(d): the product has been subject to a regulatory review period before its commercial marketing or use

The Approved Product, Mavenclad, was subject to a regulatory review period under section 505(b)(1) of the FDCA before its commercial marketing or use.

35 U.S.C. §156(a)(5)(A), 37 C.F.R. §1.720(e)(1): the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred

The active ingredient in the Approved Product is a cladribine-cyclodextrin complex. In several formulations in the Pharmacokinetic Studies and Clinical Trials leading to approval of Mavenclad, and in the commercial product of Mavenclad, the cladribine and cyclodextrin were and are present in the form of a complex. (Exhibit I, P.2.2 Drug Product information, submitted in NDA 22561 in May 2018, pages 20-32).

NDA 22561 is the first permitted commercial marketing or use of a cladribine-cyclodextrin complex under the Federal Food, Drug, and Cosmetic Act.

While cladribine-containing formulations have previously been approved under Section 505(b) of the FDCA, including an earliest approval in 1993 under the name Leustatin for treatment of hairy cell leukemia, Applicant notes that such approval was not for a product containing a cladribine-cyclodextrin complex as the active ingredient. (Exhibit L, listing and label for Leustatin (cladribine) NDA 020229 without inclusion of cyclodextrin).

37 C.F.R. §1.720(f): the application is submitted within the sixty-day period beginning on the date the product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred

This application is being submitted within the sixty-day period permitted for submission pursuant to § 1.720(f). Specifically, the sixty-day period beginning on April 1, 2019 ends on May 30, 2019, which is therefore the date of the last day on which the present application could be submitted.

35 U.S.C. §156(c)(4), 37 C.F.R. §1.720(h): no other patent term has been extended for the same regulatory review period for the product

The regulatory review period for the Approved Product has not been the basis for extension of any other patent term.

Applicant claims patent term extension of **1826 days**, calculated under 37 C.F.R. §1.775(c)-(d) as follows:

(c) The length of the regulatory review period for the Approved Product, a human drug, is 4734 days, which is the sum of —

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 ... of the [FDCA] became effective for the approved product (IND effective date April 12, 2006) and ending on the date the application was initially submitted for such product under those sections (NDA submission date September 30, 2009) ...; - 1267 days - and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under ... subsection (b) of section 505 ... of the [FDCA] (NDA submission date September 30, 2009) and ending on the date such application was approved under such section (March 29, 2019). - 3467 days

(d) The term of the patent as extended for a human drug ... will be determined by—

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period: - 3244 days (4734 days above, less 1490 days below)

(i) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section which were on and before the date on which the patent issued (May 11, 2010); - 1490 days

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. 156(d)(2)(B) by the Secretary of Health and Human Services that applicant did not act with due diligence; - 0 days

(iii) One-half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction; - 0 days

(2) By adding the number of days determined in paragraph (d)(1) of this section (3244 days) to the original term of the patent (October 16, 2026) as shortened by any terminal disclaimer; - September 3, 2035

(3) By adding 14 years to the date of approval of the application under ... subsection (b) of section 505 ... of the Federal Food, Drug, and Cosmetic Act (March 29, 2019); - March 29, 2033

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date; - March 29, 2033

(5) Because the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer; - October 16, 2031 - and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date - October 16, 2031 (1826 days after the expiration date)

* * *

37 C.F.R. §1.740(a)(13): A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services ... any information which is material to the determination of entitlement to the extension sought

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

37 C.F.R. §1.740(a)(14): The prescribed fee for receiving and acting upon the application for extension

Please charge the required fee of $1,120.00 pursuant to 37 C.F.R. §1.20(j) for receiving and acting upon this application to Deposit Account No. 601920. Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. 601920 under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. 601920.

37 C.F.R. §1.740(a)(15): The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed

Correspondence relating to the application for patent term extension should be addressed to:

Dr. Kirsten Grüneberg
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* * *

Certification under 37 C.F.R. §1.740(b)

The undersigned hereby certifies that the instant application, including exhibits and supporting papers, is being submitted as one original and two copies thereof, for a total of three copies, in accordance with 37 C.F.R. §1.740(b).

Conclusion

In accordance with the above statements and the exhibits provided herewith, Applicant respectfully requests the extension of the term of the '947 patent under 35 U.S.C. §156 due to regulatory delay.

Respectfully Submitted,
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CERTIFICATE OF MAILING

I hereby certify that this correspondence (along with any paper referred to as being attached or enclosed) and fee is being deposited with the United States Postal Service with sufficient postage as Priority Mail Express® with label number EJ 028 863 791 US in an envelope addressed to:

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

on May 24, 2019.

Signature

Dr. Kirsten Grueneberg
Reg. No. 47,297

LIST OF EXHIBITS

Exhibit	Contents
A	U.S. Patent No. 7,713,947 ("the '947 patent")
B	Certificate of Correction of June 15, 2010 in the '947 patent
C	Assignment from inventor DE LUCA to LABORATORIES SERONO SA
D	Assignment (Merger/Change of Name) from LABORATORIES SERONO SA to MERCK SERONO SA
E	Assignment from inventors YTHIER, MUNAFO, and LOPEZ-BRESNAHAN to MERCK SERONO SA
F	Letter from EMD Serono, Inc. of Billerica, MA, which is the Marketing Applicant for Mavenclad, authorizing Applicant Merck Serono SA to rely upon Marketing Applicant's activities
G	Power of Attorney submitted May 21, 2019
H	Mavenclad Label
I	P.2.2 Drug Product information, submitted in NDA 22561 in May 2018, pages 20-32
J	FDA Approval Letter for Mavenclad NDA 22561
K	Email with Timestamp sent 4:42 pm on March 29, 2019 from Sandra Folkendt (FDA) to Tammy Sarnelli (Marketing Applicant)
L	Leustatin (cladribine) NDA 020229: listing and label
M	Maintenance Fee Statement (First Maintenance Fee Payment)
N	Maintenance Fee Statement (Second Maintenance Fee Payment)
O	Letter from FDA showing date of IND application 74634
P	Letter signed October 13, 2009 from FDA to Marketing Applicant (receipt of NDA 22561)
Q	Letter signed August 22, 2011 from FDA to Marketing Applicant (receipt of withdrawal of NDA 22561)
R	Letter signed June 13, 2018 from FDA to Marketing Applicant (receipt of NDA 22561)
S	Chronology of Major Communications between FDA and Marketing Applicant (for IND application 74634 and NDA 22561)

EXHIBIT A

US007713947B2

(12) **United States Patent**
De Luca et al.

(10) **Patent No.: US 7,713,947 B2**
(45) **Date of Patent: May 11, 2010**

(54) **CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS**

(75) Inventors: **Giampiero De Luca**, Conches/Geneva (CH); **Arnaud Ythier**, Collex-Bossy (CH); **Alain Munafo**, Tartegnin (CH); **Maria Lopez-Bresnahan**, Lincoln, MA (US)

(73) Assignee: **Merck Serono S.A.**, Coinsins, Vaud (CH)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 300 days.

(21) Appl. No.: **11/722,018**

(22) PCT Filed: **Dec. 20, 2005**

(86) PCT No.: **PCT/EP2005/056954**

§ 371 (c)(1),
(2), (4) Date: **Jun. 18, 2007**

(87) PCT Pub. No.: **WO2006/067141**

PCT Pub. Date: **Jun. 29, 2006**

(65) **Prior Publication Data**

US 2009/0081163 A1 Mar. 26, 2009

Related U.S. Application Data

(60) Provisional application No. 60/638,669, filed on Dec. 22, 2004.

(30) **Foreign Application Priority Data**

Dec. 22, 2004 (EP) 04106909

(51) **Int. Cl.**
A61K 31/52 (2006.01)
A61K 31/7076 (2006.01)
A61K 38/21 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.** **514/46**; 424/85.6

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

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Primary Examiner—Elizabeth C. Kemmerer
Assistant Examiner—Kimberly A. Ballard
(74) *Attorney, Agent, or Firm*—Saliwanchik, Lloyd & Saliwanchik

(57) **ABSTRACT**

The present invention is related to the use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis, wherein the preparation is to be orally administered and wherein re-treatments are possible.

48 Claims, No Drawings

OTHER PUBLICATIONS

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CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

CROSS-REFERENCE TO RELATED APPLICATION

This application is the U.S. national stage application of International Patent Application No. PCT/EP2005/056954, filed Dec. 20, 2005, which claims the benefit of U.S. Provisional Patent Application No. 60/638,669, filed Dec. 22, 2004, the disclosures of which are hereby incorporated by reference in their entireties, including all figures, tables and amino acid or nucleic acid sequences.

FIELD OF THE INVENTION

The present invention relates to the use of multiple doses of Cladribine for the treatment of multiple sclerosis, especially relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis.

BACKGROUND OF THE INVENTION

Multiple sclerosis (MS) is the most known chronic inflammatory demyelinating disease of the central nervous system in humans. The onset of the disease typically occurs during ages 20 to 40. Women are affected approximately twice as often as men.

Over time, MS may result in the accumulation of various neurological disabilities. Clinical is disability in MS is presumed to be a result of repeated inflammatory injury with subsequent loss of myelin and axons, leading to tissue atrophy.

MS is manifested in physical symptoms (relapses and disability progression), Central Nervous System (CNS) inflammation, brain atrophy and cognitive impairment. Presenting symptoms include focal sensory deficits, focal weakness, visual problems, imbalance and fatigue. Sexual impairment and sphincter dysfunction may occur. Approximately half of the patients with MS may experience cognitive impairment or depression.

MS is now considered to be a multi-phasic disease and periods of clinical quiescence (remissions) occur between exacerbations. Remissions vary in length and may last several years but are infrequently permanent.

Four courses of the disease are individualized: relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) and progressive relapsing (PR) multiple sclerosis.

More than 80% of patients with MS will initially display a RR course with clinical exacerbation of neurological symptoms, followed by a recovery that may or may not be complete (Lublin and Reingold, *Neurology,* 1996, 46:907-911).

During RRMS, accumulation of disability results from incomplete recovery from relapses. Approximately, half of the patients with RRMS switch to a progressive course, called SPMS, 10 years after the diseased onset. During the SP phase, worsening of disability results from the accumulation of residual symptoms after exarcerbation but also from insidious progression between exacerbations (Lublin and Reingold above). 10% of MS patients have PPMS which is characterized by insidious progression of the symptoms from the disease onset. Less than 5% of patients have PRMS and are often considered to have the same prognosis as PPMS. It is suggested that distinct pathogenic mechanisms may be involved in different patient sub-groups and have wide-ranging implications for disease classification (Lassmann et al., 2001, *Trends Mol. Med.,* 7, 115-121; Lucchinetti et al., *Curr. Opin. Neurol.,* 2001, 14, 259-269).

MS onset is defined by the occurrence of the first neurological symptoms of CNS dysfunction. Advances in cerebrospinal fluid (CSF) analysis and magnetic resonance imaging (MRI) have simplified the diagnostic process and facilitated early diagnostic (Noseworthy et al., *The New England Journal of Medicine,* 2000, 343, 13, 938-952). The International Panel on the Diagnosis of MS issued revised criteria facilitating the diagnosis of MS and including MRI together with clinical and para-clinical diagnostic methods (Mc Donald et al., 2001, *Ann. Neurol.,* 50:121-127).

Current medications for MS which are disease modifying treatments, i.e. modifying the course of MS, modulate or suppress the immune system. There are four FDA approved immunomodulating agents for RRMS: three beta interferons (Betaseron®, Berlex; Avonex®, Biogen; Rebif®, Serono) and Glatimarer Acetate (Copaxone®, Amgen). There is also one FDA approved immunosuppressing drug for worsening MS, Mitoxantrone (Novantrone®, Amgen). Several other immunosuppressive agents are used, although not FDA approved.

Among them, Cladribine, a chlorinated purine analogue 2-chloro-2'deoxyadenosine analogue (2-CdA), has been suggested to be useful in the treatment of MS (EP 626853B1 and U.S. Pat. No. 5,506,214).

Several clinical studies with Cladribine in patients with multiple sclerosis have investigated the use of i.v. and s.c. Cladribine in MS.

Two double-blind, placebo controlled Phase II studies were conducted respectively in the treatment of Chronic Progressive MS (Selby et al., 1998, *Can. J. Neurol. Sci.,* 25:295-299) and Relapsing-Remitting MS respectively (Romine et al., 1999, *Proceedings of the Association of American Physicians,* 111, 1, 35-44).

In the first trial, the Cladribine dose used was 0.1 mg/kg/day for 7 days by continuous i.v. infusion. The treatment for repeated for 4 consecutive months.

In the second clinical trial, the Cladribine dose used was 0.07 mg/kg/day for 5 days by subcutaneous injection. The treatment was repeated for 6 consecutive months.

In addition, placebo controlled Phase III study was conducted in patients with primary progressive (PP) or secondary progressive (SP) multiple sclerosis (Rice at al., 2000, *Neurology,* 54, 5, 1145-1155). In this study, both patient groups received Cladribine by subcutaneous injection at a dose of 0.07 mg/kg/day. The treatment was repeated for either 2 months or 6 months.

The Phase II clinical studies provided evidence for the positive effects of Cladribine in patients with MS in terms of Kutzke Extended Disability Status Scale (EDSS), Scripps Neurologic rating Scale (SNRS) scores and Magnetic Resonance Imaging (MRI) findings (Beutler et al., 1996, *Proc. Nat. Acad. Sci. USA,* 93, 1716-1720; Romine et al., 1999 above). Phase II study results, were positive on the significant reduction of MRI-measured brain lesions (Rice at al., 2000, above).

Some adverse effects (AEs), such as increased incidence of infections related to compromised immune function or myelosuppression, were observed with the highest doses (Selby et al., 1998, above; Beutler et al., 1994, *Acta hematol,* 91:10-15). Due to the narrow margin of safety between the efficacy dose and the dose of occurrence of AEs, to date, all clinical trials for Cladribine in multiple sclerosis have been conducted using either i.v. or s.c. administration. As a result, Beutler et al. (Beutler et al., 1996, *Seminars in Hematology,*

33, 1(S1), 45-52) excluded the oral route for the treatment of multiple sclerosis with Cladribine.

Grieb et al. reported a small trial in 11 patients with remitting-relapsing multiple sclerosis (Grieb et al., 1995, *Archivum Immunologiae et Therapiae Experimentalis*, 43 (5-6), 323-327) wherein Cladribine has been orally administered during 6 monthly courses of 5 days at a total dose of about 4-5.7 mg/kg (patients of about 52 and about 75 kilos, respectively) i.e. a total effective dose of 2-2.85 mg/kg. For some patients, a single re-treatment of 5 days was performed at a cumulative dose of 0.4-0.66 mg/kg after a cladribine free-period of 3 or 6 months. The side effects observed with the regimen above were said to be less severe than the ones observed in the study on patients suffering from chronic progressive multiple sclerosis treated by i.v. infusion of Cladribine (Sipe et al., 1994, *Lancet*, 344, 9-13) but were still present. In addition, the therapeutic efficacy of the oral regimen above versus the i.v. infusion therapy was questioned (Grieb et al., 1995, above) and a group of "non-responders" has been identified (Stelmasiak et al., 1998, *Laboratory Investigations*, 4(1), 4-8).

Therefore, it would be desirable to have a method for treating multiple sclerosis comprising the oral administration of Cladribine that would permit the same or improved effect on MS lesions while decreasing the occurrence and/or severity adverse events. In addition, as MS is a chronic disease, it would be desirable to decrease the occurrence and/or severity adverse events in such a way that re-treatments are possible. A sustained benefit of Cladribine treatment between the treatment periods is also desirable.

SUMMARY OF THE INVENTION

The present invention is directed towards a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis, wherein the preparation is to be the orally administered. Particularly, the invention is directed towards a use of Cladribine for the preparation of a medicament for the treatment of relapsing-remitting multiple sclerosis or early secondary progressive multiple sclerosis and wherein re-treatments are possible.

An embodiment of the invention provides an improved dosing regimen for Cladribine in the treatment of multiple sclerosis.

An additional embodiment of the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein adverse effects are reduced, allowing further use of Cladribine.

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein the Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction treatment wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance treatment wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The "total dose" or "cumulative dose" refers to the total dose of Cladribine administered during the treatment, i.e. the dose reached at the end of the treatment that is calculated by adding the daily doses. For example, the total dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days is 3.5 mg/kg or the total dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days is 1.7 mg/kg.

"The total effective dose" or "cumulative effective dose" refers to the bioavailable dose of Cladribine after a given administration period, i.e. the bioavailable dose reached at the end of the treatment that is calculated by adding the daily doses reduced by the bioavailability coefficient. For example, the total effective dose of Cladribine corresponding to a treatment of 0.7 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 1.4 mg/kg or the total effective dose of Cladribine corresponding to a treatment of 0.35 mg/kg Cladribine per day during 5 days wherein the bioavailability of Cladribine is of about 40% is 0.7 mg/kg.

Typically, the bioavailability of Cladribine or of a Cladribine formulation used in the context of this invention is from about 30% to about 90%, preferably from about 40% to about 60%, such as about 50%.

"A week" refers to a period of time of or about 5, about 6 or about 7 days.

"A month" refers to a period of time of or about 28, about 29, about 30 or about 31 days.

"Treatment" comprises the sequential succession of an "induction treatment" and at least a "maintenance treatment". Typically, a treatment according to the invention comprises an "induction treatment" and about one or about two or about three maintenance treatments. Typically, a treatment according to the invention is of about 2 years (about 24 months) or about 3 years (about 36 months) or about 4 years (about 48 months).

An "Induction Treatment" consists in the sequential succession of (i) an induction period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered and (ii) a Cladribine-free period. An induction period lasts up to about 4 months or up to about 3 month or up to about 2 months. For example, an induction period lasts for about 2 to about 4 months. An induction period consists in the oral administration of Cladribine or a pharmaceutical preparation thereof during about 1 to about 7 days each month.

A "Cladribine-free period" is a period wherein no Cladribine is administered to the patient. During a Cladribine-free period, the patient can be free of any administration or be

dosed with a placebo-pill or another drug except. A Cladribine-free period lasts up to about 10 months or up to 9 months or up to about 8 months. For example, a Cladribine-free period lasts from about 8 to about 10 months, typically at least of about 8 months.

A "Maintenance Treatment" consists in the sequential succession of (i) a maintenance period wherein the Cladribine or the Cladribine pharmaceutical preparation of the invention is orally administered at a lower dose than the Cladribine dose orally administered during the induction treatment and (ii) a Cladribine-free period. A maintenance period lasts for up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months. For example, a maintenance period lasts for about 2 to about 4 months, preferably for about 2 months. A maintenance period consists in the oral administration of Cladribine or of a pharmaceutical preparation thereof during about 1 to about 7 days each month.

Within the context of this invention, the beneficial effect, including but not limited to an attenuation, reduction, decrease or diminishing of the pathological development after onset of the disease, may be seen after one or more a "treatments", after an "induction treatment", after a "maintenance treatment" or during a Cladribine-free period.

"Daily dose" refers to the total dose of Cladribine orally administered to the patient each day of administration. The daily dose can be reached through a single or several administrations per day, such as for example once a day, twice a day or three times a day.

The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

Patients suffering from MS can be defined for example as having clinically definite or laboratory-definite MS according to Schumacher or Poser criteria (Schumacher et al., 1965, *Ann. NY Acad. Sci.* 1965; 122:552-568; Poser et al., 1983, *Ann. Neurol.* 13(3): 227-31).

"Relapses" involve neurologic problems that occur over a short period, typically days but sometimes as short as hours or even minutes. These attacks most often involve motor, sensory, visual or coordination problems early in the disease. Later, bladder, bowel, sexual and cognitive problems may be shown. Sometimes the attack onset occurs over several weeks. Typical MS relapse involves a period of worsening, with development of neurological deficits, then a plateau, in which the patient is not getting any better but also not getting any worse followed by a recovery period. Recovery usually begins within a few weeks.

"Efficacy" of a treatment according to the invention can be measured based on changes in the course of disease in response to a use according to the invention. For example, treatment of MS efficacy can be measured by the frequency of relapses in RRMS and the presence or absence of new lesions in the CNS as detected using methods such as MRI technique (Miller et al., 1996, *Neurology,* 47(Suppl 4): S217; Evans et al., 1997, *Ann. Neurology,* 41:125-132).

The observation of the reduction and/or suppression of MRI T_1 gadolinium-enhanced lesions (thought to represent areas of active inflammation) gives a primary efficacy variable.

Secondary efficacy variables include MRI T_1 enhanced brain lesion volume, MRI T_1 enhanced lesion number, MRI T_2 lesion volume (thought to represent total disease burden, i.e. demyelination, gliosis, inflammation and axon loss), MRI T_1 enhanced hypointense lesion volume (thought to represent primarily demyelination and axon loss), time-to-progression of MS, frequency and severity of exacerbations and time-to-exacerbation, Expanded Disability Status Scale score and Scripps Neurologic Rating Scale (SNRS) score (Sipe et al., 1984, *Neurology,* 34, 1368-1372). Methods of early and accurate diagnosis of multiple sclerosis and of following the disease progression are described in Mattson, 2002, *Expert Rev. Neurotherapeutics,* 319-328.

Degree of disability of MS patients can be for example measured by Kurtzke Expanded Disability Status Scale (EDSS) score (Kurtzke, 1983, *Neurology,* 33, 1444-1452). Typically a decrease in EDSS score corresponds to an improvement in the disease and conversely, an increase in EDSS score corresponds to a worsening of the disease.

Cladribine (2-CdA)

2-CdA and its pharmacologically acceptable salts may be used in the practice of this invention.

Cladribine can be formulated in any pharmaceutical preparation suitable for oral administration. Representative oral formulations of 2-CdA are described in (WO 96/19230; WO 96/19229; U.S. Pat. Nos. 6,194,395; 5,506,214; WO 2004/087100; WO 2004/087101), the contents of which are incorporated herein by reference. Examples of ingredients for oral formulations are given below.

Processes for preparing 2-CdA are well known in the art. For example, the preparation of 2-CdA is described in (EP 173,059; WO 04/028462; WO 04/028462; U.S. Pat. No. 5,208,327; WO 00/64918) and Robins et al., *J. Am. Chem. Soc.,* 1984, 106: 6379. Alternatively, pharmaceutical preparations of 2-CdA may be purchased from Bedford Laboratories, Bedford, Ohio.

Oral administration of Cladribine may be in capsule, tablet, oral suspension, or syrup form. The tablet or capsules may contain from about 3 to 500 mg of Cladribine. Preferably they may contain about 3 to about 10 mg of Cladribine, more preferably about 3, about 5 or about 10 mg of Cladribine. The capsules may be gelatin capsules and may contain, in addition to Cladribine in the quantity indicated above, a small quantity, for example less than 5% by weight, magnesium stearate or other excipient. Tablets may contain the foregoing amount of the compound and a binder, which may be a gelatin solution, a starch paste in water, polyvinyl alcohol in water, etc. with a typical sugar coating.

Compositions

Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

Compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate). Tablets may be coated according to methods well known in the art.

Compositions of this invention may also be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. Suspending agent include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Non-aqueous vehicles include, but are not limited to, edible oils, almond oil, fractionated coconut oil, oily esters, propylene glycol, and ethyl alcohol. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid.

Combination

According to the invention, Cladribine can be administered alone or in combination with IFN-beta, prophylactically or therapeutically to an individual prior to, simultaneously or sequentially with other therapeutic regimens or agents (e.g. multiple drug regimens), in a therapeutically effective amount, especially therapeutic agents for the treatment of multiple sclerosis. Active agents that are administered simultaneously with other therapeutic agents can be administered in the same or different compositions and in the same or different routes of administration.

In one embodiment, when Cladribine is administered in combination with WFN-beta, WFN-beta is administered during the Cladribine-free period.

In another embodiment, when Cladribine is administered in combination with IFN-beta, IFN-beta is administered after the "treatment" according to the invention.

The term "interferon-beta (IFN-β)", as used herein, is intended to include fibroblast interferon in particular of human origin, as obtained by isolation from biological fluids or as obtained by DNA recombinant techniques from prokaryotic or eukaryotic host cells, as well as its salts, functional derivatives, variants, analogs and active fragments.

IFN-β suitable in accordance with the present invention is commercially available e.g. as Rebif® (Serono), Avonex® (Biogen) or Betaferon® (Schering). The use of interferons of human origin is also preferred in accordance with the present invention. The term interferon, as used herein, is intended to encompass salts, functional derivatives, variants, analogs and active fragments thereof.

Rebif® (recombinant human interferon-β) is the latest development in interferon therapy for multiple sclerosis (MS) and represents a significant advance in treatment. Rebi® is interferon (IFN)-beta 1a, produced from mammalian cell lines. It was established that interferon beta-1a given subcutaneously three times per week is efficacious in the treatment of Relapsing-Remitting Multiple Sclerosis (RRMS). Interferon beta-1a can have a positive effect on the long-term course of MS by reducing number and severity of relapses and reducing the burden of the disease and disease activity as measured by MRI.

The dosing of IFN-β in the treatment of relapsing-remitting MS according to the invention depends on the type of IFN-β used.

In accordance with the present invention, where IFN is recombinant IFN-β1b produced in *E. Coli*, commercially available under the trademark Betaseron®, it may preferably be administered sub-cutaneously every second day at a dosage of about of 250 to 300 μg or 8 MIU to 9.6 MIU per person.

In accordance with the present invention, where IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Avonex®, it may preferably be administered intramuscularly once a week at a dosage of about of 30 μg to 33 μg or 6 MIU to 6.6 MIU per person.

In accordance with the present invention, when IFN is recombinant IFN-β1a, produced in Chinese Hamster Ovary cells (CHO cells), commercially available under the trademark Rebif®, it may preferably be administered sub-cutaneously three times a week (TIW) at a dosage of 22 to 44 μg or 6 MIU to 12 MIU per person.

Patients

Patients according to the invention are patients suffering from multiple sclerosis, preferably RRMS or early SPMS.

In an embodiment of the invention, patients are selected from human males or females between 18 and 55 years age.

In another embodiment of the invention, patients had at least one relapse within the prior 12 months of the treatment.

Use According to the Invention

In one embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months or up to about 3 months or up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 2 months.

In a further embodiment, the invention provides a use according to the invention wherein the induction period lasts up to about 4 months.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months or up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts up to about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (ii) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period (ii) lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts up to about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free (iv) period lasts at least about 8 months.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free periods (ii) and/or (iv) last between about 8 and about 10 months.

In another further embodiment, the invention provides a use according to the invention wherein a placebo-pill is administered during the Cladribine-free period.

In another further embodiment, the invention provides a use according to the invention wherein the Cladribine-free period is free of any administration.

In another further embodiment, the invention provides a use according to the invention wherein the maintenance period lasts up to about 4 months, or up to about 3 months, or up to about 2 months, preferably up to about 2 months.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the maintenance period (iii) is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i)

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period (iii) is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a further embodiment, the invention provides a use of Cladribine for the preparation of a pharmaceutical formulation for the treatment of multiple sclerosis wherein the formulation is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months; the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In a preferred embodiment, the invention provides Cladribine for use as a medicament for the treatment of multiple sclerosis wherein the medicament is to be orally administered following the sequential steps below:

(i) An induction period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered;

wherein the induction period last up to about 4 months, or up to about 3 months, or up to about 2 months; the Cladribine-free period (ii) lasts up to about 10 months, or up to about 9 months, or up to about 8 months; the maintenance period (iii) lasts up to about 2 months; the Cladribine-free period (iv) lasts up to about 10 months; the total dose of Cladribine

reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated performed one, two or three times.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of Cladribine about 3 to 30 mg Cladribine, preferably 5 to 20 mg Cladribine, most preferably 10 mg Cladribine.

In another further embodiment, the invention provides a use according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a use according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered once a day during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered several times a day administered once a day during the induction period, preferably twice or three times a day, more preferably twice a day.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 1 to about 7 days per month, preferably from about 5 to about 7 days per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention whereby the pharmaceutical formulation is orally administered about 0.02 days/kg to about 0.08 days/kg per month during the maintenance period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 2 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 3 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 5 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 6 each month during the induction period.

In another embodiment, the invention provides a use of Cladribine according to the invention wherein the pharmaceutical formulation is to be orally administered at a daily dose of about 10 mg Cladribine from day 1 to about day 4 each month during the induction period and wherein the pharmaceutical formulation is a pharmaceutical formulation described in WO 2004/087101 or in WO 2004/087100.

In another embodiment, the invention provides a use of Cladribine according to any of the preceding claims wherein the pharmaceutical formulation is to be administered in combination with interferon-beta.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the induction period is from about 1.5 mg/kg to about 3.5 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total dose of Cladribine reached at the end of the maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In a preferred embodiment, the invention provides a method for the treatment of multiple sclerosis, comprising the oral administration of Cladribine or of a pharmaceutical formulation thereof in a patient in need thereof comprising the following steps:

(i) An induction period wherein Cladribine or a pharmaceutical formulation thereof is administered and wherein the total effective dose of Cladribine reached at the end of the induction period is from about 0.7 mg/kg to about 1.4 mg/kg;

(ii) A Cladribine-free period wherein no Cladribine is administered;

(iii) A maintenance period wherein Cladribine pharmaceutical formulation is administered and wherein the total effective dose of Cladribine reached at the end of the maintenance period is lower than the total effective dose of Cladribine reached at the end of the induction period (i);

(iv) A Cladribine-free period wherein no Cladribine is administered.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) to (iv) are repeated at least one or two times.

In a preferred embodiment, the invention provides a method of treating multiple sclerosis with Cladribine, wherein Cladribine is orally administered following the sequential steps below:

(i) Administering Cladribine, such that the total dose of Cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) Administering no Cladribine during a Cladribine free period;

(iii) Administering Cladribine such that the total dose of Cladribine reached at the end of a maintenance period is lower than the total dose of Cladribine reached at the end of the induction period (i);

(iv) And optionally, a Cladribine-free period wherein no Cladribine is administered.

In a further preferred embodiment, the invention provides a method wherein the induction period lasts up to about 4 months, or up to about 3 months, or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 1.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the Cladribine-free period lasts up to about 10 months, or up to about 9 months, or up to about 8 months.

In a further preferred embodiment, the invention provides a method wherein the maintenance period lasts up to about 4 months, or up to about 3 months or up to about 2 months.

In a further preferred embodiment, the invention provides a method wherein the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In a further preferred embodiment, the invention provides a method wherein the maintenance period is followed by a Cladribine-free period.

In another further embodiment, the invention provides a method according to the invention wherein the total dose of Cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of Cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein the total effective dose of Cladribine reached at the end of the induction period is about 1.4 mg/kg and the total effective dose of Cladribine reached at the end of the maintenance period is about 0.7 mg/kg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 3 to about 30 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be orally administered at a daily dose of about 10 mg.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is orally administered about 1 to about 7 days per month during the induction period.

In another further embodiment, the invention provides a method according to the invention wherein the steps (iii) are repeated at least one or two times.

In another further embodiment, the invention provides a method according to the invention wherein Cladribine is to be administered in combination with interferon-beta.

EXAMPLES

The following abbreviations refer respectively to the definitions below:

kg (kilogram), µg (microgram), mg (milligram), AEs (Adverse effects), CNS (Cnetral nervous system), CSF (Cerebrospinal fluid), EDSS (Expanded Disability Status Scale, SNRS (Scripps Neurologic Rating Scale), IFN (interferon), i.v. (intra-veinous), MIU (Million International units), MS (multiple sclerosis), MRI (Magnetic resonance imaging), p.o. (per os), PPMS (Primary progressive multiple sclerosis), PRMS (Progressive relapsing multiple sclerosis), RRMS (Relapsing-remitting multiple sclerosis), SPMS (Secondary progressive multiple sclerosis), s.c. (subcutaneous), TIW (Three times a week), 2-CdA (2-chloro-2'deoxyadenosine or Cladribine), UI; (International unit).

The efficacy and safety of oral Cladribine administration, eventually multi-dose administration, according to the invention can be assessed for example following the protocol below:

Example 1

Oral Cladribine in the Treatment of Relapsing Forms of MS

A study of sixty patients with relapsing forms of clinically definite multiple sclerosis is undertaken. Each patient is first examined for normal hepatic, renal, and bone marrow functioning to establish baseline values.

Patients are selected from Male or Female, between 18 and 55 years of age who had one or more relapses within the prior 12 months. Female patients are non-pregnant female. Patients are randomly assigned to one of the treatment groups listed in Table 1 below:

TABLE 1

Group	2-CdA
1	—
2	1.75 mg/kg
3	3.5 mg/kg

Each of the patients in Groups 2 and 3 receives 3 mg or 10 mg 2-CdA (1, 2 or 3 administration(s) a day depending on the patient's weight) combined in cyclodextrin formulation as described in WO 2004/087101, Example 3. The Compositions of the Cladribine formulations in 3 mg or 10 mg 2-CdA tablets containing hydroxypropyl-beta-cyclodextrin are listed in Table 2 below:

TABLE 2

Name of ingredients	Formula mg/tablet	Formula mg/tablet
Cladribine-2-hydroxypropyl-β-cyclodextrin- complex*	153.75 equivalent to 10 mg 2-CdA	30.60 equivalent to 3 mg 2-CdA
Sorbitol powder	44.25	68.4
Magnesium Stearate (vegetable grade)	2.0	1.00
Total	200.0	100

*Cladribine is complexed and lyophilised with 2-hydroxypropyl-β-cyclodextrin as a separate process as described in WO 2004/087101.

Examples of administration schemes for the induction period depending on the patient's weight are given below in Tables 3 and 4 for the target doses of 1.75 mg/kg and 3.5 mg/kg respectively. For the maintenance period, the example of administration scheme of Table 3 is applicable.

TABLE 3

Patient weight ranges (kg)			Total target dose (kg) equivalent		Number of pills (10 mg)/induction period		
	Mid		to 1.75 mg/kg		Month	Month	
Min	range	Max	Min	Max	1	2	Total
40	42.5	44.9	28	31.4	4	3	7
45	47.5	49.9	31.5	34.9	4	4	8
50	52.5	54.9	35	38.4	5	4	9
55	57.5	59.9	38.5	41.9	5	5	10
60	62.5	64.9	42	45.4	5	5	10
65	67.5	69.9	45.5	48.9	6	5	11
70	72.5	74.9	49	52.4	6	6	12
75	77.5	79.9	52.5	55.9	7	6	13
80	82.5	84.9	56	59.4	7	6	13
85	87.5	89.9	59.5	62.9	7	7	14
90	92.5	94.9	63	66.4	8	7	15
95	97.5	99.9	66.5	69.9	8	8	16
100	102.5	104.9	70	73.4	9	8	17
105	107.5	109.9	73.5	76.9	9	9	18
110	112.5	114.9	77	80.4	9	9	18
115	117.5	119.9	80.5	83.9	10	9	19

TABLE 4

Patient weight ranges (kg)			Total target dose (kg) equivalent		Number of pills (10 mg)/induction period				
	Mid		to 3.5 mg/kg		Month	Month	Month	Month	
Min	range	Max	Min	Max	1	2	3	4	Total
40	42.5	44.9	56	62.9	4	4	3	3	14
45	47.5	49.9	63	69.9	4	4	4	4	16
50	52.5	54.9	70	76.9	5	4	4	4	17
55	57.5	59.9	77	83.9	5	5	5	4	19
60	62.5	64.9	84	90.9	6	5	5	5	21
65	67.5	69.9	91	97.9	6	6	5	5	22
70	72.5	74.9	98	104.9	6	6	6	6	24
75	77.5	79.9	105	111.9	7	7	6	6	26
80	82.5	84.9	112	118.9	7	7	7	6	27
85	87.5	89.9	119	125.9	7	7	7	7	28
90	92.5	94.9	126	132.9	8	8	7	7	30
95	97.5	99.9	133	139.9	8	8	8	8	32
100	102.5	104.9	140	146.9	9	8	8	8	33
105	107.5	109.9	147	153.9	9	9	9	8	35
110	112.5	114.9	154	160.9	10	9	9	9	37
115	117.5	119.9	161	167.9	10	10	9	9	38

In Group 1 patients receive a placebo (saline) for 4 months followed by 8 months of no treatment.

In Group 2 patients receive a daily oral administration of Cladribine for about 5 days a month during 2 months (induction period) of 2-CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg (total dose of about 1.75 mg/kg for a bioavailability of about 40%); followed by administration of placebo for 2 months; followed by 8 months of no treatment.

In Group 3 patients receive a daily oral administration of Cladribine for about 5 days a month during 4 months (induction period) of 2-CdA cyclodextrin formulation such as the total effective dose administered at the end of the first 4 months approximates about 1.4 mg/kg (total dose of about 3.5 mg/kg for a bioavailability of about 40%); followed by 8 months of no treatment.

Beginning at month 13, all 3 patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 months of no treatment.

Finally, beginning at month 25, all patient groups receive re-treatment with Cladribine cyclodextrin formulation for about 5 days a month for 2 months (maintenance period) with the lower dose (such as the total effective dose administered at the end of the first 2 months approximates about 0.7 mg/kg) followed by 10 more months of no treatment.

Patients are monitored to determine whether there is any progression or improvement of brain lesions associated with progression of MS through MRI scans and neurological examination as described in Miller et al., 1996, above; Evans et al., 1997, above; Sipe et al., 1984, above; and Mattson, 2002, above. All patients have a baseline and MRI study (brain or spinal cord, according to localization of the lesions) at month 12.

The patient's disability progression and the time for having a first relapse are monitored as well as the proportion of relapse-fee patients at 24 months.

Lymphocyte markers and monocyte counts are monitored in the patients.

Patients in Groups 2 and 3 have a decrease in brain lesions.

The data show that the 2-CdA regimen consisting in the succession of an induction treatment and maintenance treatments is efficient in decreasing brain lesions and no severe adverse effect is observed.

The invention claimed is:

1. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine, wherein the formulation is to be orally administered following the sequential steps below:

(i) an induction period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period of between about 8 and about 10 months wherein no cladribine formulation is administered;

(iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period

is lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine formulation is administered.

2. The method according to claim 1, wherein the induction period lasts up to about 4 months.

3. The method according to claim 2, wherein the induction period lasts about 2 months.

4. The method according to claim 2, wherein the induction period lasts about 3 months.

5. The method according to claim 2, wherein the induction period lasts about 4 months.

6. The method according to claim 2, wherein the induction period lasts up to about 3 months.

7. The method according to claim 1, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

8. The method according to claim 1, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

9. The method according to claim 1, wherein the cladribine-free (iv) period lasts about 10 months.

10. The method according to claim 1, wherein the maintenance period lasts about 4 months.

11. The method according to claim 1, wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

12. The method according to claim 1, wherein the formulation is to be orally administered following the sequential steps below:

(i) an induction period wherein said cladribine formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period of between about 8 and about 10 months wherein no cladribine formulation is administered;

(iii) a maintenance period wherein said cladribine formulation is administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); and

(iv) a cladribine-free period wherein no cladribine formulation is administered;

wherein the induction period lasts up to 4 months; the cladribine-free period (ii) lasts up to 10 months; the maintenance period (iii) lasts up to 2 months; the cladribine-free period (iv) lasts up to 10 months; the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeated one, two or three times.

13. The method according to claim 12, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

14. The method according to claim 12, wherein the formulation is to be orally administered at a daily dose of 3 to 30 mg cladribine.

15. The method according to claim 14, wherein the formulation is to be orally administered at a daily dose of 10 mg cladribine.

16. The method according to claim 1, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

17. The method according to claim 1, wherein the steps (iii) to (iv) are repeated at least one or two times.

18. The method according to claim 1, wherein said cladribine formulation is to be administered in combination with interferon-beta.

19. The method according to claim 12, wherein said cladribine formulation is to be administered in combination with interferon-beta.

20. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i);

(iv) a cladribine-free period wherein no cladribine is administered.

21. The method according to claim 20, wherein the induction period lasts about 4 months.

22. The method according to claim 20, wherein the induction period lasts about 2 months.

23. The method according to claim 20, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

24. The method according to claim 20, where the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

25. The method according to claim 20, wherein the cladribine-free period (ii) lasts about 10 months.

26. The method according to claim 20, wherein the cladribine-free (iv) period lasts 10 months.

27. The method according to claim 20, wherein the maintenance period lasts about 2 months.

28. The method according to claim 20, wherein the formulation is orally administered following the sequential steps below:

(i) an induction period wherein said formulation is administered orally and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period wherein no cladribine is administered;

(iii) a maintenance period wherein said formulation is administered orally and wherein the total dose of cladribine reached at the end of the maintenance period is lower than the total dose of cladribine reached at the end of the induction period (i); (iv) a cladribine-free period wherein no cladribine is administered;

wherein the maintenance period (iii) lasts about 2 months; the cladribine-free period (iv) lasts about 10 months; the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg and steps (iii) to (iv) are repeatedly performed one, two or three times.

29. The method according to claim 20, wherein the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg and the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg.

30. The method according to claim 20, wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.

31. The method according to claim 20, wherein the formulation is orally administered at a daily dose of 10 mg cladribine.

32. The method according to claim 20, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

33. The method according to claim 20, wherein the steps (iii) to (iv) are repeated at least one time.

34. The method according to claim 20, wherein the steps (iii) to (iv) are repeated at least two times.

35. The method according to claim 20, wherein the formulation is administered in combination with interferon-beta.

36. A method of treating multiple sclerosis comprising the oral administration of a formulation comprising cladribine following the sequential steps below:

(i) an induction period lasting from about 2 months to about 4 months wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the induction period is from about 1.7 mg/kg to about 3.5 mg/kg;

(ii) a cladribine-free period lasting from about 8 months to about 10 months, wherein no cladribine is administered;

(iii) a maintenance period lasting from about 2 months to about 4 months, wherein said formulation is orally administered and wherein the total dose of cladribine reached at the end of the maintenance period is about 1.7 mg/kg;

(iv) a cladribine-free period wherein no cladribine is administered.

37. The method according to claim 36, wherein the induction period lasts about 4 months.

38. The method according to claim 36, wherein the induction period lasts about 2 months.

39. The method according to claim 36, wherein the total dose of cladribine reached at the end of the induction period is about 1.7 mg/kg.

40. The method according to claim 36, where the total dose of cladribine reached at the end of the induction period is about 3.5 mg/kg.

41. The method according to claim 36, wherein the cladribine-free period (ii) lasts about 10 months.

42. The method according to claim 36, wherein the cladribine-free (iv) period lasts 10 months.

43. The method according to claim 36, wherein the maintenance period lasts about 2 months.

44. The method according to claim 36, wherein the formulation is orally administered at a daily dose of 3 to 30 mg cladribine.

45. The method according to claim 36, wherein the formulation is orally administered at a daily dose of 10 mg cladribine.

46. The method according to claim 36, wherein the formulation is orally administered 1 to 7 days per month during the induction period.

47. The method according to claim 36, wherein the steps (iii) to (iv) are repeated at least one or two times.

48. The method according to claim 36, wherein the formulation is administered in combination with interferon-beta.

* * * * *

EXHIBIT B

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,713,947 B2
APPLICATION NO. : 11/722018
DATED : May 11, 2010
INVENTOR(S) : Giampiero De Luca et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,
Line 31, "Clinical is disability" should read --Clinical disability--.

Column 7,
Line 32, "WFN-beta, WFN-beta" should read --IFN-beta, IFN-beta--.

Column 14,
Line 12, "UI; (International unit)" should read --UI (International unit)--.

Signed and Sealed this

Fifteenth Day of June, 2010

David J. Kappos

David J. Kappos
Director of the United States Patent and Trademark Office

EXHIBIT C

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
GIAMPIERO DE LUCA	07/12/2007

RECEIVING PARTY DATA

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PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	11722018

OP $40.00 11722018

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ATTORNEY DOCKET NUMBER:	SER-125
NAME OF SUBMITTER:	FRANK C. EISENSCHENK, PH.D.

Total Attachments: 2
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SER-125

ASSIGNMENT

WHEREAS, I, the undersigned, residing at the indicated address given below, have invented certain new and useful improvements in **CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS**, for which an application for United States Letters Patent was filed June 18, 2007, as Serial No. 11/722,018.

WHEREAS, LABORATOIRES SERONO S.A., a corporation of the country of ~~France~~ Switzerland, having a place of business at Zone Industrielle de l'Ouriettaz, CH-1170, Aubonne, Switzerland, is desirous of acquiring the entire right, title, and interest in and to said invention and in and to any Letters Patent which may be granted therefor in the United States and in any and all foreign countries;

12/07/2007

NOW, THEREFORE, in view of LABORATOIRES SERONO S.A.'s review and evaluation of our patent disclosure and other valuable consideration, receipt of which is hereby acknowledged, I, the undersigned, have sold, assigned, and transferred, and by these presents do sell, assign, and transfer, unto said LABORATOIRES SERONO S.A., its successors and assigns, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title, and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, and extensions thereof.

I hereby authorize and request the Patent Office Officials in the United States and in any and all foreign countries to issue any and all of said Letters Patent, when granted, to LABORATOIRES SERONO S.A., as the assignees of the entire right, title, and interest in and to the same, for the sole use and behoof of LABORATOIRES SERONO S.A., its successors and assigns.

FURTHER, I agree that I will communicate to LABORATOIRES SERONO S.A., or its representatives, any facts known to me respecting said invention; testify in any legal proceedings; sign all lawful papers; execute all divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to LABORATOIRES SERONO S.A.; make all rightful oaths; and generally do everything possible to aid LABORATOIRES SERONO S.A., its successors and assigns, to obtain and enforce proper protection for said invention in the United States and in any and all foreign countries.

IN TESTIMONY WHEREOF, I have hereunto set my hand this 12/07 day of July, 2007.

Signed _____

Giampiero de Luca
Chemin des Conches 15B
CH-1231 Conches/Geneva
Switzerland

WITNESS:

Signature: _____

Printed Name: David RICOL

Date: July 12th, 2007

EXHIBIT D

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	CHANGE OF NAME

CONVEYING PARTY DATA

Name	Execution Date
LABORATOIRES SERONO SA	12/12/2008

RECEIVING PARTY DATA

Name:	MERCK SERONO SA
Street Address:	Centre Industriel
City:	Coinsins, Vaud
State/Country:	SWITZERLAND
Postal Code:	1267

PROPERTY NUMBERS Total: 51

Property Type	Number
Application Number:	10515032
Application Number:	10510015
Application Number:	10499100
Application Number:	10517726
Application Number:	10510014
Application Number:	10540234
Application Number:	10548364
Application Number:	10556417
Application Number:	10546843
Application Number:	10576509
Application Number:	12341490
Application Number:	10573369
Application Number:	10570122
Application Number:	10573625
Application Number:	10583218

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Application Number:	11659174
Application Number:	11575415
Application Number:	11722533
Application Number:	11915913
Application Number:	12064287
Application Number:	11915476
Application Number:	11912432
Application Number:	11997181
Application Number:	11916097
Application Number:	12158572
Application Number:	12067221
Application Number:	12094905
Application Number:	12067224
Application Number:	12094869
Application Number:	12096110
Application Number:	12096125
Application Number:	12094921
Application Number:	12278831
Application Number:	12158539
Application Number:	12096107
Application Number:	12301249
Application Number:	11915508
Application Number:	11915521
Application Number:	12064284
Application Number:	10565763
Application Number:	11720560
Application Number:	11722033
Application Number:	11722527
Application Number:	11722018
Application Number:	11814389
Application Number:	10579105
Application Number:	10738123
Application Number:	11025834
Application Number:	12137898
Application Number:	12492387

Application Number:	12492371

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Total Attachments: 21

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Béatrice EHLERS
NOTARY

ARTICLES OF ASSOCIATION

of

Merck Serono SA

a public limited company with registered office in Coinsins

*****

12 December 2008

*****

PATENT

MERCK SERONO SA

ARTICLES OF ASSOCIATION

TITLE I
NAME - REGISTERED OFFICE
PURPOSE - DURATION

Article 1: Name

Under the name MERCK SERONO SA, a public limited liability company governed by these articles of association and by Title XXVI of the Swiss Code of Obligations (hereinafter also referred to as CO), is hereby constituted.

Article 2: Registered office

The registered office of the company is at Coinsins (Vaud Canton).

Article 3: Purpose

The purpose of the company is:
(1) the conduct of the business of a holding company (acquiring and administering participations both in Switzerland and abroad) in the pharmaceutical and allied fields,
(2) research, development, creation, manufacture, consultancy, commercial sale and utilisation of technologies for the life sciences,
(3) registration and utilisation of patents,
(4) synthesis and commercial sale of biological products for therapeutic purposes,
(5) conclusion of partnership agreements, mergers and acquisitions of companies in the same business areas. The company may also effect all financial, commercial, industrial and real estate transactions and conclude all contracts appropriate to the development of its purpose or having a direct or indirect bearing upon such purpose.

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Article 4: Duration

The company is incorporated for an indefinite duration.

TITLE II
SHARE CAPITAL
SHARES

Article 5: Share capital

The share capital is set at the sum of CHF 383,758,575 (three hundred and eighty-three million seven hundred and fifty-eight thousand five hundred and seventy-five francs), divided into

a) 11,013,040 registered "A" shares with limited transferability with a nominal value of CHF 10 (ten francs) each, fully paid up, and
b) 10,945,127 "B" bearer shares with a nominal value of CHF 25 (twenty-five francs) each, fully paid up.

Article 5 bis: Conditional capital

A. Conditional capital for option and/or convertible loans

The share capital of the company shall be increased by CHF 36,300,000 (thirty-six million three hundred thousand francs) at most, by the issue of 1,452,000 (one million four hundred and fifty-two thousand) "B" type bearer shares with a nominal value of CHF 25 (twenty-five) francs each to be paid up in full by the exercise of option and/or conversion rights granted in relation to the loans issued by member companies of the Serono Group.

The amount and conditions of the loans, together with the procedures and conditions for the exercise of option and/or conversion rights and the issue price are to be determined by the Board of Directors. The holders of convertible bonds or option rights carried by option bonds are entitled to acquire new shares.

The Board of Directors may issue loans which are directly underwritten by a consortium and subsequently placed with the public, subject to the following provisions.

The Board of Directors determines the conditions for the exercise of the preferential subscription right. Preferential subscription rights which have not been exercised

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revert to the company. The Board of Directors may place them on market terms or allow them to expire.
The Board of Directors may cancel the shareholders' preferential subscription right if loans are issued to finance the acquisition of participations or other rights in companies or to finance research and development projects. If the Board of Directors abolishes the shareholders' preferential subscription right, the following provisions shall apply: (a) conversion rights may be exercised only for a maximum period of 15 years and option rights for 7 years from the date of issue of the related loan; (b) convertible and/or option loans must be issued on the standard market conditions (including the standard market conditions relating to protection of option and/or conversion right holders against dilution), and (c) the conversion and/or option price must correspond at least to the average of the prices paid on the Zurich stock market for shares in the company during the 5 day period prior to the determination of the definitive issue conditions for the convertible or option loan concerned.

B. Conditional capital for a stock option plan

The company's share capital shall be increased by CHF 14,452,550 (fourteen million four hundred and fifty-two thousand five hundred and fifty francs) at most, i.e. 578,102 (five hundred and seventy-eight thousand one hundred and two) "B" type bearer shares with a nominal value of CHF 25 (twenty-five francs) each, to be paid up in full by the exercise of option rights which the Board of Directors intends to grant to the staff of the member companies of the Serono Group and to the directors of the company.

The shareholders' subscription right does not apply to these new shares.

The Board of Directors shall stipulate in a regulation the conditions and procedures for granting options and for their exercise.

The shares may be subscribed at a price which is lower than the stock market price.

Article 5 ter: Authorised capital

Until 25 April 2008 the Board of Directors is authorised to increase the share capital by a maximum of CHF 190,471,500 (one hundred and ninety million four hundred and seventy-one thousand five hundred francs) by issuing a maximum of 7,618,860 (seven million six hundred and eighteen thousand eight hundred and sixty) "B" type bearer shares with a nominal value of CHF 25 (twenty-five francs) each, fully paid up. The Board of Directors may arrange for the share capital to be increased in its entirety or by tranches. Preferential subscription rights which have been granted

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but not exercised shall be placed at the disposal of the Board of Directors which shall use them in the interests of the company.

The Board of Directors is authorised to exclude the preferential subscription right of the shareholders in favour of a bank or another institution which directly underwrites the shares chosen by the Board of Directors if the bank or institution which underwrites the shares undertakes to offer the shareholders a right to subscribe to the newly issued shares in proportion to their current participation. The Board of Directors is likewise authorised to exclude the shareholders' preferential subscription right and to assign the shares or the preferential right to subscribe to shares to third parties in the event of the acquisition of a company or parts of a company, the taking of a participation in a business or a company, or similar transactions and the financing of such transactions.

The share issue price, the way in which payment for the shares is to be made and the date from which the new shares shall give an entitlement to dividends and the conditions for the exercise of the preferential subscription right shall be determined by the Board of Directors.

Article 6: Shares

6.1 Shares are of the registered or bearer type. They are numbered and signed by a director whose signature may be printed.

Each share gives entitlement to a proportional part of the profit and of the proceeds of liquidation.

6.2 In lieu of single registered or bearer shares, the company may issue certificates representing more than one share.

6.3 **Registered shares**
Registered shares are indivisible in relation to the company which acknowledges only one holder of each registered share. Shareholders who own registered shares must notify any change of address to the company. Any communication by the company to the shareholders is deemed to be valid when it is notified to the last recorded address of the shareholder.

6.4 **Register of registered shares**
The Board of Directors keeps a register of registered shares which indicates the name and address of the owners and beneficiaries from usufruct in registered shares.

Only the persons whose names appear on this register are regarded as being the owners of, or beneficiaries of usufruct in, registered shares in relation to the company.

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No entry in the share register shall be made between the day on which the General Meeting is convened and the day following the date of the General Meeting.

6.5 **Transfer of registered shares**

The transfer of registered shares must be approved by the company. The Board of Directors has authority to decide. The request for authorisation must include a statement by which the purchaser of the shares certifies that he is taking the shares over in his own name and for his own account. The company will inform the applicant whether the transfer has been authorised or declined.

Entry in the register will be declined if the applicant has not specifically stated that he is purchasing the shares in his own name and for his own account.

Entry in the register may be declined for justified reasons associated with the registered purpose or the economic independence of the company and, in particular, when the purchaser is a person who competes with the company or a company or business in which it holds participations.

The company may, without stating reasons, withhold its approval for a share transfer by offering to take over the shares from the seller for its own account, for the account of other shareholders or for that of third parties at the real value at the time when the application for transfer is received by the company.

In the event of transfer by inheritance, the company must enter in the share register the name of the acquiring party, save where there is a justified reason for not doing so within the meaning of paragraph 3 above. In that assumption, if the company proposes to refuse the transfer, it must offer to take the shares over for its own account, for the account of other shareholders or for that of third parties at the real value at the time when the application for entry in the register is received by the company.

If the company proposes to purchase shares for the account of shareholders, it must respect the principle of equal treatment of the holders of registered shares.

After hearing the persons concerned, the Board of Directors may cancel with retroactive effect, the entries in the share register made on the basis of inaccurate declarations.

The above provisions likewise apply to the creation of usufruct in registered shares of the company.

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Bruxelles 14 Ct

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Registered shares cannot be the subject of a pledge, guarantee or charge of any nature whatsoever without the specific prior approval of the Board of Directors which is free to decide whether to state reasons for its decision.

Reservations concerning the free transfer of registered shares will be indicated on the documents which represent the shares.

The provisions of Article 6.5 may be amended solely by a decision taken by a majority as stipulated in article 704, para 1, CO.

6.6 **Conversion of shares**

The General Meeting may decide at any time to convert all or some of the registered shares into bearer shares and vice versa.

Article 7: Increase of the share capital

7.1 The General Meeting may at any time decide to increase the share capital by issuing new registered or bearer shares. Each series of shares may itself be the subject of a specific issue.

7.2 Every shareholder is entitled to the proportion of newly issued shares corresponding to his previous participation. Where an increase in the share capital comprises an increase of registered shares and bearer shares in the same proportion, each holder of registered shares is entitled to subscribe to the registered shares only in proportion to the number of his registered shares and each shareholder who owns bearer shares is only entitled to subscribe to new bearer shares in proportion to the number of his shares.

TITLE III
ORGANISATION OF THE COMPANY

A. General Meeting

Article 8

8.1 The General Meeting is the supreme body of the company. Its decisions are binding on all of the shareholders.

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8.2 Decisions of the General Meeting which are in breach of the law or articles of association may be contested by the Board of Directors and by each shareholder under the conditions stipulated in article 706 of the Code of Obligations.

Article 9

The General Meeting of shareholders has the inalienable right to:

9.1 adopt and amend the articles of association

9.2 appoint and dismiss members of the Board of Directors and the auditors

9.3 approve the annual report and financial statements of the group

9.4 approve the annual financial statements and determine the appropriation of the profit and, in particular, set the dividend.

9.5 grant a release to the members of the Board of Directors

9.6 take all decisions which are reserved for it by the law and by the articles of association.

Article 10

10.1 No decision may be taken upon matters which have not been placed on the agenda, save on the proposal to convene an Extraordinary General Meeting or to establish a special audit.

10.2 There is no need for an advance announcement of proposals which fall within the framework of items placed on the agenda or of deliberations which do not have to be followed by a vote.

Article 11

11.1 The General Meeting is held at the registered office of the company or at the place designated by the Board of Directors.

11.2 The Ordinary General Meeting is held each year within six month of the end of the financial year.

11.3 Extraordinary General Meetings are convened as often as is necessary, in particular in the cases stipulated by law and by decision of the General Meeting itself.

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Article 12

The General Meeting is convened by the Board of Directors and, if necessary, by the auditors. The liquidators are likewise entitled to convene a meeting.

Article 13

13.1 The General Meeting is convened not less than twenty days before the date set for it to be held by registered letter sent to each of the registered shareholders at the address stated in the register of registered shares and by publication in the Feuille Officielle Suisse du Commerce (Swiss Official Commercial Gazette).

13.2 The invitation to attend the General Meeting must indicate the items placed on the agenda, together with the motions of the Board of Directors and of the shareholders who have asked for the meeting to be convened or for an item to be placed on its agenda, provided that this has been notified in writing to the Secretariat of the Board of Directors not less than 45 days before the date set for the meeting. The invitation to attend must also state the date, place and time of the meeting.

13.3 Proposals for amendments to the articles of association shall be placed at the disposal of shareholders at the registered office of the company; an indication that they are so available must be given in the invitation to attend the meeting.

13.4 Invitations to attend the Ordinary General Meeting must inform the shareholders that the annual report, the profit and loss account together with the balance sheet and financial statements of the group and the auditor's report are available for consultation by the shareholders at the registered office of the company not less than twenty days before the General Meeting.

Article 14

Owners or representatives of all the shares may, if there is no opposition, hold a General Meeting without observing the formalities stipulated for it to be convened. As long as they are all present, this meeting is entitled to deliberate and act validly on all the matters which fall within the terms of reference of the General Meeting.

Article 15

Each share gives the entitlement to one vote.

Article 16

Each registered shareholder may arrange for all or some of his shares to be represented by a different person who must carry a written proxy.

Article 17

17.1 As a general rule, the General Meeting is validly constituted regardless of the number of shares which are represented.

17.2 Save where otherwise stipulated in the law or articles of association, the General Meeting takes its decisions and holds its elections by an absolute majority of the votes carried by the shares which are represented.

17.3 A decision of the General Meeting which receives not less than two-thirds of the votes carried by the shares which are represented and an absolute majority of the nominal values represented is required to change the registered purpose, introduce shares with privileged voting rights, restrict the transferability of registered shares, proceed to an authorised or conditional increase of the share capital, increase the share capital by means of equity, against a contribution in kind or with a view to the acquisition of assets and the granting of special advantages, limitation or cancellation of the preferential subscription right, transfer of the registered office of the company and winding up of the company without liquidation.

Article 18

18.1 Minutes of the General Meeting are written and must indicate the number, type, nominal value and category of the shares represented by the shareholders, the official bodies and the independent representatives and custodial representatives, the decisions and outcome of the elections, the requests for information and the answers given, together with statements which the shareholders ask to be recorded. The minutes are to be signed by the Chairman and by the Secretary of the meeting.

18.2 The extracts of the minutes which are issued must be certified true copies by a director or by any other person designated for this purpose.

Article 19

19.1 The General Meeting is chaired by the Chairman of the Board of Directors or by some other director designated by the Board of Directors. Failing this, a chairman of the day shall be appointed by the General Meeting.

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19.2 The Chairman of the General Meeting appoints the secretary and the teller or tellers.

B. BOARD OF DIRECTORS

Article 20

20.1 The Board of Directors of the company comprises one or more members.

20.2 (Deleted)

Article 21

21.1 The Directors are appointed for a one-year term of office.

21.2 They may be re-elected indefinitely.

21.3 The Board of Directors shall appoint its Chairman and Secretary by a simple majority.

Article 22

22.1 The Board of Directors is convened by the Chairman or, on his instructions, by the Secretary as often as business so requires.

22.2 Minutes of its deliberations and decisions shall be written and signed by the Chairman and Secretary.

Article 23

23.1 Decisions of the Board of Directors are taken by a majority of the members present provided, however, that they constitute a majority of the Board of Directors.

23.2 In the event of a tied vote, the Chairman shall have a casting vote.

23.3 The decisions of the Board of Directors may also be taken in the form of approval given in writing to a proposal by a majority of all the directors who must all be informed of the proposal, unless a discussion is requested by any one of the members. These decisions must be recorded in the minutes.

Article 24

The Board of Directors has the most extensive possible powers to manage the company. It is authorised to take decisions on all matters which are not assigned to, or reserved for, the General Meeting and other bodies of the company.

Article 25

25.1 The Board may entrust all or part of the management and representation of the company to one or more directors (delegates) or to third parties who need not necessarily be shareholders.

25.2 It appoints procuration holders and other authorised representatives of the company.

25.3 It grants the right to sign individually or jointly on behalf of the company.

25.4 (Deleted)

Article 26

The Board of Directors shall adopt organisational rules.

C. EXECUTIVE COMMITTEE

(Deleted)

D. AUDIT BODY

Article 27

The General Meeting appoints the audit body to serve for one financial year if an ordinary or restricted audit must be performed.

It may decide not to elect an audit body, if:

1. the company is not subject to an ordinary audit
2. all of the shareholders agree to this, and

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3. the company workforce does not exceed 10 full-time posts on an annual average.

This waiver shall likewise apply to subsequent years.

However, each shareholder is entitled to request a restricted audit no later than ten days before the General Meeting. A General Meeting (extraordinary) must then elect the audit body.

The statutory provisions apply to the tasks of the audit body.

In the event of an ordinary audit, the audit body must be present at the General Meeting. This may dispense with the presence of the audit body by a decision taken unanimously.

Article 27 bis

One or more natural persons or corporate bodies, together with partnerships, may act as the audit body.

The audit body must have its domicile, registered office or a branch entered in the register of commerce in Switzerland. When the company has more than one audit body, one at least must meet this requirement.

When the company is required to submit its annual financial statements for ordinary verification by an audit body in virtue of Art. 727 paras. 1, 2 or 3 and 727 para. 2 CO, the General Meeting shall elect an expert auditor approved within the meaning of the federal law on supervision of auditors of 16 December 2005 to act as the audit body.

When the company is required to submit its annual financial statements to a restricted verification by an audit body, the General Meeting shall elect an approved auditor within the meaning of the federal law on the supervision of auditors of 16 December 2005 to serve as the audit body. The right to dispense with the election of an audit body is reserved. The audit body must be independent within the meaning of Art. 728 or 729 CO.

The mandate of the audit body ends upon the approval of the latest annual financial statements. Its term of office may be renewed. The General Meeting may at any time dismiss the audit body with immediate effect.

TITLE IV
ANNUAL FINANCIAL STATEMENTS AND APPROPRIATION OF THE PROFIT

Article 28

The financial year begins on the first of January and ends on the thirty-first of December.

Article 29

29.1 The annual financial statements are drawn up in compliance with the provisions of Articles 662 to 670 CO.

29.2 The financial statements are drawn up as of on the thirty-first of December.

Article 30

30.1 Each year, one-twentieth of the profit for the financial year shall be set aside to a general reserve until the latter reaches one-fifth of the share capital which has already been paid up. Further amounts shall be set aside if any part of the reserve is used up.

30.2 The balance of the profit shall be appropriated in compliance with the decisions of the General Meeting, after consulting the Board of Directors.

30.3 The binding provisions of law concerning statutory reserves must be respected.

Article 31

The dividend shall be paid at the time fixed by the Board of Directors. Any dividend which has not been claimed within five years of the date on which it falls due shall be automatically time-barred in favour of the company.

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TITLE V
LIQUIDATION

Article 32

32.1 When a decision to wind up the company is taken, the liquidation shall be effected by the Board of Directors, save where otherwise decided by the General Meeting.

32.2 At least one of the liquidators must be domiciled in Switzerland and have authority to represent the company.

32.3 The liquidators shall agree among themselves upon the method of signing on behalf of the company.

Article 33

33.1 In the course of liquidation, the powers of the bodies of the company are restricted to the actions required for this operation and which, by their nature, do not fall within the province of the liquidators.

33.2 The General Meeting of shareholders retains the right to approve the liquidation accounts and to grant a release for them.

33.3 The liquidator or liquidators cannot transfer to third parties against payment or against any other consideration, the assets and liabilities of the company which has been wound up, save in virtue of a decision taken by the General Meeting.

TITLE VI
PUBLICATIONS

Article 34

Publications for the company shall be made in the Feuille Officielle Suisse du Commerce (Swiss Official Commercial Gazette).

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ARTICLES OF ASSOCIATION ADOPTED by the constituent General Meeting of 20 May 1987 and amended at the Extraordinary General Meeting of 12 December 2008.

Certified:

Beatrice EHLERS
NOTARY

Signed

Attestation

We hereby certify that, to the best of our knowledge, this is a correct translation of the respective document.

Bern, 08.06.2009

Inter-Translations SA, Bern

Inter-Translations SA
Pavillonweg 14 · CH-3001 Bern

Danielle Cesarov-Zaugg

SA
Bern

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Béatrice EHLERS
NOTARY

MINUTES

of the Extraordinary General Meeting of Shareholders of

Laboratoires Serono SA

changed to

Merck Serono SA

a limited liability company with registered office in Coinsins

******

Minute No. 337 dated 12 December 2008

******

Inter-Translations SA
Pavillonweg 14 · CH-3001 Bern

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Minute No. 337

RECORD OF PROCEEDINGS

IN THE YEAR TWO THOUSAND AND EIGHT, on Friday twelve December, at 10 am, I, the undersigned, BEATRICE EHLERS, notary in Lausanne for the Canton of Vaud, acting at the request of the Board of Directors, drew up the following authentic record of the proceedings of the Extraordinary General Meeting of Shareholders of

Laboratoires Serono SA

a limited liability company with registered office in Coinsins.

The meeting was chaired by Maître Markus Funk, domiciled in Chêne-Bougeries.

The undersigned notary drafted the record of proceedings which was drawn up in the authentic form required by law.

The Chairman noted the fact that the entire share capital amounting to 11,013,040 (eleven million thirteen thousand and forty) registered shares with a nominal value of CHF 10 (ten francs) each and 10,945,127 (ten million nine hundred and forty-five thousand one hundred and twenty-seven) bearer shares of CHF 25 (twenty-five francs) was represented, as stated in the attendance register which was produced to remain enclosed in the file of the company at the office of the undersigned notary; the meeting was therefore able to hold valid deliberations pursuant to the provisions of Article 701 of the Swiss Code of Obligations.

The agenda proposed by the Chairman and adopted unanimously was as follows:

1. Change of name – amendment to the articles of association
2. Other changes to the articles of association
3. Other business

1. Change of name – amendment to the articles of association

The Chairman explained the reasons for which it had been felt appropriate by the Board to recommend a change of name to the meeting; he proposed that the meeting should agree to adopt "Merck Serono SA" as the official name of the company in future.

The meeting unanimously agreed to the proposed name for the company.

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On the basis of the decision which had thus been taken, the Chairman proposed that Article 1 of the articles of association be amended to now read as follows:

"Article 1: Name
Under the name Merck Serono SA, a public limited liability company governed by these articles of association and by title XXVI of the Swiss Code of Obligations (hereinafter also referred to as CO) is hereby constituted".

The new wording of article 1 was adopted unanimously.

2. Other changes to the articles of association
The Chairman explained to the meeting that the Board of Directors had felt it appropriate to use the present General Meeting as an opportunity to update the articles of association following the entry into force of the new law on companies on 1 January 2008. He therefore proposed the amendments set out below to the following articles:

The new wording of Article 9, para. 1, would be as follows:

"The General Meeting of shareholders has the inalienable right:
[...]"

Article 20, section 20.1, would now read as follows:

"The Board of Directors of the company comprises one or more members".

Article 27 is cancelled and replaced by Articles 27 and 27 bis to read as follows:

"Article 27
The General Meeting appoints the audit body for a term of one financial year if an ordinary or restricted audit has to be performed.

It may refrain from electing an audit body if:

1. *The company is not required to undergo an ordinary audit*
2. *The totality of the shareholders agree to this, and*
3. *The staff complement of the company does not exceed 10 full-time posts on an annual average.*

This waiver likewise applies to subsequent years.

However, each shareholder is entitled to require a restricted audit to take place no later than ten days before the General Meeting. An (extraordinary) General Meeting must then elect the audit body.

The tasks of the audit body shall be determined by the statutory provisions.

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In the event of an ordinary audit, the audit body must attend the General Meeting. The latter may waive the requirement for the audit body to be present by a unanimous decision.

Article 27 bis
One or more natural persons or corporate bodies may be elected to act as the audit body, as may partnerships.
The domicile, registered office or a branch establishment of the audit body must be entered in the register of commerce in Switzerland. If the company has more than one audit body, at least one of them must satisfy this requirement.
If the company is required to submit its annual account statements for an ordinary audit by an audit body in virtue of Art 727, para. 1, ch. 2 or ch. 3 and 727, para. 2 CO, the General Meeting shall elect an approved expert auditor within the meaning of the federal law on the supervision of auditors of 16 December 2005 to act as the audit body.

Where the company is required to submit its annual account statements for a restricted audit by an audit body, the General Meeting shall elect an approved auditor within the meaning of the federal law on the supervision of auditors of 16 December 2005 to act as the audit body. The waiver of the election of an audit body is reserved.

The audit body must be independent within the meaning of Art 728 or 729 CO.
The mandate of the audit body ends with the approval of the final annual account statements. Its term of office may be renewed. The General Meeting may dismiss the audit body with immediate effect at any time".

The above amendments to the articles of association were all adopted unanimously.

3. Other business
The meeting gave full authority to the undersigned notary to arrange for the present record to be entered in the register of commerce.

There being no other items on the agenda and nobody else wishing to speak, the meeting was closed after these minutes had been read out and approved, ending with the signing by the Chairman and the notary in the year, month and on the day indicated above in Lausanne, at ten fifteen am.

The minute is signed: M. Funk – B. Ehlers, not.

SECOND CERTIFIED TRUE COPY
Delivered to the company,

Certified by:

(signature) B Ehlers
(Seal of Béatrice Ehlers NOTARY)

PATENT

Attestation

We hereby certify that, to the best of our knowledge, this is a correct translation of the respective document.

Bern, 08.07.2009

Inter-Translations SA, Bern

Inter-Translations SA
Pavillonweg 14 • CH-3001 Bern

Danielle Cesarov-Zaugg

EXHIBIT E

PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
ARNAUD YTHIER	07/15/2009
ALAIN MUNAFO	07/07/2009
MARIA LOPEZ-BRESNAHAN	03/11/2010

RECEIVING PARTY DATA

Name:	MERCK SERONO SA
Street Address:	CENTRE INDUSTRIEL
City:	COINSINS, VAUD
State/Country:	SWITZERLAND
Postal Code:	1267

PROPERTY NUMBERS Total: 1

Property Type	Number
Application Number:	11722018

OP $40.00 11722018

CORRESPONDENCE DATA

Fax Number: (352)372-5800
Correspondence will be sent via US Mail when the fax attempt is unsuccessful.
Phone: 3523758100
Email: FCE@SLSPATENTS.COM
Correspondent Name: FRANK C. EISENSCHENK, PH.D.
Address Line 1: P.O. BOX 142950
Address Line 4: GAINESVILLE, FLORIDA 32614-2950

ATTORNEY DOCKET NUMBER:	SER.125
NAME OF SUBMITTER:	FRANK C. EISENSCHENK, PH.D.

Total Attachments: 4
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source=executed-Asgn#page2.tif

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ASSIGNMENT

WHEREAS, we, the undersigned, residing at the indicated addresses given below, have invented certain new and useful improvements in **CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS**, for which an application for United States Letters Patent was filed June 18, 2007, as Serial No. 11/722,018.

WHEREAS, MERCK SERONO S.A., a corporation of the country of Switzerland, having a place of business at Centre Industriel, 1267 Coinsins, Vaud, Switzerland, is desirous of acquiring the entire right, title, and interest in and to said invention and in and to any Letters Patent which may be granted therefor in the United States and in any and all foreign countries;

NOW, THEREFORE, in view of MERCK SERONO S.A.'s review and evaluation of our patent disclosure and other valuable consideration, receipt of which is hereby acknowledged, I, the undersigned, have sold, assigned, and transferred, and by these presents do sell, assign, and transfer, unto said MERCK SERONO S.A., its successors and assigns, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title, and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, and extensions thereof.

We hereby authorize and request the Patent Office Officials in the United States and in any and all foreign countries to issue any and all of said Letters Patent, when granted, to MERCK SERONO S.A., as the assignees of the entire right, title, and interest in and to the same, for the sole use and behoof of MERCK SERONO S.A., its successors and assigns.

FURTHER, we agree that we will communicate to MERCK SERONO S.A., or its representatives, any facts known to us respecting said invention; testify in any legal proceedings; sign all lawful papers; execute all divisional, continuation, substitution, renewal, and reissue applications; execute all necessary assignment papers to cause any and all of said Letters Patent to be issued to MERCK SERONO S.A.; make all rightful oaths; and generally do everything possible to aid MERCK SERONO S.A., its successors and assigns, to obtain and enforce proper protection for said invention in the United States and in any and all foreign countries.

IN TESTIMONY WHEREOF, I have hereunto set my hand this 15th day of July, 2009.

Signed _____

Arnaud Ythier
Route de Vireloup 88
1239 Collex-Bossy
Switzerland

WITNESS:

Signature: _____

Printed Name: CAROL JASCI

Date: 15.7.2009

IN TESTIMONY WHEREOF, I have hereunto set my hand this 07 day of July, 2009.

Signed _____

Alain Munafo
Rue des Pressoirs 6
1180 Tartegnin
Switzerland

WITNESS:

Signature: _____

Printed Name: CECE FORSMANN

Date: July 7th, 2009

IN TESTIMONY WHEREOF, I have hereunto set my hand this 11th day of March, 2010.

Signed _____

Maria Lopez-Bresnahan
145 South Great Road
Lincoln, MA 01773

WITNESS:

Signature: _____

Printed Name: Victoria Bresnahan

Date: 11- March - 2010

EXHIBIT F

EMD SERONO

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner for Patent Examination Policy
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

May 21, 2019

Re: Patent Term Extension for U.S. Patent No. 7,713,947

Dear Ms. Till:

This will acknowledge the approval by the FDA of New Drug Application (NDA) No. 022561 for Mavenclad (cladribine). NDA No. 022561 was submitted by EMD Serono, Inc.

On behalf of EMD Serono, Inc., Marketing Applicant for NDA No. 022561 for Mavenclad (cladribine), its predecessors, and affiliates, EMD Serono, Inc. hereby authorizes the patent owner of record, Merck Serono SA, in connection with this application for extension of the patent term of U.S. Patent No. 7,713,947, to rely upon the activities of EMD Serono, Inc., its predecessors, and affiliates, undertaken in connection with seeking approval by the Food and Drug Administration of NDA No. 022561. EMD Serono, Inc. and Merck Serono SA are both subsidiaries of Merck KGaA.

Respectfully submitted,

Signature: 

Name: Michael MacDougall
Title: Senior Vice President, General Counsel & Secretary
Company: EMD Serono, Inc.



EXHIBIT G

Copy as filed May 21, 2019

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

This form is to be submitted with the Power of Attorney by Applicant Form to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form.

Application Number	11/722,018
Patent Number	7,713,947
Filing Date	June 18, 2007
Issue Date	May 11, 2010
First Named Inventor	Giampiero De Luca
Art Unit	1649
Examiner Name	BALLARD, KIMBERLY
Attorney Docket Number	000758US
Title	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Signature of Applicant or Patent Practitioner

Signature	/Kirsten Grueneberg/
Name	Dr. Kirsten Grueneberg
Reg. No.	47,297
Customer No.	151167

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

*Total of __1__ form(s) is/are submitted.

Copy as filed May 21, 2019

PTO/SB/81A (12-08)
Approved for use through 03/31/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995 no persons are required to respond to a collection of information unless it displays a valid OMB control number

PATENT - POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Patent Number	7,713,947
Issue Date	May 11, 2010
First Named Inventor	Giampiero De Luca
Title	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
Attorney Docket No.	000758US

I hereby revoke all previous powers of attorney given in the above-identified patent.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) with respect to the patent identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

151167

OR

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Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Inventor or Patent Owner

Signature	Prisca Ballmoos	Date	May 21, 2019
Name	Prisca VON BALLMOOS / Willem DE WEERD	Telephone	
Title and Company	Authorized Representative Merck Serono S.A. / Authorized Representative Merck Serono S.A.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Merck Serono S.A.

Application No./Patent No.: 7,713,947 Filed/Issue Date: May 11, 2010

Titled: CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Merck Serono S.A., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel_____, Frame_____, or a copy* is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Giampiero DE LUCA To: LABORATOIRES SERONO S.A.

The document was recorded in the United States Patent and Trademark Office at Reel 019685, Frame 0061, or a copy* is attached.

2. From: LABORATOIRES SERONO SA To: MERCK SERONO SA

The document was recorded in the United States Patent and Trademark Office at Reel 023601, Frame 0156, or a copy* is attached.

3. From: Arnaud YTHIER; Alain MUNAFO; and Maria LOPEZ-BRESNAHAN To: MERCK SERONO S.A.

The document was recorded in the United States Patent and Trademark Office at Reel 024080, Frame 0041, or a copy* is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ *As required by 37 CFR 3.73(b)(1)(i), if a copy/copies is/are attached, the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Kirsten Grueneberg/ May 21, 2019

Signature Date

Dr. Kirsten Grueneberg 47,297

Printed or Typed Name Title or Registration Number

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

EXHIBIT H

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MAVENCLAD safely and effectively. See full prescribing information for MAVENCLAD.

MAVENCLAD® (cladribine) tablets, for oral use
Initial U.S. Approval: 1993

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY
See full prescribing information for complete boxed warning.

- **Malignancies**

MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy. (5.1)

- **Risk of Teratogenicity**

MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the risk of fetal harm. (5.2)

----------INDICATIONS AND USAGE----------

MAVENCLAD is a purine antimetabolite indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS *[see Warnings and Precautions (5)]*. (1)

Limitations of Use

MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile *[see Warnings and Precautions (5)]*. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assessments are required prior to starting each MAVENCLAD treatment course. (2.1)
- Cumulative dosage of 3.5 mg/kg administered orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles. (2.2)
- MAVENCLAD is a cytotoxic drug. (2.4)
- Separate administration from any other oral drug by at least 3 hours. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg (3)

----------CONTRAINDICATIONS----------

- Patients with current malignancy. (4)
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. (4, 8.3)
- HIV infection. (4)
- Active chronic infections (e.g., hepatitis or tuberculosis). (4)
- History of hypersensitivity to cladribine. (4, 5.8)
- Women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose. (4, 8.2)

----------WARNINGS AND PRECAUTIONS----------

- Lymphopenia: Monitor lymphocyte counts before, during and after treatment. (5.3)
- Infections: Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. (5.4)
- Hematologic toxicity: Measure complete blood count annually if clinically indicated after treatment. (5.5)
- Graft-versus-host-disease with blood transfusion: Irradiation of cellular blood components is recommended. (5.6)
- Liver injury: Obtain tests prior to treatment. Discontinue if clinically significant injury is suspected. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Immunosuppressive drugs: Consider overlapping effects on immune system, when used sequentially. Concomitant use not recommended. (7.1)
- Hematotoxic drugs: Monitor patients for additive effects on the hematological profile. (7.3)
- Antiviral and antiretroviral drugs: Avoid concomitant use. (7.4)
- BCRP or ENT/CNT inhibitors: May alter bioavailability of cladribine. Avoid concomitant use. (7.5)

See 17 for PATIENT COUNSELING INFORMATION **and Medication Guide.**

Revised: 3/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND RISK OF TERATOGENICITY

- **Malignancies**

Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

- **Risk of Teratogenicity**

MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant *[see Contraindications (4), Warnings and Precautions (5.2), and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

MAVENCLAD is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS *[see Warnings and Precautions (5)]*.

Limitations of Use

MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile *[see Warnings and Precautions (5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to Starting Each MAVENCLAD Treatment Course

Cancer Screening

Follow standard cancer screening guidelines because of the risk of malignancies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Pregnancy

Exclude pregnancy prior to treatment with MAVENCLAD in females of reproductive potential *[see Contraindications (4), Warnings and Precautions (5.2), and Use in Specific Populations (8.1, 8.3)]*.

Complete Blood Count (CBC)

Obtain a CBC with differential including lymphocyte count *[see Dosage and Administration (2.5) and Warnings and Precautions (5.3)]*. Lymphocytes must be:

- within normal limits before initiating the first treatment course
- at least 800 cells per microliter before initiating the second treatment course

If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with MAVENCLAD.

Infections *[see Warnings and Precautions (5.4)]*

- Exclude HIV infection.
- Perform tuberculosis screening.
- Screen for hepatitis B and C.
- Evaluate for acute infection. Consider a delay in MAVENCLAD treatment until any acute infection is fully controlled.
- Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of MAVENCLAD.
- Administer all immunizations according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

Liver Injury

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels *[see Warnings and Precautions (5.7)]*.

2.2 Recommended Dosage

The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course) (see Table 1). Each treatment course is divided into 2 treatment cycles:

Administration of First Treatment Course

- First Course/First Cycle: start any time.
- First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle.

Administration of Second Treatment Course

- Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.
- Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle.

Table 1 Dose of MAVENCLAD per Cycle by Patient Weight in Each Treatment Course

Weight Range	**Dose in mg (Number of 10 mg Tablets) per Cycle**	
kg	First Cycle	Second Cycle
40* to less than 50	40 mg (4 tablets)	40 mg (4 tablets)
50 to less than 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to less than 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to less than 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to less than 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to less than 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to less than 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

*The use of MAVENCLAD in patients weighing less than 40 kg has not been investigated.

Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days *[see How Supplied/Storage and Handling (16.1)]*. Do not administer more than 2 tablets daily.

Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy *[see Warnings and Precautions (5.1)]*. The safety and efficacy of reinitiating MAVENCLAD more than 2 years after completing 2 treatment courses has not been studied.

2.3 Missed Dose

If a dose is missed, patients should not take double or extra doses.

If a dose is not taken on the scheduled day, then the patient must take the missed dose on the following day and extend the number of days in that treatment cycle. If two consecutive doses are missed, the treatment cycle is extended by 2 days.

2.4 Administration

MAVENCLAD tablets are taken orally, with water, and swallowed whole without chewing. MAVENCLAD can be taken with or without food.

Separate administration of MAVENCLAD and any other oral drugs by at least 3 hours during the 4 to 5 day MAVENCLAD treatment cycles *[see Clinical Pharmacology (12.6)]*.

MAVENCLAD is a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]*. MAVENCLAD is an uncoated tablet and must be swallowed immediately once removed from the blister. If a tablet is left on a surface, or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed with water.

The patient's hands must be dry when handling the tablets and washed thoroughly afterwards. Avoid prolonged contact with skin.

2.5 Laboratory Testing and Monitoring to Assess Safety

Cancer Screening

Follow standard cancer screening guidelines in patients treated with MAVENCLAD *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

Complete Blood Count

Obtain complete blood count (CBC) with differential including lymphocyte count:

- before initiating the first treatment course of MAVENCLAD
- before initiating the second treatment course of MAVENCLAD
- 2 and 6 months after start of treatment in each treatment course; if the lymphocyte count at month 2 is below 200 cells per microliter, monitor monthly until month 6. *See Warnings and Precautions (5.3, 5.4)* for instructions based on the patient's lymphocyte counts and clinical status (e.g., infections). Hold MAVENCLAD therapy if the lymphocyte count is below 200 cells per microliter
- periodically thereafter and when clinically indicated *[see Warnings and Precautions (5.5)]*

2.6 Recommended Concomitant Medication

Herpes Prophylaxis

Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter *[see Warnings and Precautions (5.4)]*.

3 DOSAGE FORMS AND STRENGTHS

MAVENCLAD is available as 10 mg tablets. The tablets are uncoated, white, round, biconvex, and engraved with a "C" on one side and "10" on the other side.

4 CONTRAINDICATIONS

MAVENCLAD is contraindicated:

- in patients with current malignancy *[see Warnings and Precautions (5.1)]*.
- in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. May cause fetal harm *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.
- in patients infected with the human immunodeficiency virus (HIV) *[see Warnings and Precautions (5.4)]*.
- in patients with active chronic infections (e.g., hepatitis or tuberculosis) *[see Warnings and Precautions (5.4)]*.
- in patients with a history of hypersensitivity to cladribine *[see Warnings and Precautions (5.8)]*.

- in women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose *[see Use in Specific Populations (8.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Malignancies

Treatment with MAVENCLAD may increase the risk of malignancy. In controlled and extension clinical studies worldwide, malignancies occurred more frequently in MAVENCLAD-treated patients [10 events in 3,754 patient-years (0.27 events per 100 patient-years)], compared to placebo patients [3 events in 2,275 patient-years (0.13 events per 100 patient-years)]. Malignancy cases in MAVENCLAD patients included metastatic pancreatic carcinoma, malignant melanoma (2 cases), ovarian cancer, compared to malignancy cases in placebo patients, all of which were curable by surgical resection [basal cell carcinoma, cervical carcinoma in situ (2 cases)]. The incidence of malignancies in United States MAVENCLAD clinical study patients was higher than the rest of the world [4 events in 189 patient-years (2.21 events per 100 patient-years) compared to 0 events in United States placebo patients]; however, the United States results were based on a limited amount of patient data.

After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years *[see Dosage and Administration (2.2)]*. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy [7 events in 790 patient-years (0.91 events per 100 patient-years) calculated from the start of cladribine treatment in Year 3]. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

5.2 Risk of Teratogenicity

MAVENCLAD may cause fetal harm when administered to pregnant women. Malformations and embryolethality occurred in animals *[see Use in Specific Populations (8.1)]*. Advise women of the potential risk to a fetus during MAVENCLAD dosing and for 6 months after the last dose in each treatment course.

In females of reproductive potential, pregnancy should be excluded before initiation of each treatment course of MAVENCLAD and prevented by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment *[see Use in Specific Populations (8.1, 8.3)]*. MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception.

5.3 Lymphopenia

MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. In patients treated with a cumulative dose of MAVENCLAD 3.5 mg per kg over 2 courses as monotherapy, 26% and 1% had nadir absolute lymphocyte counts less than 500 and less than 200 cells per microliter, respectively. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells per microliter; median time to recovery to at least 800 cells per microliter was approximately 28 weeks.

Additive hematological adverse reactions may be expected if MAVENCLAD is administered prior to or concomitantly with other drugs that affect the hematological profile *[see Drug Interactions (7.3)]*. The incidence of lymphopenia less than 500 cells per microliter was higher in patients who had used drugs to treat relapsing forms of MS prior to study entry (32.1%), compared to those with no prior use of these drugs (23.8%).

Obtain complete blood count (CBC) with differential including lymphocyte count prior to, during, and after treatment with MAVENCLAD. *See Dosage and Administration (2.1, 2.5) and Warnings and Precautions (5.4)* for timing of CBC measurements and additional instructions based on the patient's lymphocyte counts and clinical status (e.g., infections).

5.4 Infections

MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of placebo patients in clinical studies. The most frequent serious infections in MAVENCLAD-treated patients included herpes zoster and pyelonephritis *(see Herpes Virus Infections)*. Fungal infections were observed, including cases of coccidioidomycosis.

HIV infection, active tuberculosis, and active hepatitis must be excluded before initiation of each treatment course of MAVENCLAD *[see Contraindications (4)]*.

Consider a delay in initiation of MAVENCLAD in patients with an acute infection until the infection is fully controlled.

Reference ID: 4410993

Initiation of MAVENCLAD in patients currently receiving immunosuppressive or myelosuppressive therapy is not recommended *[see Drug Interactions (7.1)]*. Concomitant use of MAVENCLAD with these therapies could increase the risk of immunosuppression.

Tuberculosis

Three of 1,976 (0.2%) cladribine-treated patients in the clinical program developed tuberculosis. All three cases occurred in regions where tuberculosis is endemic. One case of tuberculosis was fatal, and two cases resolved with treatment.

Perform tuberculosis screening prior to initiation of the first and second treatment course of MAVENCLAD. Latent tuberculosis infections may be activated with use of MAVENCLAD. In patients with tuberculosis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Hepatitis

One clinical study patient died from fulminant hepatitis B infection. Perform screening for hepatitis B and C prior to initiation of the first and second treatment course of MAVENCLAD. Latent hepatitis infections may be activated with use of MAVENCLAD. Patients who are carriers of hepatitis B or C virus may be at risk of irreversible liver damage caused by virus reactivation. In patients with hepatitis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Herpes Virus Infections

In controlled clinical studies, 6% of MAVENCLAD-treated patients developed a herpes viral infection compared to 2% of placebo patients. The most frequent types of herpes viral infections were herpes zoster infections (2.0% vs. 0.2%) and oral herpes (2.6% vs. 1.2%). Serious herpes zoster infections occurred in 0.2% of MAVENCLAD-treated patients.

Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.

The incidence of herpes zoster was higher during the period of absolute lymphocyte count less than 500 cells per microliter, compared to the time when the patients were not experiencing this degree of lymphopenia. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter.

Patients with lymphocyte counts below 500 cells per microliter should be monitored for signs and symptoms suggestive of infections, including herpes infections. If such signs and symptoms occur, initiate treatment as clinically indicated. Consider interruption or delay of MAVENCLAD until resolution of the infection.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No case of PML has been reported in clinical studies of cladribine in patients with multiple sclerosis. In patients treated with parenteral cladribine for oncologic indications, cases of PML have been reported in the postmarketing setting.

Obtain a baseline (within 3 months) magnetic resonance imaging (MRI) before initiating the first treatment course of MAVENCLAD. At the first sign or symptom suggestive of PML, withhold MAVENCLAD and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms.

Vaccinations

Administer all immunizations according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD, because of a risk of active vaccine infection *(see Herpes Virus Infections)*. Avoid vaccination with live-attenuated or live vaccines during and after MAVENCLAD treatment while the patient's white blood cell counts are not within normal limits.

5.5 Hematologic Toxicity

In addition to lymphopenia *[see Warnings and Precautions (5.3)]*, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. Mild to moderate decreases in neutrophil counts (cell count between 1,000 cells per microliter and < lower limit of normal (LLN)) were observed in 27% of MAVENCLAD-treated patients, compared to 13% of placebo patients whereas severe decreases in neutrophil counts (cell count below 1,000 cells per microliter) were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Decreases in hemoglobin levels, in general mild to moderate (hemoglobin 8.0 g per dL to < LLN), were observed in 26% of MAVENCLAD-treated patients, compared to 19% of placebo patients. Decreases in platelet counts were generally mild (cell count 75,000 cells per microliter to < LLN) and were observed in 11% of MAVENCLAD-treated patients, compared to 4% of placebo patients.

In clinical studies at dosages similar to or higher than the approved MAVENCLAD dosage, serious cases of thrombocytopenia, neutropenia, and pancytopenia (some with documented bone marrow hypoplasia) requiring transfusion and granulocyte-colony stimulating factor treatment have been reported *[see Warnings and Precautions (5.6)* for information regarding graft-versus-host disease with blood transfusion*]*.

Obtain complete blood count (CBC) with differential prior to, during, and after treatment with MAVENCLAD *[see Dosage and Administration (2.1, 2.5)]*.

5.6 Graft-Versus-Host Disease With Blood Transfusion

Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.

In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to decrease the risk of transfusion-related graft-versus-host disease. Consultation with a hematologist is advised.

5.7 Liver Injury

In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) considered related to treatment, compared to 0 placebo patients. Onset has ranged from a few weeks to several months after initiation of treatment with MAVENCLAD. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 20-fold the upper limit of normal, have been observed. These abnormalities resolved upon treatment discontinuation.

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to the first and second treatment course *[see Dosage and Administration (2.1)]*. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with MAVENCLAD, as appropriate.

5.8 Hypersensitivity

In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD (e.g., dermatitis, pruritis) occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. One patient had a serious hypersensitivity reaction with rash, mucous membrane ulceration, throat swelling, vertigo, diplopia, and headache after the first dose of MAVENCLAD.

If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine *[see Contraindications (4)]*.

5.9 Cardiac Failure

In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling).

6 ADVERSE REACTIONS

The following serious adverse reactions and potential risks are discussed, or discussed in greater detail, in other sections of the labeling:

- Malignancies *[see Warnings and Precautions (5.1)]*
- Risk of Teratogenicity *[see Warnings and Precautions (5.2)]*
- Lymphopenia *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.5)]*
- Graft-Versus-Host Disease With Blood Transfusion *[see Warnings and Precautions (5.6)]*
- Liver Injury *[see Warnings and Precautions (5.7)]*
- Hypersensitivity *[see Warnings and Precautions (5.8)]*
- Cardiac Failure *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In the clinical trial program of cladribine in MS, 1,976 patients received cladribine for a total of 9,509 patient years. The mean time on study including follow-up was approximately 4.8 years, and approximately 24% of cladribine-treated patients had approximately 8 years of time on study including follow-up. Of these, 923 patients aged 18 to 66 years received MAVENCLAD as monotherapy at a cumulative dose of 3.5 mg per kg.

Table 2 shows adverse reactions in Study 1 *[see Clinical Studies (14)]* with an incidence of at least 5% for MAVENCLAD and higher than placebo. The most common (> 20%) adverse reactions reported in Study 1 are upper respiratory tract infection, headache, and lymphopenia.

Table 2 **Adverse Reactions in Study 1 with an Incidence of at Least 5% for MAVENCLAD and Higher than Placebo**

	MAVENCLAD (N=440) %	Placebo (N=435) %
Upper respiratory tract infection	38	32
Headache	25	19
Lymphopenia	24	2
Nausea	10	9
Back pain	8	6
Arthralgia and arthritis	7	5
Insomnia	6	4
Bronchitis	5	3
Hypertension	5	3
Fever	5	3
Depression	5	3

Hypersensitivity
In clinical studies, 11% of MAVENCLAD patients had hypersensitivity adverse reactions, compared to 7% of placebo patients *[see Warnings and Precautions (5.8)]*.

Alopecia
Alopecia occurred in 3% of MAVENCLAD-treated patients compared to 1% of placebo patients.

Myelodysplastic Syndrome
Cases of myelodysplastic syndrome have been reported in patients that had received parenteral cladribine at a higher dosage than that approved for MAVENCLAD. These cases occurred several years after treatment.

Herpes Meningoencephalitis
Fatal herpes meningoencephalitis occurred in one MAVENCLAD-treated patient, at a higher dosage and longer duration of therapy than the approved MAVENCLAD dosage and in combination with interferon beta-1a treatment.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
SJS and TEN are identified risks of parenteral cladribine for the treatment of oncologic indications.

Seizures
In clinical studies, serious events of seizure occurred in 0.3% of MAVENCLAD-treated patients compared to 0 placebo patients. Serious events included generalized tonic-clonic seizures and status epilepticus. It is unknown whether these events were related to the effects of multiple sclerosis alone, to MAVENCLAD, or to a combination of both.

7 DRUG INTERACTIONS

Table 3 Drug Interactions with MAVENCLAD

7.1 Immunomodulatory, Immunosuppressive, or Myelosuppressive Drugs	
Clinical Impact	Concomitant use of MAVENCLAD with immunomodulatory, immunosuppressive, or myelosuppressive drugs may increase the risk of adverse reactions because of the additive effects on the immune system *[see Warnings and Precautions (5.4)]*.
Prevention or Management	Concomitant use with myelosuppressive or other immunosuppressive drugs is not recommended. Acute short-term therapy with corticosteroids can be administered. In patients who have previously been treated with immunomodulatory or immunosuppressive drugs, consider potential additive effect, the mode of action, and duration of effect of the other drugs prior to initiation of MAVENCLAD.
7.2 Interferon-Beta	
Clinical Impact	Concomitant use of MAVENCLAD with interferon-beta did not change the exposure of cladribine to a clinically significant effect; however, lymphopenia risk may be increased *[see Warnings and Precautions (5.3)]*.
Prevention or Management	Concomitant use is not recommended.
7.3 Hematotoxic Drugs	
Clinical Impact	Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects *[see Warnings and Precautions (5.5)]*.
Prevention or Management	Monitor hematological parameters.
7.4 Antiviral and Antiretroviral Drugs	
Clinical Impact	Compounds that require intracellular phosphorylation to become active (e.g., lamivudine, zalcitabine, ribavirin, stavudine, and zidovudine) could interfere with the intracellular phosphorylation and activity of cladribine.
Prevention or Management	Avoid concomitant use.

7.5 Potent ENT, CNT and BCRP Transporter Inhibitors	
Clinical Impact	Cladribine is a substrate of breast cancer resistance protein (BCRP), equilibrative nucleoside (ENT1), and concentrative nucleoside (CNT3) transport proteins. The bioavailability, intracellular distribution, and renal elimination of cladribine may be altered by potent ENT1, CNT3, and BCRP transporter inhibitors.
Prevention or Management	Avoid co-administration of potent ENT1, CNT3, or BCRP transporter inhibitors (e.g., ritonavir, eltrombopag, curcumin, cyclosporine, dilazep, nifedipine, nimodipine, cilostazol, sulindac, dipyridamole, or reserpine) during the 4 to 5 day MAVENCLAD treatment cycles. If this is not possible, consider selection of alternative concomitant drugs with no or minimal ENT1, CNT3, or BCRP transporter inhibiting properties. If this is not possible, dose reduction to the minimum mandatory dose of drugs containing these compounds, separation in the timing of administration, and careful patient monitoring is recommended.
7.6 Potent BCRP and P-gp Transporter Inducers	
Clinical Impact	Possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered.
Prevention or Management	Consider a possible decrease in cladribine efficacy if potent BCRP (e.g., corticosteroids) or P-gp (e.g., rifampicin, St. John's Wort) transporter inducers are co-administered.
7.7 Hormonal Contraceptives	
Clinical Impact	It is currently unknown whether MAVENCLAD may reduce the effectiveness of systemically acting hormonal contraceptives.
Prevention or Management	Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MAVENCLAD is contraindicated in pregnant women and in females and males of reproductive potential who do not plan to use effective contraception. There are no adequate data on the developmental risk associated with use of MAVENCLAD in pregnant women. Cladribine was embryolethal when administered to pregnant mice and produced malformations in mice and rabbits *[see Data]*. The observed developmental effects are consistent with the effects of cladribine on DNA *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data
When cladribine was administered intravenously (0, 0.5, 1.5, or 3 mg/kg/day) to pregnant mice during the period of organogenesis, fetal growth retardation and malformations (including exencephaly and cleft palate) and embryofetal death were observed at the highest dose tested. An increase in skeletal variations was observed at all but the lowest dose tested. There was no evidence of maternal toxicity.

When cladribine was administered intravenously (0, 0.3, 1, and 3 mg/kg/day) to pregnant rabbits during the period of organogenesis, fetal growth retardation and a high incidence of craniofacial and limb malformations were observed at the highest dose tested, in the absence of maternal toxicity.

When cladribine was administered intravenously (0, 0.5, 1.5, or 3.0 mg/kg/day) to mice throughout pregnancy and lactation, skeletal anomalies and embryolethality were observed at all but the lowest dose tested.

8.2 Lactation

Risk Summary

MAVENCLAD is contraindicated in breastfeeding women because of the potential for serious adverse reactions in breastfed infants *[see Contraindications (4) and Warnings and Precautions (5)]*. Advise women not to breastfeed during dosing with MAVENCLAD and for 10 days after the last dose.

There are no data on the presence of cladribine in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

In females of reproductive potential, pregnancy should be excluded before the initiation of each treatment course of MAVENCLAD *[see Use in Specific Populations (8.1)]*.

Contraception

Females
Females of reproductive potential should prevent pregnancy by use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course. It is unknown if MAVENCLAD may reduce the effectiveness of the systemically acting hormonal contraceptives. Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course. Women who become pregnant during MAVENCLAD therapy should discontinue treatment *[see Warnings and Precautions (5.2) and Drug Interactions (7.7)]*.

Males
As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected. Therefore, male patients of reproductive potential should take precautions to prevent pregnancy of their partner during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course *[see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients (below 18 years of age) have not been established. Use of MAVENCLAD is not recommended in pediatric patients because of the risk of malignancies *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies with MAVENCLAD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution is recommended when MAVENCLAD is used in elderly patients, taking into account the potential greater frequency of decreased hepatic, renal, or cardiac function, concomitant diseases, and other drug therapy.

8.6 Patients with Renal Impairment

The concentration of cladribine is predicted to increase in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. No dosage adjustment is recommended in patients with mild renal impairment (creatinine clearance 60 to 89 mL per minute). MAVENCLAD is not recommended in patients with moderate to severe renal impairment (creatinine clearance below 60 mL per minute) *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown *[see Clinical Pharmacology (12.3)]*. No dosage adjustment is recommended in patients with mild hepatic impairment. MAVENCLAD is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score greater than 6) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

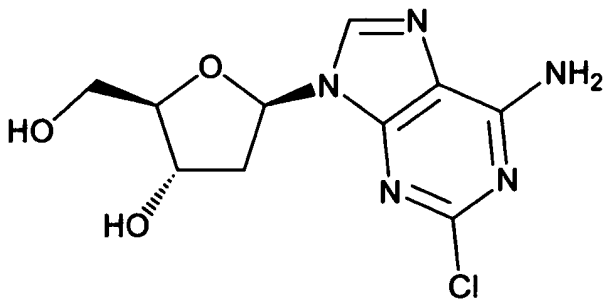
There is no experience with overdose of MAVENCLAD. Lymphopenia is known to be dose-dependent. Particularly close monitoring of hematological parameters is recommended in patients who have been exposed to an overdose of MAVENCLAD *[see Warnings and Precautions (5.3, 5.5)]*.

There is no known specific antidote to an overdose of MAVENCLAD. Treatment consists of careful observation and initiation of appropriate supportive measures. Discontinuation of MAVENCLAD may need to be considered. Because of the rapid and extensive intracellular and tissue distribution, hemodialysis is unlikely to eliminate cladribine to a significant extent.

11 DESCRIPTION

MAVENCLAD contains the nucleoside metabolic inhibitor cladribine, which is a white or almost white, non-hydroscopic, crystalline powder with the molecular formula $C_{10}H_{12}ClN_5O_3$ and molecular weight 285.69. It differs in structure from the naturally occurring nucleoside, deoxyadenosine, by the substitution of chlorine for hydrogen in the 2-position of the purine ring.

The chemical name of cladribine is 2-chloro-2′-deoxy-adenosine. The structural formula is shown below:



Cladribine is stable at slightly basic and at neutral pH. The main degradation pathway is hydrolysis and at acidic pH significant decomposition occurs with time. The ionization behavior of the molecule over the pH range 0 to 12 is characterized by a single pKa of approximately 1.21.

MAVENCLAD is provided as 10 mg tablets for oral use. Each MAVENCLAD 10 mg tablet contains cladribine as an active ingredient and hydroxypropyl betadex, magnesium stearate, and sorbitol as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes.

12.2 Pharmacodynamics

MAVENCLAD causes a dose-dependent reduction in lymphocyte count. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment cycle and were lower with each additional treatment cycle. At the end of Year 2, 2% of patients continued to have absolute lymphocyte counts less than 500 cells per microliter. The median time to recovery from lymphocyte counts less than 500 cells per microliter to at least 800 cells per microliter was approximately 28 weeks *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

Cladribine is a prodrug that becomes active upon phosphorylation to its 2-chlorodeoxyadenosine triphosphate (Cd-ATP) metabolite.

The pharmacokinetic parameters presented below were assessed following oral administration of cladribine 10 mg, unless otherwise specified. The cladribine mean maximum concentration (C_{max}) was in the range of 22 to 29 ng/ mL and corresponding mean AUC was in the range of 80 to 101 ng•h/mL.

The C_{max} and AUC of cladribine increased proportionally across a dose range from 3 to 20 mg.

No accumulation of cladribine concentration in plasma was observed after repeated dosing.

Absorption

The bioavailability of cladribine was approximately 40%. Following fasted administration of cladribine, the median time to maximum concentration (T_{max}) was 0.5 h (range 0.5 to 1.5 hours).

Effect of Food
Following administration of cladribine with a high fat meal, the geometric mean C_{max} decreased by 29% and AUC was unchanged. The T_{max} was prolonged to 1.5 hours (range 1 to 3 hours). This difference is not expected to be clinically significant.

Distribution

Cladribine mean apparent volume of distribution ranges from 480 to 490 liters. The plasma protein binding of cladribine is 20% and is independent of concentration, in vitro.

Intracellular concentrations of cladribine and/or its metabolites in human lymphocytes were approximately 30 to 40 times extracellular, in vitro.

Cladribine has the potential to penetrate the blood brain barrier. A cerebrospinal fluid/plasma concentration ratio of approximately 0.25 was observed in cancer patients.

Elimination

Cladribine estimated terminal half-life is approximately 1 day. The intracellular half-life of the cladribine phosphorylated metabolites cladribine monophosphate (Cd-AMP) is 15 hours and Cd-ATP is 10 hours. Cladribine estimated median apparent renal clearance is 22.2 liter per hour and non-renal clearance is 23.4 liter per hour.

Metabolism
Cladribine is a prodrug that is phosphorylated to Cd-AMP by deoxycytidine kinase (and also by deoxyguanosine kinase in the mitochondria) in lymphocytes. Cd-AMP is further phosphorylated to cladribine diphosphate (Cd-ADP) and the active moiety Cd-ATP. The dephosphorylation and deactivation of Cd-AMP is catalyzed by cytoplasmic 5'-nucleotidase (5'-NTase).

The metabolism of cladribine in whole blood has not been fully characterized. However, extensive whole blood and negligible hepatic enzyme metabolism was observed, in vitro.

Excretion
After administration of 10 mg oral cladribine in MS patients, 28.5 [20] (mean [SD]) percent of the dose was excreted unchanged via the renal route. Renal clearance exceeded the glomerular filtration rate, indicating active renal secretion of cladribine.

Specific Populations

No studies have been conducted to evaluate the pharmacokinetics of cladribine in elderly or in patients with renal or hepatic impairment.

There were no clinically significant differences in the pharmacokinetics of cladribine based on age (range 18 to 65 years) or gender. The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown.

Patients with Renal Impairment
Renal clearance of cladribine was shown to be dependent on creatinine clearance (CL_{CR}). No dedicated studies have been conducted in patients with renal impairment, however patients with mild renal impairment (CL_{CR} of 60 mL to below 90 mL per minute) were included in Study 1. A pooled pharmacokinetic analysis estimated a decrease of 18% in total clearance in a typical subject with a CL_{CR} of 65 mL per minute leading to an increase in cladribine exposure of 25%. Clinical experience in patients with moderate to severe renal impairment (i.e., CL_{CR} below 60 mL per minute) is limited *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Clinical Studies
No clinically significant differences in cladribine pharmacokinetics were observed when used concomitantly with pantoprazole or interferon beta-1a.

In Vitro Studies
It has been reported that lamivudine can inhibit the phosphorylation of cladribine intracellularly. Potential competition for intracellular phosphorylation exists between cladribine and compounds that require intracellular phosphorylation to become active (e.g., lamivudine, zalcitabine, ribavirin, stavudine, and zidovudine).

Cytochrome P450 (CYP) Enzymes: Cladribine is not a substrate of cytochrome P450 enzymes and does not show significant potential to act as inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Cladribine has no clinically meaningful inductive effect on CYP1A2, CYP2B6 and CYP3A4 enzymes.

Transporter Systems: Cladribine is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), equilibrative nucleoside transporter 1 (ENT1) and concentrative nucleoside transporter 3 (CNT3). Inhibition of BCRP in the gastrointestinal tract may increase the oral bioavailability and systemic exposure of cladribine. Intracellular distribution and renal elimination of cladribine may be altered by potent ENT1, CNT3 transporter inhibitors.

12.6 Hydroxypropyl Betadex-Related Complex Formation

MAVENCLAD contains hydroxypropyl betadex that may be available for complex formation with the active ingredients of other drugs. Complex formation between free hydroxypropyl betadex, released from the cladribine tablet formulation, and concomitant ibuprofen, furosemide, and gabapentin was observed. Concomitant use with MAVENCLAD may increase the bioavailability of other drugs (especially agents with low solubility), which may increase the risk or severity of adverse reactions *[see Dosage and Administration (2.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In mice administered cladribine (0, 0.1, 1, or 10 mg/kg) by subcutaneous injection intermittently (7 daily doses followed by 21 days of non-dosing per cycle) for 22 months, an increase in Harderian gland tumors (adenoma) was observed at the highest dose tested.

Mutagenesis

Cladribine was negative for mutagenicity in in vitro (reverse mutation in bacteria, CHO/HGPRT mammalian cell) assays.

Cladribine was positive for clastogenicity in an in vitro mammalian cell assay, in the absence and presence of metabolic activation, and in an in vivo mouse micronucleus assay.

Impairment of Fertility

When cladribine (0, 1, 5, 10, or 30 mg/kg/day) was administered by subcutaneous injection to male mice prior to and during mating to untreated females, no effects on fertility were observed. However, an increase in non-motile sperm was observed at the highest dose tested. In female mice, administration of cladribine (0, 1, 2, 4, or 8 mg/kg/day) by subcutaneous injection prior to and during mating to untreated males and continuing to gestation day 6 caused an increase in embryolethality at the highest dose tested.

In monkeys administered cladribine (0, 0.15, 0.3, or 1.0 mg/kg) by subcutaneous injection intermittently (7 consecutive daily doses followed by 21 days of non-dosing per cycle) for one year, testicular degeneration was observed at the highest dose tested.

14 CLINICAL STUDIES

The efficacy of MAVENCLAD was demonstrated in a 96-week randomized, double-blind, placebo-controlled clinical study in patients with relapsing forms of MS (Study 1; NCT00213135).

Patients were required to have at least 1 relapse in the previous 12 months. The median age was 39 years (range 18 to 65) and the female-to-male ratio was approximately 2:1. The mean duration of MS prior to study enrollment was 8.7 years, and the median baseline neurological disability based on Kurtzke Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0. Over two thirds of the study patients were treatment-naive for drugs used to treat relapsing forms of MS.

1,326 patients were randomized to receive either placebo (n = 437), or a cumulative oral dosage of MAVENCLAD 3.5 mg per kg (n = 433) or 5.25 mg per kg body weight (n = 456) over the 96-week study period in 2 treatment courses. Patients randomized to the 3.5 mg per kg cumulative dose received a first treatment course at Weeks 1 and 5 of the first year and a second treatment course at Weeks 1 and 5 of the second year *[see Dosage and Administration (2.2)]*. Patients randomized to the 5.25 mg per kg cumulative dose received additional treatment at Weeks 9 and 13 of the first year. Higher cumulative doses did not add any clinically meaningful benefit, but were associated with a higher incidence in grade 3 lymphopenia or higher (44.9% in the 5.25 mg per kg group vs. 25.6% in the 3.5 mg per kg group). Ninety-two percent of patients treated with MAVENCLAD 3.5 mg per kg and 87% of patients receiving placebo completed the full 96 weeks of the study.

The primary outcome of Study 1 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the time to first qualifying relapse, the mean number of MRI T1 Gadolinium-enhancing (Gd+) lesions, and new or enlarging MRI T2 hyperintense lesions. Disability progression was measured in terms of a 3-month sustained change in EDSS score of at least one point, if baseline EDSS score was between 0.5 and 4.5 inclusively, or at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least 3 months.

MAVENCLAD 3.5 mg per kg significantly lowered the annualized relapse rate. The results from Study 1 are presented in Table 4.

Table 4 Clinical Outcomes in Study 1 (96 Weeks) - Primary and Secondary Endpoints

Endpoints	MAVENCLAD Cumulative Dose 3.5 mg per kg (n = 433)	Placebo (n = 437)
Clinical Endpoints		
Annualized relapse rate (ARR)	0.14*	0.33
Relative reduction in ARR	58%	
Proportion of patients without relapse	81%**	63%
Time to 3-month confirmed EDSS progression, HR	0.67**	
Proportion of patients with 3-month EDSS progression	13%	19%
MRI Endpoints		
Median Number of Active T1 Gd+ Lesions	0*	0.33
Median Number of Active T2 Lesions	0*	0.67

* $p < 0.001$ compared to placebo
** nominal $p < 0.05$ compared to placebo
HR: Hazard Ratio

15 REFERENCES

1 "OSHA Hazardous Drugs". OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MAVENCLAD tablets, 10 mg, are uncoated, white, round, biconvex, and engraved with a "C" on one side and "10" on the other side. Each tablet is packaged in a child-resistant day pack containing one or two tablets in a blister card.

Dispense one box for each treatment cycle with a Medication Guide *[see Dosage and Administration (2.2)]*.

Presentations

NDC 44087-400-11	Box of 1 tablet: One day pack containing one tablet.
NDC 44087-400-12	Box of 2 tablets: One day pack containing two tablets.
NDC 44087-400-04	Box of 4 tablets: Four day packs each containing one tablet.
NDC 44087-400-05	Box of 5 tablets: Five day packs each containing one tablet.
NDC 44087-400-06	Box of 6 tablets: One day pack containing two tablets. Four day packs each containing one tablet.
NDC 44087-400-07	Box of 7 tablets: Two day packs each containing two tablets. Three day packs each containing one tablet.
NDC 44087-400-08	Box of 8 tablets: Three day packs each containing two tablets. Two day packs each containing one tablet.
NDC 44087-400-09	Box of 9 tablets: Four day packs each containing two tablets. One day pack containing one tablet.
NDC 44087-400-10	Box of 10 tablets: Five day packs each containing two tablets.

16.2 Storage and Handling

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Store in original package in order to protect from moisture.

MAVENCLAD is a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]*.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Malignancies

Inform patients that MAVENCLAD may increase their risk of malignancies. Instruct patients to follow standard cancer screening guidelines *[see Dosage and Administration (2) and Warnings and Precautions (5.1)]*.

Risk of Teratogenicity

Inform patients that MAVENCLAD may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Before initiating each treatment course, inform patients about the potential risk to the fetus, if female patients or partners of male patients get pregnant during MAVENCLAD dosing or within 6 months after the last dose in each treatment course *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.

Instruct female patients of childbearing potential to use effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course to avoid pregnancy. Advise women using systemically acting hormonal contraceptives to add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course because MAVENCLAD may reduce the effectiveness of the hormonal contraceptive *[see Drug Interactions (7.7)]*.

Instruct male patients to take precautions to prevent pregnancy of their partner during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course.

Advise patients that female patients or partners of male patients who get pregnant immediately inform their healthcare provider.

Lactation

Inform women that they cannot breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose *[see Use in Specific Populations (8.2)]*.

Lymphopenia and Other Hematologic Toxicity

Inform patients that MAVENCLAD may decrease lymphocyte counts and may also decrease counts of other blood cells. A blood test should be obtained before starting a treatment course, 2 and 6 months after start of treatment in each treatment course, periodically thereafter, and when clinically needed. Advise patients to keep all appointments for lymphocyte monitoring during and after MAVENCLAD treatment *[see Dosage and Administration (2.5) and Warnings and Precautions (5.3, 5.5)]*.

Infections

Inform patients that use of MAVENCLAD may increase the risk of infections. Instruct patients to notify their healthcare provider promptly if fever or other signs of infection such as aching, painful muscles, headache, generally feeling unwell or loss of appetite occur while on therapy or after a course of treatment *[see Warnings and Precautions (5.4)]*.

Advise patients that PML has happened with parenteral cladribine used in oncologic indications. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes *[see Warnings and Precautions (5.4)]*.

Liver Injury

Inform patients that MAVENCLAD may cause liver injury. Instruct patients treated with MAVENCLAD to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. A blood test should be obtained prior to each treatment course with MAVENCLAD and as clinically indicated thereafter *[see Warnings and Precautions (5.7)]*.

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious or severe hypersensitivity reactions, including skin reactions *[see Warnings and Precautions (5.8)]*.

Cardiac Failure

Advise patients that MAVENCLAD may cause cardiac failure. Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling) *[see Warnings and Precautions (5.9)]*.

Treatment Handling and Administration

Instruct patients that MAVENCLAD is a cytotoxic drug and to use care when handling MAVENCLAD tablets, limit direct skin contact with the tablets, and wash exposed areas thoroughly. Advise patients to keep the tablets in the original package until just prior to each scheduled dose and consult their pharmacist on the proper disposal of unused tablets *[see Dosage and Administration (2.4) and How Supplied/Storage and Handling (16.2)]*.

Distributed by:
EMD Serono, Inc.
Rockland, MA 02370

MAVENCLAD is a registered trademark of Merck KGaA, Darmstadt, Germany.

MEDICATION GUIDE
MAVENCLAD® (MAY-ven-klad)
(cladribine)
tablets, for oral use

What is the most important information I should know about MAVENCLAD?
MAVENCLAD can cause serious side effects, including:

- **Risk of cancer (malignancies).** Treatment with MAVENCLAD may increase your risk of developing cancer. Talk to your healthcare provider about your risk of developing cancer if you receive MAVENCLAD. You should follow your healthcare provider instructions about screening for cancer.
- **MAVENCLAD may cause birth defects if used during pregnancy. Females must not be pregnant when they start treatment with MAVENCLAD or become pregnant during MAVENCLAD dosing and within 6 months after the last dose of each yearly treatment course. Stop your treatment with MAVENCLAD and call your healthcare provider right away if you become pregnant during treatment with MAVENCLAD.**
  - For females who are able to become pregnant:
    - Your healthcare provider should order a pregnancy test for you before you begin your first and second yearly treatment course of MAVENCLAD to make sure that you are not pregnant. Your healthcare provider will decide when to do the test.
    - Use effective birth control (contraception) on the days on which you take MAVENCLAD and for at least 6 months after the last dose of each yearly treatment course.
      - Talk to your healthcare provider if you use oral contraceptives (the "pill").
      - You should use a second method of birth control on the days on which you take MAVENCLAD and for at least 4 weeks after your last dose of each yearly treatment course.
  - For males with female partners who are able to become pregnant:
    - Use effective birth control (contraception) during the days on which you take MAVENCLAD and for at least 6 months after the last dose of each yearly treatment course.

What is MAVENCLAD?
MAVENCLAD is a prescription medicine used to treat relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, MAVENCLAD is generally used in people who have tried another MS medicine that they could not tolerate or that has not worked well enough.

MAVENCLAD is not recommended for use in people with clinically isolated syndrome (CIS).

It is not known if MAVENCLAD is safe and effective in children under 18 years of age.

Do not take MAVENCLAD if you:

- have cancer (malignancy).
- are pregnant, plan to become pregnant, or are a woman of childbearing age or a man able to father a child and you are not using birth control. See "**What is the most important information I should know about MAVENCLAD?**"
- are human immunodeficiency virus (HIV) positive.
- have active infections, including tuberculosis (TB), hepatitis B or C.
- are allergic to cladribine.
- are breastfeeding. See "**Before you take MAVENCLAD, tell your healthcare provider about all of your medical conditions, including if you:**"

Before you take MAVENCLAD, tell your healthcare provider about all of your medical conditions, including if you:

- think you have an infection.
- have heart failure.
- have liver or kidney problems.
- have taken, take, or plan to take medicines that affect your immune system or your blood cells, or other treatments for MS. Certain medicines can increase your risk of getting an infection.
- have had a recent vaccination or are scheduled to receive any vaccinations. You should not receive live or live-attenuated vaccines within the 4 to 6 weeks preceding your treatment with MAVENCLAD. You should not receive these types of vaccines during your treatment with MAVENCLAD and until your healthcare provider tells you that your immune system is no longer weakened.
- have or have had cancer.
- are breastfeeding or plan to breastfeed. It is not known if MAVENCLAD passes into your breast milk. Do not breastfeed on the days, on which you take MAVENCLAD, and for 10 days after the last dose. See "**Do not** take

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MAVENCLAD if you:"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take MAVENCLAD?

- MAVENCLAD is given as two yearly treatment courses.
- Each yearly treatment course consists of 2 treatment weeks (also called cycles) that will be about a month apart. Your healthcare provider will tell you when you have to start your treatment weeks and how many tablets per week you need, depending on your weight. Each treatment week is 4 or 5 days.
- Your pharmacist will dispense a carton of MAVENCLAD for each treatment week. The prescribed number of tablets per day are provided in child resistant day packs.
- Take MAVENCLAD exactly as your healthcare provider tells you. Do not change your dose or stop taking MAVENCLAD unless your healthcare provider tells you to.
- Take MAVENCLAD with water and swallow whole without chewing. MAVENCLAD can be taken with or without food.
- Swallow MAVENCLAD right away after opening the blister pack.
- Your hands must be dry when handling MAVENCLAD and washed well with water afterwards.
- Limit contact with your skin. Avoid touching your nose, eyes and other parts of the body. If you get MAVENCLAD on your skin or on any surface, wash it right away with water.
- Take MAVENCLAD at least 3 hours apart from other medicines taken by mouth during the 4- to 5-day MAVENCLAD treatment week.
- If you miss a dose, take it as soon as you remember on the same day. If the whole day passes before you remember, take your missed dose the next day. **Do not take 2 doses at the same time**. Instead, you will extend the number of days in that treatment week.

Your healthcare provider will continue to monitor your health during the 2 yearly treatment courses, and for at least another 2 years during which you do not need to take MAVENCLAD. It is not known if MAVENCLAD is safe and effective in people who restart MAVENCLAD treatment more than 2 years after completing 2 yearly treatment courses.

What are the possible side effects of MAVENCLAD?

MAVENCLAD can cause serious side effects, including:

- See **"What is the most important information I should know about MAVENCLAD?"**
- **low blood cell counts**. Low blood cell counts have happened and can increase your risk of infections during your treatment with MAVENCLAD. Your healthcare provider will do blood tests before you start treatment with MAVENCLAD, during your treatment with MAVENCLAD, and afterward, as needed.
- **serious infections such as:**
  - **TB, hepatitis B or C, and shingles (herpes zoster).** Fatal cases of TB and hepatitis have happened with cladribine during clinical studies. Tell your healthcare provider right away if you get any symptoms of the following infection related problems or if any of the symptoms get worse, including:
    - fever
    - aching painful muscles
    - headache
    - feeling of being generally unwell
    - loss of appetite
    - burning, tingling, numbness or itchiness of the skin in the affected area
    - skin blotches, blistered rash and severe pain
  - **progressive multifocal leukoencephalopathy (PML).** PML is a rare brain infection that usually leads to death or severe disability. Although PML has not been seen in MS patients taking MAVENCLAD, it may happen in people with weakened immune systems. Symptoms of PML get worse over days to weeks. Call your healthcare provider right away if you have any new or worsening neurologic signs or symptoms of PML, that have lasted several days, including:
    - weakness on 1 side of your body
    - loss or coordination in your arms and legs
    - decreased strength
    - problems with balance
    - changes in your vision
    - changes in your thinking or memory
    - confusion
    - changes in your personality
- **liver problems.** MAVENCLAD may cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking MAVENCLAD. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - nausea
  - vomiting
  - stomach pain
  - tiredness
  - loss of appetite
  - your skin or the whites or your eyes turn yellow
  - dark urine

- **allergic reactions (hypersensitivities)**. MAVENCLAD can cause serious allergic reactions. Stop your treatment with MAVENCLAD and go to the closest emergency room for medical help right away if you have any signs or symptoms of allergic reactions. Symptoms of an allergic reaction may include: skin rash, swelling or itching of the face, lips, tongue or throat, or trouble breathing.
- **heart failure**. MAVENCLAD may cause heart failure, which means your heart may not pump as well as it should. Call your healthcare provider or go to the closest emergency room for medical help right away if you have any signs or symptoms such as shortness of breath, a fast or irregular heart beat, or unusual swelling in your body.

Your healthcare provider may delay or completely stop treatment with MAVENCLAD if you have severe side effects.

The most common side effects of MAVENCLAD include:

- upper respiratory infection
- headache
- low white blood cell counts

These are not all the possible side effects of MAVENCLAD. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAVENCLAD?

- MAVENCLAD comes in a child resistant package.
- Store MAVENCLAD at room temperature between 68°F and 77°F (20°C and 25°C).
- Store MAVENCLAD in the original package to protect from moisture.
- Ask your healthcare provider or pharmacist about how to safely throw away any unused or expired MAVENCLAD tablets and packaging.

Keep MAVENCLAD and all medicines out of the reach of children.

General information about the safe and effective use of MAVENCLAD

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MAVENCLAD for a condition for which it was not prescribed. Do not give MAVENCLAD to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider for information about MAVENCLAD that is written for health professionals.

What are the ingredients in MAVENCLAD?

Active ingredient: cladribine

Inactive ingredients: hydroxypropyl betadex, magnesium stearate, and sorbitol.

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MAVENCLAD is a registered trademark of Merck KGaA, Darmstadt, Germany.

For more information, call toll-free1-877-447-3243 or go to www.mavenclad.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 3/2019

EXHIBIT I

Conclusion:

Based on the results, the optimized complexation process was applied for the manufacture of the cladribine / hydroxypropyl betadex complex for Phase I clinical PK studies [redacted] the complex formed at the ratio of 1:14 w/w was selected for the manufacture of a 10 mg cladribine tablet for further Phase I/II/III clinical trials as well as for the commercial formulation.

1.3.4 Characterization of the Cladribine / Hydroxypropyl Betadex Complex

Characterization studies as follows were carried out on the complex:

- Powder X-Ray Diffraction (PXRD) and Differential Scanning Calorimetry (DSC)
- Solid-state Cross Polarization Magic Angle Spinning (CP-MAS) Nuclear Magnetic Resonance (NMR) Spectroscopy
- High Resolution 2D-NMR Spectroscopy
- Properties in Solution

1.3.4.1 Powder X-Ray Diffraction (PXRD) and Differential Scanning Calorimetry (DSC)

Lyophilized cladribine / hydroxypropyl betadex complex samples were investigated at the ratio 1:14 w/w by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) for the identification of the physical form. For comparison purposes, cladribine and hydroxypropyl betadex lyophilized samples were also analyzed. For assessment of detection limits of potentially free (uncomplexed) cladribine, samples of lyophilized complex spiked with defined aliquots of crystalline cladribine and with defined aliquots of amorphous cladribine were prepared and also studied by PXRD and DSC.

[redacted]

[redacted]

[redacted]

Conclusion:

PXRD demonstrated that amorphous phase is obtained from the lyophilization process. Free crystalline cladribine is not detected in PXRD with limit of detection of free crystalline cladribine established at [redacted]%.

DSC demonstrated that the amorphous phase comprises a complex of cladribine and hydroxypropyl betadex.

1.3.4.2 Solid-state Cross Polarization Magic Angle Spinning (CP-MAS) Nuclear Magnetic Resonance (NMR) Spectroscopy

The complex of cladribine and hydroxypropyl betadex was investigated by 1D and 2D NMR methods. In a first step, the ^{13}C-cross polarized NMR spectra (^{13}C-CP NMR) of cladribine (both crystalline and amorphous form), hydroxypropyl betadex and the complex were recorded. [redacted]

[redacted]



Conclusion:

The results imply a different chemical environment for the cladribine molecules in the hydroxypropyl betadex complex, most likely driven by an intermolecular interaction.

1.3.4.3 High Resolution 2D NMR Spectroscopy

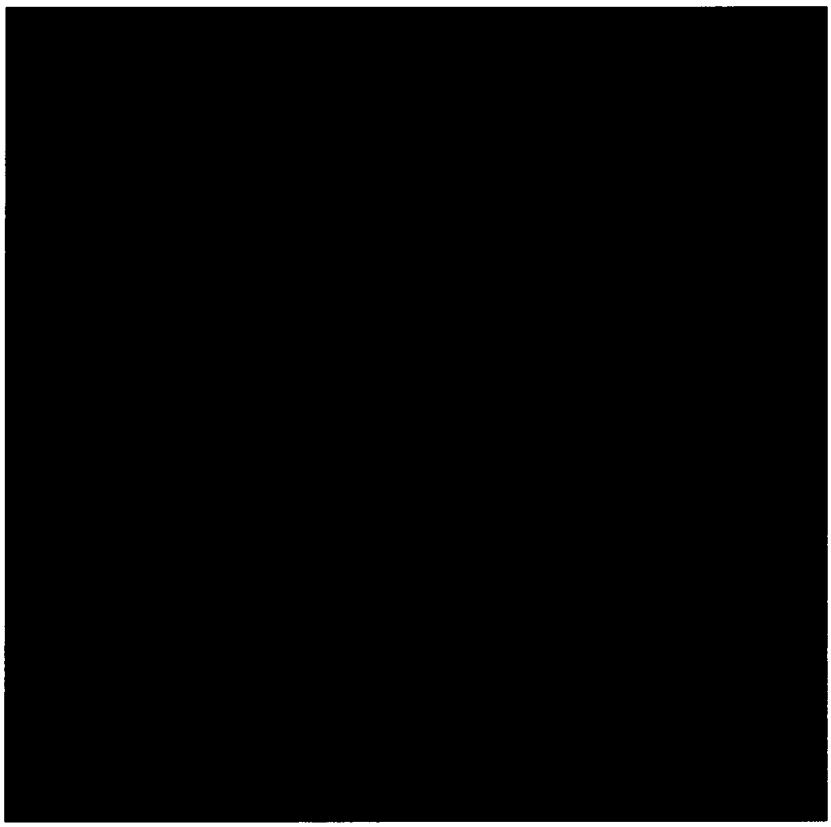
High resolution 2D NMR experiments were carried out in order to better understand the molecular interaction in the cladribine / hydroxypropyl betadex complex, namely TOCSY and ROESY (2).

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

Conclusion:

The cladribine / hydroxypropyl betadex complex is based on non-covalent interaction proving close spatial proximity between cladribine and the anomeric hydrogen on the hydroxypropyl betadex.

The 2D NMR data suggest formation of an inclusion complex.

1.3.4.4 Properties in Solution

Solubility studies were performed on free cladribine and complexed cladribine with hydroxypropyl betadex at different pH values [redacted]. Solubility of cladribine is enhanced when complexed. In addition, the studies show that hydrolysis rate of cladribine in acidic solution is significantly reduced for complexed cladribine compared to free cladribine and, hence, substantiate the interaction of cladribine with hydroxypropyl betadex [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Conclusion:

The results of the solubility studies demonstrate that cladribine shows an enhanced solubility and is stabilized in acidic solution when complexed by hydroxypropyl betadex. The formation of the impurity [redacted] is delayed by the complex formation.

[redacted]

1.4 Formulations used for Phase I Pharmacokinetic Studies

The [redacted] formulations developed, namely cladribine / cyclodextrin complex tablets ([redacted] mg and 10 mg), [redacted] The compositions of the [redacted] oral formulations used in the Phase I studies are presented in the tables below (see Table 6 through [redacted]).

Table 6 Composition of Cladribine / Hydroxypropyl Betadex Complex Tablet [redacted] mg (Batch N0120)

[redacted]

Table 7 **Composition of Cladribine / Hydroxypropyl Betadex Complex Tablet 10.0 mg (Batch N0126)**

Component	Formula (mg / Tablet)	Function
Cladribine	10.00	Active ingredient
Hydroxypropyl betadex	143.75	Solubility enhancer Stabilizing agent
Sorbitol	[redacted]	
Magnesium stearate		
Total Tablet Weight		-

[redacted]

1.5 Formulation Selected for Further Phase I/II/III Clinical Trials

Based on the results of the Phase I studies [redacted], the 10 mg cladribine / hydroxypropyl betadex complex tablet was selected for further Phase I/II/III clinical trials. The composition of the tablets applied for the Phase I/II/III clinical trials was identical to the 10 mg cladribine cyclodextrin tablet used for studies [redacted].

[redacted]

The Phase I/II/III clinical studies performed with the application of the 10 mg cladribine tablets are listed in Table 10.

Table 10 Cladribine Tablet Batches Used in Further Phase I/II/III Clinical Studies

Clinical Phase	Study Name	Clinical Batch No.
I	[redacted]	[redacted]
I	[redacted]	[redacted]
II	[redacted]	[redacted]
III	CLARITY – Efficacy & safety v. placebo, pivotal	[redacted]
III	[redacted]	[redacted]
III	[redacted]	[redacted]
III	CLARITY Extension – Safety, tolerability, and efficacy v. placebo	[redacted]
III	ORACLE – Efficacy and safety v. placebo	[redacted]

1.6 Commercial Formulation

To sustain a blend with [redacted], minor modifications of the formulation were made to obtain a process easily reproducible at a commercial scale. There was no change of the 14:1 w/w ratio between hydroxypropyl betadex and cladribine. [redacted]

[redacted]

[redacted]

Table 11 Composition of Cladribine 10 mg Tablets (Clinical versus Commercial Formulation)

Component	Clinical Formulation (mg / Tablet)	Commercial Formulation (mg / Tablet)	Function
Drug substance			
Cladribine	10.00	10.00	Active ingredient
Other ingredients			
Hydroxypropyl betadex (HPβCD)	143.76	143.76	Solubility enhancer Stabilizing agent
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Tablet Weight	[redacted]	[redacted]	

For batch N0126, the amount of hydroxypropyl betadex was 143.75 mg [redacted]

In addition, the shape of the tablet was modified [redacted]

[redacted]

1.6.1 Comparability of Commercial and Clinical Formulations

Prior to recommending the use of the optimized formulation for commercial use, a detailed comparability exercise was performed. The quantitative composition of the "clinical" 10 mg cladribine / hydroxypropyl betadex tablets is comparable with that of the optimized "commercial" final product. [redacted]

[redacted]

EXHIBIT J

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22561

NDA APPROVAL

EMD Serono, Inc.
Attention: Tammy Sarnelli, MPA
Head of Global Regulatory Affairs-Immunology and Neurology
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Sarnelli:

Please refer to your New Drug Application (NDA) dated May 30, 2018, received May 31, 2018, and your amendments, submitted under section 505(b)(1) Federal Food, Drug, and Cosmetic Act (FDCA) for Mavenclad (cladribine) tablets, 10 mg.

We also refer to your NDA originally submitted September 30, 2009; to our Complete Response letter dated February 28, 2011; and to your NDA withdrawal request dated August 19, 2011. Your NDA submission dated May 31, 2018, is considered a "resubmission after withdrawal" and responds to all of the items listed in our February 28, 2011, Complete Response letter.

This NDA provides for the use of Mavenclad (cladribine) tablets, 10 mg, for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

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The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on January 30, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 22561**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. The long-term risk of malignancies in adult subjects treated with cladribine is an unacceptable risk in pediatric patients.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of malignancy or assess a known serious risk of teratogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3592-1 Conduct an observational study to assess the long-term risk of malignancy for Mavenclad compared to other therapies used in the treatment of adults with relapsing forms of multiple sclerosis. Describe and justify the choice of appropriate comparator population(s) and estimated background rate(s) relative to

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cladribine-exposed patients; clearly define the primary comparator population. Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms. For the Mavenclad-exposed and comparator(s) cohorts, clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment.

The timetable you submitted on March 19, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2019
Final Protocol Submission:	09/2020
Study Completion:	02/2033
Final Report Submission:	02/2034

3592-2 Establish a worldwide Pregnancy Surveillance Program to collect and analyze information for a minimum of 10 years on pregnancy complications and birth outcomes in women exposed to Mavenclad during pregnancy. Provide a complete protocol which includes details regarding how you plan to encourage patients and providers to report pregnancy exposures (e.g., telephone contact number and/or website in prescribing information), measures to ensure complete data capture regarding pregnancy outcomes, and any adverse effects in offspring and plans for comprehensive data analysis and yearly reporting.

The timetable you submitted on March 21, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	08/2019
Final Protocol Submission:	09/2020
Annual Interim Report:	09/2021
	09/2022
	09/2023
	09/2024
	09/2025
	09/2026
	09/2027
	09/2028
	09/2029
	09/2030
Study Completion:	02/2031
Final Report Submission:	02/2032

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Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of a drug-drug interaction between Mavenclad and oral contraceptives.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trials:

3592-3 Conduct a clinical drug-drug interaction trial to evaluate the effect of cladribine on the pharmacokinetics (PK) of oral contraceptives. Include an evaluation of the effect on the components ethinyl estradiol (EE) and norelgestromin (NGMN).

The timetable you submitted on March 19, 2019, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	06/2019
Final Protocol Submission:	06/2020
Trial Completion:	08/2023
Final Report Submission:	08/2024

Submit clinical protocols to your IND 74634, with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocols for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required

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under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for malignancies, opportunistic infections, graft-versus-host disease with blood transfusion, liver injury, serious skin reactions, and acute cardiac failure after exposure to Mavenclad. We request that you provide expedited reports directly to the Division of Neurology Products. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)].

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information, Medication Guide, and Patient Package Insert (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Sandra Folkendt, Senior Regulatory Project Manager, at (240) 402-2804.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Prescribing Information
Medication Guide

Reference ID: 4410993

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIC P BASTINGS
03/29/2019 04:27:10 PM

EXHIBIT K

[redacted]

From: Folkendt, Sandra <Sandra.Folkendt@fda.hhs.gov>
Sent: Friday, March 29, 2019 4:42 PM
To: Tammy Sarnelli <tammy.sarnelli@emdserono.com>
Subject: NDA 22561 Action Letter

Hello Tammy,

Please find attached a courtesy copy of the action letter for NDA 22561. A hard copy will be provided by mail. Kindly confirm receipt of this message.

Have a nice weekend!
Sandy

Sandra Folkendt
Regulatory Health Project Manager

Center of Drug Evaluation and Research
Division of Neurology Products
U.S. Food and Drug Administration
Tel: 240 402-2804
Sandra.Folkendt@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

EXHIBIT L

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New Drug Application (NDA): 020229
Company: JANSSEN PHARMS

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Products on NDA 020229

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Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
LEUSTATIN	CLADRIBINE	1MG/ML **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	INJECTABLE;INJECTION	Discontinued	None	Yes	No

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 020229

Original Approvals or Tentative Approvals

CSV Excel Print

Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert	Notes
02/26/1993	ORIG-1	Approval	Type 1 - New Molecular Entity	STANDARD		Withdrawn FR Effective 11/03/2016 Label is not available on this site.

Showing 1 to 1 of 1 entries

Supplements

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Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert
08/02/2012	SUPPL-34		**Label (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020 Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/**
06/29/2006	SUPPL-30		**Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/**

Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert
08/22/2002	SUPPL-21		Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/
08/20/2002	SUPPL-7		Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/
08/20/2002	SUPPL-4		Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/

Showing 1 to 5 of 5 entries

Labels for NDA 020229

LEUSTATIN® (cladribine)
Injection
For Intravenous Infusion Only

WARNING

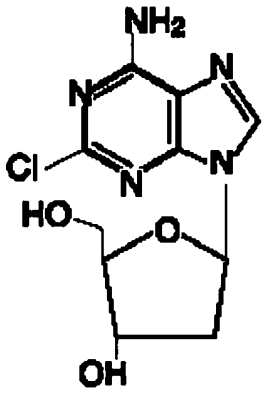
LEUSTATIN (cladribine) Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who received LEUSTATIN Injection by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Acute nephrotoxicity has been observed with high doses of LEUSTATIN (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.

DESCRIPTION

LEUSTATIN (cladribine) Injection (also commonly known as 2-chloro-2′-deoxy-β-D-adenosine) is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. LEUSTATIN Injection is available in single-use vials containing 10 mg (1 mg/mL) of cladribine, a chlorinated purine nucleoside analog. Each milliliter of LEUSTATIN Injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3±0.3.

The chemical name for cladribine is 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine and the structure is represented below:



cladribine MW 285.7

CLINICAL PHARMACOLOGY

Cellular Resistance and Sensitivity:

The selective toxicity of 2-chloro-2′-deoxy-β-D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2′-deoxy- β -D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2′-deoxy- β -D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2′-deoxy- β -D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2′-deoxy- β -D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2′-deoxy- β -D-adenosine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

Pharmacokinetics

In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of LEUSTATIN Injection (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with an estimated systemic clearance of 663.5 mL/h/kg when LEUSTATIN was given by continuous infusion over 7 days. In Hairy Cell Leukemia patients, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome.

In another study, 8 patients with hematologic malignancies received a two (2) hour infusion of LEUSTATIN Injection (0.12 mg/kg). The mean end-of-infusion plasma LEUSTATIN concentration was 48±19 ng/mL. For 5 of these patients, the disappearance of LEUSTATIN could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were 978±422 mL/h/kg and 4.5±2.8 L/kg, respectively.

Cladribine plasma concentration after intravenous administration declines multi-exponentially with an average half-life of 6.7 +/- 2.5 hours. In general, the apparent volume of distribution of cladribine is approximately 9 L/kg, indicating an extensive distribution in body tissues.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

LEUSTATIN is bound approximately 20% to plasma proteins.

Except for some understanding of the mechanism of cellular toxicity, no other information is available on the metabolism of LEUSTATIN in humans. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5-day continuous intravenous infusion of 3.5-8.1 mg/m^2/day of LEUSTATIN. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

CLINICAL STUDIES

Two single-center open label studies of LEUSTATIN (cladribine) have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 89 patients were treated with a single course of LEUSTATIN Injection given by continuous intravenous infusion for 7 days at a dose of

0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7-day continuous intravenous infusion of LEUSTATIN Injection at a comparable dose of 3.6 mg/m^2/day. A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the hemoglobin to 12 g/dL, platelet count to 100 x 10^9/L, and absolute neutrophil count to 1500 x 10^6/L. A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells remain in the bone marrow. A partial response (PR) required that hairy cells in the bone marrow be decreased by at least 50% from baseline and the same response for hematologic parameters as for complete response. A pathologic relapse was defined as an increase in bone marrow hairy cells to 25% of pretreatment levels. A clinical relapse was defined as the recurrence of cytopenias, specifically, decreases in hemoglobin $\geq$ 2 g/dL, ANC $\geq$ 25% or platelet counts $\geq$ 50,000. Patients who met the criteria for a complete response but subsequently were found to have evidence of bone marrow hairy cells (< 25% of pretreatment levels) were reclassified as partial responses and were not considered to be complete responses with relapse.

Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria described above, the complete response rates in patients treated with LEUSTATIN Injection were 65% and 68% for Study A and Study B, respectively, yielding a combined complete response rate of 66%. Overall response rates (i.e., Complete plus Good Partial plus Partial Responses) were 89% and 86% in Study A and Study B, respectively, for a combined overall response rate of 88% in evaluable patients treated with LEUSTATIN Injection.

Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and $\leq$ 13 cm on CT scan), the complete response rates for Study A and Study B were 54% and 53%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for Studies A and B, respectively, yielding a combined overall response rate of 89%.

RESPONSE RATES TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	CR	Overall
Evaluable Patients N=106	66%	88%
Intent-to-treat Population N=123	54%	89%

In these studies, 60% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving

LEUSTATIN as a first-line treatment. The remaining 40% of the patients received LEUSTATIN as a second-line treatment, having been treated previously with other agents, including α-interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 92%, compared with 84% for previously treated patients. LEUSTATIN is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to α-interferon.

OVERALL RESPONSE RATES (CR + GPR + PR) TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	OVERALL RESPONSE (N = 123)	NR + RELAPSE
No Prior Chemotherapy	68/74	6 + 4
	92%	14%
Any Prior Chemotherapy	41/49	8 + 3
	84%	22%
Previous Splenectomy	32/41*	9 + 1
	78%	24%
Previous Interferon	40/48	8 + 3
	83%	23%
Interferon Refractory	6/11*	5 + 2
	55%	64%
Previous Deoxycoformycin	3/6*	3 + 1
	50%	66%

NR = No Response
* $P < 0.05$

After a reversible decline, normalization of peripheral blood counts (Hemoglobin >12.0 g/dL, Platelets >100 x 10^9/L, Absolute Neutrophil Count (ANC) >1500 x 10^6/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 9 weeks from the start of treatment (Range: 2 to 72). The median time to normalization of Platelet Count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with complete response. Platelet recovery may be delayed in a minority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding LEUSTATIN therapy. (see also WARNINGS, PRECAUTIONS and ADVERSE REACTIONS)

LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA TIME TO NORMALIZATION OF PERIPHERAL BLOOD COUNTS

Parameter	Median Time to Normalization of Count*
Platelet Count	2 weeks
Absolute Neutrophil Count	5 weeks
Hemoglobin	8 weeks
ANC, Hemoglobin and Platelet Count	9 weeks

* Day 1 = First day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of data cut-off, the median duration of complete response was greater than 8 months and ranged to 25+ months. Among 93 responding patients, seven had shown evidence of disease progression at the time of the data cut-off. In four of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in three patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of LEUSTATIN received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

INDICATIONS FOR USE

LEUSTATIN Injection is indicated for the treatment of active Hairy Cell Leukemia as defined by clinically significant anemia, neutropenia, thrombocytopenia or disease-related symptoms.

CONTRAINDICATIONS

LEUSTATIN Injection is contraindicated in those patients who are hypersensitive to this drug or any of its components.

WARNINGS

Due to increased risk of infection in the setting of immunosuppression with chemotherapy including LEUSTATIN, it is recommended not to administer live attenuated vaccines to patients receiving LEUSTATIN Injection.

Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with LEUSTATIN, especially at high doses. At initiation of treatment, most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell

Leukemia. Following treatment with LEUSTATIN, further hematologic impairment occurred before recovery of peripheral blood counts began. During the first two weeks after treatment initiation, mean Platelet Count, ANC, and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 5 and Week 8, respectively. The myelosuppressive effects of LEUSTATIN were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTATIN Injection, is recommended (see PRECAUTIONS).

Fever ($T \geq 100°F$) was associated with the use of LEUSTATIN in approximately two-thirds of patients (131/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics. Overall, 47% (93/196) of all patients had fever in the setting of neutropenia (ANC $\leq$ 1000), including 62 patients (32%) with severe neutropenia (i.e., ANC $\leq$ 500).

In a Phase I investigational study using LEUSTATIN in high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. Thirty-one (31) poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins Lymphoma (2 cases) received LEUSTATIN for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with LEUSTATIN, 6 patients (19%) developed manifestations of renal dysfunction (e.g., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven (11) patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadriparesis) of the upper and/or lower extremities, first noted 35 to 84 days after starting high dose therapy with LEUSTATIN. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease. Severe neurologic toxicity has also been noted with high doses of another drug in this class.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

In patients with Hairy Cell Leukemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of nephrologic toxicities.

Serious (e.g. respiratory infection, pneumonia and viral skin infections), including fatal infections (e.g. sepsis) were reported (see ADVERSE REACTIONS).

Of the 196 Hairy Cell Leukemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following LEUSTATIN therapy. Of the 8 deaths, 6 occurred in previously treated patients who were refractory to α interferon.

Benzyl alcohol is a constituent of the recommended diluent for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. (see DOSAGE AND ADMINISTRATION)

Pregnancy Category D:

LEUSTATIN can cause fetal harm when administered to a pregnant woman. Although there is no evidence of teratogenicity in humans due to LEUSTATIN, other drugs which inhibit DNA synthesis have been reported to be teratogenic in humans. Cladribine is teratogenic in animals. Advise females of reproductive potential to use highly effective contraception during treatment with LEUSTATIN. If LEUSTATIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m^2) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3.0 mg/kg/day (9 mg/m^2). Fetal death and malformations were observed in rabbits that received 3.0 mg/kg/day (33.0 mg/m^2). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m^2) or in rabbits at 1.0 mg/kg/day (11.0 mg/m^2).

PRECAUTIONS

General:

LEUSTATIN Injection is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment of peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g., infection or bleeding). As with other potent chemotherapeutic agents, monitoring of renal and hepatic function is also recommended, especially in patients with underlying kidney or liver dysfunction (see WARNINGS and ADVERSE REACTIONS).

Fever was a frequently observed side effect during the first month on study. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated. Although 69% of patients developed fevers, less than 1/3 of febrile events were associated with documented infection. Given the known myelosuppressive effects of LEUSTATIN, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections (see WARNINGS and ADVERSE REACTIONS).

There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of LEUSTATIN has been described. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency (see WARNINGS).

Rare cases of tumor lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden.

LEUSTATIN Injection must be diluted in designated intravenous solutions prior to administration (see DOSAGE AND ADMINISTRATION).

Laboratory Tests:

During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached 100 x 10^9/L by Day 12, the mean Absolute Neutrophil Count reached 1500 x 10^6/L by Week 5 and the mean Hemoglobin reached 12 g/dL by Week 8.

After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTATIN. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

Drug Interactions:

There are no known drug interactions with LEUSTATIN Injection. Caution should be exercised if LEUSTATIN Injection is administered before, after, or in conjunction with other drugs known to cause immunosuppression or myelosuppression. (see WARNINGS)

Carcinogenesis:

No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

Mutagenesis:

As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test).

Impairment of Fertility:

The effect on human fertility is unknown. When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells.

Pregnancy:

Pregnancy Category D: (see WARNINGS).

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving patients 1-21 years old with relapsed acute leukemia, LEUSTATIN was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m^2/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m^2/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study [(1)] (see WARNINGS and ADVERSE REACTIONS).

Geriatric Use

Clinical studies of LEUSTATIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients.

ADVERSE REACTIONS

Clinical Trials Experience

Adverse drug reactions reported by ≥ 1% of LEUSTATIN-treated patients with HCL noted in the HCL clinical dataset (studies K90-091 and L91-048, n=576) are shown in the table below.

Adverse Drug Reactions in ≥ 1% of Patients Treated With LEUSTATIN in HCL Clinical Trials	
System Organ Class Preferred Term	**LEUSTATIN (n=576)** **%**
Blood and Lymphatic System Disorder (see also sections WARNINGS and PRECAUTIONS)	
Anemia	1
Febrile neutropenia	8
Psychiatric Disorders	
Anxiety	1
Insomnia	3
Nervous System Disorders	
Dizziness	6
Headache	14
Cardiac Disorders	
Tachycardia	2
Respiratory, Thoracic and Mediastinal Disorders	
Breath sounds abnormal	4
Cough	7
Dyspnea*	5
Rales	1
Gastrointestinal Disorders	
Abdominal pain**	4

Constipation	4
Diarrhea	7
Flatulence	1
Nausea	22
Vomiting	9
Skin and Subcutaneous Tissue Disorders	
Ecchymosis	2
Hyperhidrosis	3
Petechiae	2
Pruritus	2
Rash***	16
Musculoskeletal, Connective Tissue, and Bone Disorders	
Arthralgia	3
Myalgia	6
Pain****	6
General Disorders and Administration Site Conditions (see also sections WARNINGS and PRECAUTIONS)	
Administration site reaction*****	11
Asthenia	6
Chills	2
Decreased appetite	8
Fatigue	31
Malaise	5
Muscular weakness	1
Edema peripheral	2
Pyrexia	33
Injury, Poisoning and Procedural Complications	
Contusion	1

* Dyspnea includes dyspnea, dyspnea exertional, and wheezing
** Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain (lower and upper)
*** Rash includes erythema, rash, and rash (macular, macula-papular, papular, pruritic, pustular and erythematous)
**** Pain includes pain, back pain, chest pain, arthritis pain, bone pain, and pain in extremity
***** Administration site reaction includes administration site reaction, catheter site (cellulitis, erythema, hemorrhage, and pain), and infusion site reaction(erythema, edema, and pain)

The following safety data are based on 196 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus an additional 72 patients enrolled at the same two centers after the original enrollment cutoff. In Month 1 of the Hairy Cell Leukemia clinical trials, severe neutropenia was noted in 70% of patients, fever in 69%, and infection was documented in 28%. Most non-hematologic adverse experiences were mild to moderate in severity.

Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC < 500 x 10^6/L) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (Hemoglobin < 8.5 g/dL) developed in 37% of patients, compared with 10% initially and thrombocytopenia (Platelets < 20 x 10^9/L) developed in 12% of patients, compared to 4% in whom it was noted initially.

During the first month, 54 of 196 patients (28%) exhibited documented evidence of infection. Serious infections (e.g., septicemia, pneumonia) were reported in 6% of all

patients; the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 6%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding LEUSTATIN therapy.

During the first month, 11% of patients experienced severe fever (i.e., ≥104°F). Documented infections were noted in fewer than one-third of febrile episodes. Of the 196 patients studied, 19 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven (7) of 8 documented episodes of herpes zoster occurred during the month following treatment. Fourteen (14) of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics. (see WARNINGS and PRECAUTIONS)

Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts. Prior to treatment, the mean CD4 count was 766/μL. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/μL. Fifteen (15) months after treatment, mean CD4 counts remained below 500/μL. CD8 counts behaved similarly, though increasing counts were observed after 9 months. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow cellularity of < 35% was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as day 1010. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

The vast majority of rashes were mild. Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine.

When used in other clinical settings the following ADRs were reported: bacteremia, cellulitis, localized infection, pneumonia, anemia, thrombocytopenia (with bleeding or petechiae), phlebitis, purpura, crepitations, localized edema and edema.

For a description of adverse reactions associated with use of high doses in non-Hairy Cell Leukemia patients, see WARNINGS.

Postmarketing Experience

The following additional adverse reactions have been reported since the drug became commercially available. These adverse reactions have been reported primarily in patients who received multiple courses of LEUSTATIN Injection:

Infections and infestations: Septic shock. Opportunistic infections have occurred in the acute phase of treatment.

Blood and lymphatic system disorders: Bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; hemolytic anemia (including autoimmune hemolytic anemia), which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment. Rare cases of myelodysplastic syndrome have been reported.

Immune system disorders: Hypersensitivity.

Metabolism and nutrition disorders: Tumor lysis syndrome.

Psychiatric disorders: Confusion (including disorientation).

Hepatobiliary disorders: Reversible, generally mild increases in bilirubin (uncommon) and transaminases.

Nervous System disorders: Depressed level of consciousness, neurological toxicity (including peripheral sensory neuropathy, motor neuropathy (paralysis), polyneuropathy, paraparesis); however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Eye disorders: Conjunctivitis.

Respiratory, thoracic and mediastinal disorders: Pulmonary interstitial infiltrates (including lung infiltration, interstitial lung disease, pneumonitis and pulmonary fibrosis); in most cases, an infectious etiology was identified.

Skin and tissue disorders: Urticaria, hypereosinophilia; Stevens-Johnson. In isolated cases toxic epidermal necrolysis has been reported in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause these syndromes.

Renal and urinary disorders: Renal failure (including renal failure acute, renal impairment).

OVERDOSAGE

High doses of LEUSTATIN have been associated with: irreversible neurologic toxicity (paraparesis/quadriparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia (see WARNINGS). There is no known specific antidote to overdosage. Treatment of overdosage consists of discontinuation of LEUSTATIN, careful observation and appropriate supportive measures. It is not known whether the drug can be removed from the circulation by dialysis or hemofiltration.

DOSAGE AND ADMINISTRATION

Usual Dose:

The recommended dose and schedule of LEUSTATIN Injection for active Hairy Cell Leukemia is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of LEUSTATIN Injection for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs (see WARNINGS).

Specific risk factors predisposing to increased toxicity from LEUSTATIN have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic and non-hematologic toxicity (see WARNINGS and PRECAUTIONS).

Preparation and Administration of Intravenous Solutions:

LEUSTATIN Injection must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, **aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN Injection solutions.**

To prepare a single daily dose:

LEUSTATIN Injection should be passed through a sterile 0.22μm disposable hydrophilic syringe filter prior to introduction into the infusion bag, prior to each daily infusion. Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of LEUSTATIN Injection through the sterile filter to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days. **The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.** Admixtures of

LEUSTATIN Injection are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex®† PVC infusion containers. **Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.**

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
24-hour infusion method	1(day) x 0.09 mg/kg	0.9% Sodium Chloride Injection, USP	500 mL

To prepare a 7-day infusion:

The 7-day infusion solution should only be prepared with Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved). In order to minimize the risk of microbial contamination, both LEUSTATIN Injection and the diluent should be passed through a sterile 0.22 μm disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of LEUSTATIN Injection (7 days x 0.09 mg/kg or mL/kg) to the infusion reservoir through the sterile filter.

Then add a calculated amount of Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved) also through the filter to bring the total volume of the solution to 100 mL. After completing solution preparation, clamp off the line, disconnect and discard the filter. Aseptically aspirate air bubbles from the reservoir as necessary using the syringe and a dry second sterile filter or a sterile vent filter assembly. Reclamp the line and discard the syringe and filter assembly. Infuse continuously over 7 days. Solutions prepared with Bacteriostatic Sodium Chloride Injection for individuals weighing more than 85 kg may have reduced preservative effectiveness due to greater dilution of the benzyl alcohol preservative. Admixtures for the 7-day infusion have demonstrated acceptable chemical and physical stability for at least 7 days in the SIMS Deltec MEDICATION CASSETTE™ Reservoir‡.

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
7-day infusion method (use sterile 0.22μ filter when preparing infusion solution)	7 (days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol)	q.s. to 100 mL

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing LEUSTATIN Injection should not be mixed with other intravenous drugs or additives or infused

simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates (see WARNINGS).

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to start of administration. Vials of LEUSTATIN Injection are for single-use only. Any unused portion should be discarded in an appropriate manner (see Handling and Disposal).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN Injection to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

Chemical Stability of Vials:

When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of LEUSTATIN Injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of LEUSTATIN Injection is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to administration.

Handling and Disposal:

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN Injection. The use of disposable gloves and protective garments is recommended. If LEUSTATIN Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your Institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

HOW SUPPLIED

LEUSTATIN Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine as 10 mL filled into a single-use clear flint

glass 20 mL vial. LEUSTATIN Injection is supplied in 10 mL (1 mg/mL) single-use vials (NDC 59676-201-01) available in a treatment set (case) of seven vials.

Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

REFERENCES:

1. Santana VM, Mirro J, Harwood FC, *et al*: A phase I clinical trial of 2-Chloro-deoxyadenosine in pediatric patients with acute leukemia. J. Clin. Onc., **9**: 416 (1991).

2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402.

3. AMA Council Report. Guidelines for Handling Parenteral Antineoplastics, JAMA, March 15 (1985).

4. National Study Commission on Cytotoxic Exposure--Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents, Med. J. Australia **1**:425 (1983).

6. Jones RB, *et al.* Safe Handling of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. Ca--A Cancer Journal for Clinicians, Sept/Oct. 258-263 (1983).

7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic Drugs in Hospitals. Am. J. Hosp. Pharm., **42**:131 (1985).

8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (antineoplastic) Drugs. Am. J. Hosp. Pharm., **43**:1193 (1986).

† Viaflex® containers, manufactured by Baxter Healthcare Corporation - Code No. 2B8013 (tested in 1991)

‡ MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 602100A (tested in 1991)

Centocor Ortho Biotech Products, L.P. [new code]
Raritan, NJ 08869 Revised July 2012

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EXHIBIT M

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT CORRESPONDENCE ADDRESS	CUSTOMER #	ENTITY STATUS	STATEMENT GENERATED
SALIWANCHIK, LLOYD & EISENSCHENK A PROFESSIONAL ASSOCIATION PO BOX 142950 GAINESVILLE, US 32614	23557	UNDISCOUNTED	05/19/2019 17:50:15

Invention

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
7713947	11722018	06/18/2007	05/11/2010

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
10/16/2013	10/17/2013	101713RAMBULKS00007497504623	MERCK SERONO S.A.	$1,600.00

Fee Code	Description	Sale ID	Fee Amount
1551	MAINTENANCE FEE DUE AT 3.5 YEARS	101713RAMBULKS00007497	$1,600.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

EXHIBIT N

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT CORRESPONDENCE ADDRESS	CUSTOMER #	ENTITY STATUS	STATEMENT GENERATED
SALIWANCHIK, LLOYD & EISENSCHENK A PROFESSIONAL ASSOCIATION PO BOX 142950 GAINESVILLE, US 32614	23557	UNDISCOUNTED	05/19/2019 17:50:17

Invention

CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
7713947	11722018	06/18/2007	05/11/2010

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
10/26/2017	10/26/2017	102617INTMTFEE00008419504623		$3,600.00

Fee Code	Description	Sale ID	Fee Amount
1552	MAINTENANCE FEE DUE AT 7.5 YEARS	102617INTMTFEE00008419	$3,600.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

EXHIBIT O

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 74,634

Serono, Inc.
Attention: Pamela Williamson Joyce, RAC
Vice President, Regulatory Affairs and Quality Assurance
One Technology Place
Rockland, MA 02370

Dear Ms. Williamson Joyce:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	74,634
Sponsor:	Serono, Inc.
Name of Drug:	Cladribine, oral
Date of Submission:	March 10, 2006
Date of Receipt:	March 13, 2006

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, on or before April 12, 2006, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies, we will notify you immediately that (1) clinical studies may not be initiated under this IND ("clinical hold") or that (2) certain restrictions apply to clinical studies under this IND ("partial clinical hold"). In the event of such notification, you must not initiate or you must restrict such studies until you have submitted information to correct the deficiencies, and we have notified you that the information you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if the drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call James H. Reese, Ph.D., Regulatory Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Supervisory Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robbin Nighswander
4/5/2006 01:46:37 PM

EXHIBIT P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-561

NDA ACKNOWLEDGMENT

EMD Serono, Inc.
Attention: Jill P. Hillier, Ph.D.
Director, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Dr. Hillier:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Cladribine, oral

Date of Application: September 29, 2009

Date of Receipt: September 30, 2009

Our Reference Number: NDA 22-561

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 30, 2009, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm

If you have any questions, call James H. Reese, Ph.D., RAC, Senior Regulatory Health Project Manager, at 301-796-1136.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22561	ORIG-1	EMD SERONO INC	CLADRIBINE

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/s/

RUSSELL G KATZ
10/13/2009

EXHIBIT Q

DEPARTMENT OF HEALTH AND HUMAN SERVICES

RECEIVED

Food and Drug Administration
Silver Spring MD 20993

AUG 25 2011

NDA 022561

REGULATORY AFFAIRS

ACKNOWLEDGE REQUEST TO WITHDRAW PENDING NDA

EMD Serono, Inc.
Attention: Peter DiRoma
Vice President, Global Regulatory Affairs
One Technology Place
Rockland, MA 02370

Dear Mr. DiRoma:

We have received your August 19, 2011, correspondence on August 19, 2011, notifying us that you are withdrawing your new drug application (NDA) for cladribine tablets.

This application was filed on July 27, 2010.

In accordance with 21 CFR 314.65, this application is withdrawn as of August 19, 2011. If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission.

In addition, the resubmitted application should address the deficiencies identified in our February 28, 2011, complete response letter.

If you have any questions, call LCDR Hamet Touré, Regulatory Project Manager at (301) 796-7534.

Sincerely,

{See appended electronic signature page}

Russell Katz, M. D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
08/22/2011

EXHIBIT R

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22561

NDA ACKNOWLEDGMENT

EMD Serono R&D Institute, Inc.
Attention: Lynne Baron, MS, MBA
Sr. Manager, Global and Regulatory Affairs
45A Middlesex Turnpike
Billerica, MA 01821

Dear Ms. Baron:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug: Mavenclad (cladribine) 10 mg, tablet

Date of Application: May 31, 2018

Date of Receipt: May 31, 2018

Our Reference Number: NDA 22561

We note that this application has the following regulatory history:

- originally submitted on September 30, 2009,
- resubmitted May 28, 2010,
- received a Complete Response letter on February 28, 2011, and
- withdrawn on August 19, 2011.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 30, 2018, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

Reference ID: 4277314

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

If you have any questions, please call me at (240) 402-2804.

Sincerely,

{See appended electronic signature page}

Sandra Folkendt
Regulatory Health Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Reference ID: 4277314

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA N FOLKENDT
06/13/2018

Reference ID: 4277314

EXHIBIT S

IND #74,634
Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
000	Original IND	3/10/06
001	Information Amendment	4/10/06
002	Protocol Amendment: New investigator	4/17/06
003	Type B Meeting Summary	5/4/06
004	Protocol Amendment: New Investigators	5/10/06
005	Safety Report 510002E06TUN	6/7/06
006	New Investigators Protocol Amendment	6/14/06
007	Fast Track Application	6/30/06
008	Follow Up #1 for 15 Day Alert Report of 510002E06TUN	7/5/06
009	New Investigators: Protocol Amendment	7/17/06
010	Information Amendment: Pharm / Tox	7/29/06
011	Follow Up #2 to 15 Day Alert Report of 510002E06TUN	7/26/06
012	F/U # 3 to 15 Day Alert Report of 510002E05TUN	8/3/06
013	Response to request for Information	8/9/06
014	Revised Investigator Brochure	8/9/06
015	Response to Request for Information – Pancytopenia	8/22/06
016	Response to Request for Information – Pharmacology & Toxicology	8/22/06
017	Protocol Amendment: New Investigator	8/23/06
018	Response to non-clinical request of August 10, 2006	8/24/06
019	F/U# 5 510002E06TUN	9/13/06

IND #74,634
Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
020	Protocol Amendment & Response to request	9/18/06
021	Protocol Amendment: Revised 1572	9/19/06
022	15 Day Alert Report 51002E06DEU	9/21/06
023	New Protocol 26593 cross reference 5371 (SN298)	9/26/06
024	Protocol Amendment	10/12/06
025	F/U#5 to 510002E06TUN	10/25/06
026	Response to Request : Non-Clinical Report	10/27/06
027	F/U#6 to 15 Day Alert report of 510002E06TUN	11/10/06
028	F/U#7 to 15 Day Alert Report of 510002E06TUN	11/20/06
029	Information Amendment: CMC	11/21/06
030	Protocol Amendment: New Investigators	11/28/06
031	15 Day Alert Report of 510002E06TUN	12/7/06
032	Response to Request for Information	12/18/06
033	Protocol Amendment: New Investigators	12/20/06
034	Protocol Amendment: New Investigators	1/17/07
035	Initial 15 Day Alert Report for 510001E07CHE	1/24/07
036	15 Day Alert report 510001E07CAN	1/31/07
037	15 Day Alert Report 510001E07DEU (Correction see 189 in IND 45,033)	1/16/07
038	F/U 15 Day Alert Report 510001E07DEU	2/8/07
039	Response to Request for Info.	2/9/07

IND #74,634
Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
040	Initial Safety Report 510001E06GBR	2/9/07
041	Initial Safety Report 510001E07ITA	2/13/07
042	Company Name Change notification	2/20/07
043	F/U#1 to 15 Day 510001E07CHE	2/16/07
044	New Investigators Cross reference BB-IND 5371	2/26/07
045	Initial 510001E07PUN	3/5/07
046	Initial 510001E06DEU	3/14/07
047	Protocol Amendment: New Investigators BB-IND 5371	3/22/07
048	Initial Report 510001E07FIN	4/9/07
049	Change in Protocol Amendment: 25643	4/23/07
050	Initial 510001E07SVK	4/27/07
051	Initial 510001E07FIN #1	4/27/07
052	F/U#2 to 510001E07DEU	5/1/07
053	Protocol Amendment: New Investigators 26593	5/4/07
054	Protocol Amendment: Revised 1572 for 25643	5/7/07
055	Initial 15 Day 510004E07CAN	5/10/07
056	F/U #1 to 15 Day 510001E07SVK	5/11/07
057	F/U#2 to 15 Day 510001E07CHE	5/16/07
058	F/U#1 to 15 Day 510001E07TUN	5/18/07
059	Protocol Amendment: New Investigator 26593	5/23/07

IND #74,634
Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
060	Response to Request for Information	5/24/07
061	F/U#1 to 15 day Alert Report 510004E07CAN	5/24/07
062	Annual Report	6/11/07
063	F/U #1 to 15 Day Alert report 510001E07ITA	6/12/07
064	Initial 15 Day Alert Report 51006E07CAN	6/19/07
065	F/U#2 to 15 Day Alert Report of 510001E07SVK	6/25/07
066	Protocol Amendment 25643: Revised 1572	6/26/07
067	Protocol Amendment: New Investigator 26593	6/29/07
068	F/U#3 to 15 Day Alert Report 510001E07DEU	7/5/07
069	F/U#2 to 15 Day Alert Report 510001E07FIN	7/6/07
070	F/U#2 to 15 Day Alert Report 510001E07TUN	7/17/07
071	Initial 15 Day Alert Report 510004E07USA	7/20/07
072	Response to Request for Information	7/26/07
073	Information Amendment: CMC	7/31/07
074	F/U#2 to 510004E07CAN	8/1/07
075	Information Amendment: New Protocol 27820	8/6/07
076	F/U#1 to 510004E07USA	8/10/07
077	F/U#3 to 510001E07FIN	8/20/07
078	Protocol Amendment: New Investigator 26593	8/20/07
079	Initial 510005E07USA	9/7/07

IND #74,634
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SER – SEQ NO	CONTENT	DATE
080	Protocol Amendment: 26593	9/25/07
081	Revised Investigator Brochure	9/27/07
082	Protocol Amendment: Revised 1572	9/28/07
083	F/U#1 to 510005E07USA	10/11/07
084	Initial 510004E07DEU	10/23/07
085	Initial 510007E07CAN	10/30/07
086	F/U#1 510004E07DEU	11/7/07
087	F/U#1 to 510007E07CAN	11/13/07
088	F/U#2 to 510004E07DEU	11/20/07
089	Initial 510010E07RUS	11/21/07
090	F/U#2 to 510007E07CAN	11/28/07
091	F/U#3 to 510004E07DEU	12/1/07
092	Cross Reference to 5371 # 26593	12/12/07
093	Response to Request for Information	12/14/07
094	Proposal for Carcinogencity Study	12/14/07
095	Information Clinical Safety Update for 26593	12/20/07
096	Initial 510003E07CHE	12/21/07
097	F/U#4 to 510004E07DEU	12/21/07
098	Protocol amendment: Revised 1572	12/21/07
099	Initial 510002E07GBR	1/3/08

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100	F/U#3 to 510001E07CHE	1/7/08
101	Information Amendment: CMC	1/25/08
102	Clinical Safety : Safety Issue Report II	1/31/08
103	Response to Request	2/7/08
104	F/U#4 to 510001E07FIN	2/20/08
105	F/U#9 510002E06TUN	2/25/08
106	F/U#1 to 510002E07GBR	3/3/08
107	Initial 510002E08GBR	3/25/08
108	F/U#1 to 510002E07CHE	3/25/08
109	Protocol Amendment: New Investigator	3/31/08
110	Protocol Amendment: New Investigator	4/18/08
111	Initial 510001E08POL	4/23/08
112	F/U#1 to 510001E08POL	5/7/08
113	Protocol Amendment # 26593	5/12/08
114	Initial 510005E08USA	6/4/08
115	Response to Request for Information	6/9/08
116	Annual Report	6/11/08
117	F/U#1 to 510005E08USA	6/12/08
118	F/U#1 to 510001E06DEU	6/24/08
119	Protocol Amendment	6/25/08

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120	Initial 510001E08TUN	7/3/08
121	F/U#1 to 510010E07RUS	7/9/08
122	F/U#2 to 510004E07USA	7/15/08
123	CMC Amendment	7/28/08
124	New Protocol 28821	7/31/08
125	New Investigators 27820	8/5/08
126	Initial 510003E08RUS	9/8/08
127	F/U#5 to 510001E07FIN	9/16/08
128	Revised Informed Consent Form 28821	9/22/08
129	New Investigator	9/24/08
130	Revised Investigators Brochure Ed. #6	9/29/08
131	F/U#1 to 510003E08RUS	9/30/08
132	Amendment #9 25643	10/8/08
133	F/U#1 to 510002E06DEU	10/14/08
134	F/U#2 & F/U#3	10/17/08
135	Amendment to CMC Amendment	10/22/08
136	Protocol Amendment: New Investigator	10/22/08
137	Initial 510012E07RUS	10/24/08
138	New Investigators 27820	11/11/08
139	F/U#1 to 510001E07CAN	11/12/08

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140	F/U#2 to 510005E08USA	11/13/08
141	General Correspondence	11/18/08
142	F/U#1 to 510001E08TUN & F/U#4 to 510004E07USA	11/18/08
143	Initial 510001E08EST	11/19/08
144	Information Amendment: SAP	11/20/08
145	Information Amendment: Trade Name Review	11/20/08
146	F/U#1 to 510006E07CAN	11/21/08
147	Initial 510004E08RUS	11/25/08
148	F/U#3 to 51000E07CAN	11/26/08
149	F/U#1 to 510001E08EST	12/5/08
150	F/U#2 to 510003E08RUS	12/8/08
151	F/U#1 to 510002E08GBR	12/9/08
152	F/U#3 to 510007E07CAN	12/10/08
153	New Investigators Protocol 26593	12/12/08
154	F/U#2 to 510001E08EST	12/16/08
155	F/U#10 510003E06TUN	12/17/08
156	F/U#5 and Initial	12/18/08
157	New Investigators 28821	12/19/08
158	F/U#11 to 510002E06TUN	12/23/08
159	F/U #1 510004E08RUS	1/2/09

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160	New Investigator 26593	1/16/09
161	New Investigator 28821	1/16/09
162	F/U#1 to 510006E08RUS	2/6/09
163	Request for Type B Pre-NDA Mtg	2/17/09
164	Request for Proprietary Name Review	2/18/09
165	CMC Amendment	2/20/09
166	New Investigators 28821	2/23/09
167	New Investigators 26593	2/23/09
168	F/U#3 to 510006E08RUS	2/23/09
169	Initial 510001E09SRB	3/3/09
170	F/U#3 to 510006E08RUS	3/17/09
171	F/U#2 to 510001E07ITA	3/18/09
172	Request for Proprietary Name review	3/18/09
173	Initial 510001E07GRC, F/U#1 to 510001E09SRB	3/19/09
174	F/U#3 to 510001E06DEU, F/U#5 to 510004E07DEU	3/25/09
175	New Inv. 28821	3/30/09
176	New Inv. 27820	3/30/09
177	Protocol Amendment #3 to ONWARD Study 26593	4/6/09
178	Pre-NDA Briefing Document	4/9/09
179	F/U#1 to 510012E07RUS	4/15/09

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180	Protocol Amendment #2 CLARITY Ext 27820	4/21/09
181	F/U#1 to 510001E07GRC	4/24/09
182	New Investigator 28821	4/24/09
183	F/U#2 to 510001E09SRB	5/5/09
184	Initial 510001E09CAN	5/12/09
185	F/U#2 to 510005E07USA	5/15/09
186	New Investigator 28821 Oracle	5/20/09
187	F/U#1 to 510001E09CAN	5/21/09
188	F/U#3 to 510005E08USA	5/26/09
189	Initial 51002E09CAN	5/27/09
190	Initial 510001E09RUS	6/1/09
191	F/U#3 to 510001E07ITA, F/U#2 to 51000E07GRC, Initial 510003E09SRB	6/4/09
192	F/U#1 to 510001E09RUS	6/8/09
193	F/U#1 to 510002E09CAN	6/9/09
194	Annual Report	6/11/09
195	CMC Amendment: 48 Months Shelf Life Ext	6/17/09
196	F/U#1 to 510003E09SRB	6/17/09
197	F/U#2 to 510003E09CAN, F/U#1 to 510001E09RUS	6/18/09
198	New Investigator 28821	6/22/09
199	F/U#3 to 510005E07USA	6/26/09

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200	Response to Request for Information	6/30/09
201	Initial 510002E09RUS	7/1/09
202	New Protocol : Clinical Safety registry	7/6/09
203	Initial 510004E09USA	7/7/09
204	Initial 510003E09USA	7/15/09
205	F/U#4 510006E08RUS	7/17/09
206	Request for Safety Mtg Risk Evaluation	7/17/09
207	F/U#2 to 510001E09CAN	7/22/09
208	Initial 510002E09ESP	7/28/09
209	Initial 510004E09RUS	7/29/09
210	New Investigators for 28821	7/31/09
211	Questions for Mtg Request	7/31/09
212	F/U#1 to 510003E09USA	8/3/09
213	Initial 510001E09ESP	8/10/09
214	F/U#1 to 510007E07CAN and Initial 510003E09CAN	8/11/09
215	F/U#1 to 510004E09RUS	8/12/09
216	F/U#1 to 510002E09RUS	8/14/09
217	New Investigators for Protocol 28821	8/18/09
218	F/U#1 to 510004E09USA	8/18/09
219	F/U#2 to 510004E09RUS	8/19/09

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220	Request for Pediatric Waiver	8/21/09
221	F/U#2 510004E09USA	8/24/09
222	F/U#3's 510001E09CAN & 510001E09SRB F/U#1 to 510002E09ESP	8/25/09
223	F/U#2 to 51000E09SRB	8/26/09
224	F/U#2 to 510004E09USA	9/1/09
225	New Investigators-Waiver Sweden/Norway	9/17/09
226	F/U#1 510001E09RUS	9/23/09
227	Response to Request for Information - 28821	10/6/09
228	F/U#2 to 510001E09ESP	10/8/09
229	F/U#5 to 510006E08RUS	10/14/09
230	Initial 510003E09FRA F/U#4 to 510004E09USA	11/4/09
231	FU 5 510004E09USA	11-12-09
232	INIT 510009E09RUS	11-18-09
233	INIT 510001E09GBR	11-23-09
234	NEW INV PROT 28821	11-30-09
235	INIT 510010E09RUS	12-9-09
236	FU 1 510001E09GBR INIT 510004E09CAN	12-16-09
237	FU 2 510006E07CAN	12-17-09
238	FU 1 510010E09RUS	12-22-09
239	FU 2 510010E09RUS	1-7-10

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240	FU 1 510003E09FRA	1-14-10
241	FU 6 510004E09USA	1-14-10
242	INIT 510001E10DEU	1-19-10
243	FU 3 510004E09RUS	1-22-10
244	INIT 510001E10USA FU 1 510004E09CAN	1-26-10
245	FU 3 510010E09RUS	1-29-10
246	FU 1 510001E10DEU INIT 510001E10RUS	2-2-10
247	FU 2 510001E09GBR	2-5-10
248	ORACLE 28821 AMEND 3	2-9-10
249	FU 1 510009E09RUS	2-9-10
250	F/U #7 510004E09USA	02/11/10
251	Investigators Brochure – Ed. 7	02/12/10
252	F/U 1 510001E10RUS	2-24-10
253	F/U 2 510001E10DEU	3-1-10
254	F/U 1 510003E09CAN	3-5-10
255	510003E10MAR INITIAL	3-12-10
256	Protocol Amendment 3 Replacement	3-16-10
257	F/U 5 510007E07CAN F/U 8 510004E09USA	3-17-10
258	F/U 2 510004E09CAN F/U 9 510004E09USA	3-22-10
259	F/U 3 5190001E10DEU Initial 510005E10USA	3-25-10

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SER – SEQ NO	CONTENT	DATE
260	Initial 510006E10USA	3-26-10
261	Request for Rolling Submission	3-26-10
262	Oracle 28821 New Investigators	3-26-10
263	Initial 510012E09RUS	4-01-10
264	F/U #10 510004E09USA	4-08-10
265	F/U #2 510009E09RUS	4-09-10
266	Protocol Amendment 4 – 28821	4-20-10
267	F/U #3 510001E09GBR	4-21-10
268	F/U#2 510003E09CAN, F/U#3 510003E09SRB F/U #11 510004E09USA	4-30-10
269	Initial 7002393	5-5-10
270	F/U #5 510003E09CAN	5-12-10
271	Initial 7004670	5-14-10
272	F/U #1 510001E10USA	5-18-10
273	Initial 7005088	5-27-10
274	Initial 7006418	6-3-10
275	F/U #1 7002393	6-7-10
276	Annual Report	6-11-10
277	F/U #1 70064818	6-14-10
278	F/U #2 7006418	6-17-10
279	F/U #3 7006418	6-21-10

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280	F/U #4 7006418 F/U #1 510006E10USA	6-22-10
281	F/U #5 7006418	6-28-10
282	F/U #1 510003E10MAR	7-5-10
283	Clarity Ext. Amendment 3	7-9-10
284	F/U #2 510003E10MAR	7-15-10
285	Initial 510003E09LBN	7-19-10
286	F/U #6 7006418	7-26-10
287	F/U #7 7006418	7-30-10
288	F/U #1 510005E10USA	8-9-10
289	F/U #1 7004670 F/U #12 510004E09USA	8-12-10
290	SAP for Protocol 27820 Amendment 3	8-16-10
291	Initial 7013214 Initial 7013215	8-17-10
292	F/U #1 510003E09LBN F/U #1 7005088	8-18-10
293	F/U #2 7005088	8-19-10
294	F/U #4 510001E10DEU	8-24-10
295	F/U #13 510004E09USA	8-25-10
296	F/U #3 7005088 F/U #2 7004670	8-26-10
297	Initial 7015319	8-30-10
298	Oracle 28821 New Investigators	8-30-10
299	F/U #1 7013214 F/U #1 7013215	9-1-10

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300	Initial 7015119 & 7014989 F/U 2 510001E07CAN, F/U 4 510004E09RUS	9-2-10
301	F/U 3 510009E09RUS F/U 3 510001E07CAN	9-3-10
302	Initial 510009E07RUS, 510001E07SRB 510001E07/UKR	9-7-10
303	F/U 4 510001E09GBR, F/U 3 7004670 F/U 4 510001E07ITA, F/U 2 510006E10USA F/U 6 510006E08RUS, F/U 1 510001E07FIN	9-9-10
304	Initial 7016360, Initial 7016689	9-13-10
305	Initial 7017132	9-15-10
306	F/U #5 510001E10DEU Initial 510002E10USA	9-16-10
307	F/U 6 510001E10DEU, F/U 1 7014989 F/U 2 510005E10USA	9-17-10
308	F/U 1 7015119 F/U 4 510001E06DEU	9-20-10
309	CMC Amendment – Stats of DP	9-23-10
310	F/U 5 510001E07ITA, F/U 2 510003E09FRA F/U 3 510006E10USA, Initial 7017149, 7014718, F/U 5 7005088, F/U 6 7005088 F/U 2 510001E08POL	9-24-10
311	F/U 1 7017132	9-27-10
312	F/U 2 7002393, F/U 2 7005319 F/U 3 7015319, F/U 2 7017132	9-30-10
313	F/U 1 7016360	10-5-10
314	F/U 6 7005088	10-6-10
315	F/U 5 510001E09GBR	10-8-10
316	F/U 4 7015319	10-15-10
317	F/U 2 510002E09RUS, Initial 7021039 F/U 1 7014718, F/U 3 7017132	10-19-10
318	F/U 1 7017149	10-22-10

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319	Initial 7019448	10-25-10
320	F/U 4 7017132	10-26-10
321	F/U 1 7021039	10-28-10
322	F/U 7 510001E09GBR	11-1-10
323	F/U 8 7006418, F/U 2 7016360 Initial 7023305, F/U 2 7021039	11-2-10
324	F/U 3 7019448	11-3-10
325	F/U 9 7006418	11-5-10
326	F/U 2 7013214, F/U 2 7013215	11-11-10
327	F/U 5 7017132 F/U 2 7017149	11-17-10
328	F/U 10 7006418	11-18-10
329	F/U 3 7021039	11-19-10
330	F/U 6 510001E07ITA, F/U 1 7023305, Initial 7026942	11-22-10
331	F/U 4 510009E09RUS F/U 1 7006418	11-23-10
332	F/U 5 510009E09RUS F/U 5 7015319	11-24-10
333	F/U 4 7004670	12-1-10
334	F/U 2 7014718 Initial 7028748	12-2-10
335	F/U 5 7004670	12-8-10
336	F/U 1 7028748	12-9-10
337	F/U 3 510003E09FRA	12-10-10
338	F/U 7 510006E08RUS	12-13-10

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339	F/U 3 7014718, F/U 1 7030335 Initial 7030335	12-14-10
340	F/U 6 7017132	12-21-10
341	F/U 3 51000E09CAN, F/U 12 7006418 F/U 6 7015319	12-23-10
342	F/U 4 510001E07CHE F/U 6 510009E09Rus	12-29-10
343	F/U 2 7030335	1-5-11
344	Revised IB v8.0	1-14-11
345	F/U 4 7021039	1-19-11
346	F/U 5 7021039	1-25-11
347	F/U 4 510005E07USA	1-28-11
348	Initial 7040290 F/U 6 7021039	2-12-11
349	F/U 7 7021039 Initial 7041399	2-23-11
350	General Corresp. Oracle CTFG	2-28-11
351	New Investigators: Oracle 28821 & Onward 26593	3-2-11
352	F/U 1 7041399 Initial 7043041	3-3-11
353	F/U 1 7043041, F/U 2 7043041 F/U 3 7016360	3-4-11
354	F/U 2 7041399	3-9-11
355	F/U 3 7043041 F/U 2 510002E10USA	3-14-11
356	Initial 7039801 Initial 7047529	3-22-11
357	F/U 7 7015319, F/U 2 7023305 F/U 1 7047529	3-28-11
358	Initial 7047972 F/U 8 7015319	3-29-11

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359	F/U 1 7039801	3-30-11
360	Revised ICF: 26593, 28821 & Premiere	3-31-11
361	F/U 3 7023305	4-4-11
362	F/U 4 5100010e09rus	4-6-11
363	New Non-IND Investigators: 28821	4-6-11
364	F/U 13 7006418 Initial 7044421	4-7-11
365	F/U 5 510003E10MAR	4-12-11
366	F/U 2 7039801 F/U 2 7047529	4-13-11
367	Clarity Ext 27820, Amendment 4 & Revised ICF	4-13-11
368	F/U 4 510003E10MAR, F/U 3 & 4 7047529	4-15-11
369	F/U 1 7044421	4-21-11
370	F/U 14 7006418	4-25-11
371	F/U 5 510003E10MAR F/U 2 7014989	4-26-11
372	F/U 5 7047529	4-27-11
373	F/U 6 7047529 Initial 7052709	5-4-11
374	F/U 4 7016360	5-10-11
375	Initial 7057609 Initial 7057926	5-16-11
376	F/U 1 7047972 Initial 7059309	5-24-11
377	Initial 7053426, Initial 7060061 Initial 7060149	5-27-11
378	F/U 8 7021039, F/U 1 7059309 F/U 7 7005088, F/U 7 7047529, F/U 1 7057926	6-1-11

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379	F/U 3 7013214 F/U 3 7013215	6-2-11
380	Initial 7061169 Initial 7061816	6-6-11
381	F/U 1 7060149 F/U 1 7053426	6-8-11
382	Annual Report	6-9-11
383	F/U 1 7057609	6-13-11
384	F/U 8 7047529 Initial 7063170	6-16-11
385	F/U 2 7057609 Initial 7063793	6-17-11
386	Initial 7064728	6-22-11
387	F/U 2 7060149 F/U 1 7063170	6-28-11
388	Initial 7065584	6-30-11
389	F/U 1 7052709 F/U 1 7063793	7-1-11
390	Initial 7068227	7-13-11
391	F/U 4 510004E09CAN, F/U 3 7014989 F/U 2 7059309	7-20-11
392	F/U 5 5100109RUS F/U 2 7047972	7-25-11
393	F/U 14 510004E09USA, F/U 9 7015319 F/U 3 7059309	8-1-11
394	F/U 1 7065584 F/U 2 7052709	8/3/11
395	Initial 7072634	8/8/11
396	F/U 3 7047972	8-10-11
397	Initial 7073386 F/U 2 7065584	8-11-11
398	Initial 7045053 F/U 1 7072634	8-16-11

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399	F/U 15 510004E09USA F/U 6 510010E09RUS	8-22-11
400	F/U 4 7059309	8-31-11
401	F/U 6 510003E10MAR	9-6-11
402	F/U 5 7059309, Initial 7060478 & 7076477, F/U 1 7073386	9-14-11
403	Amendment 5 for 28821, 26593 & rev ICF's for Premiere Registry	9-16-11
404	Initial 7069384 & 7076391	9-19-11
405	F/U 4 7047972 F/U 6 7059309	9-22-11
406	F/U 1 7064228	10-13-11
407	F/U 4 7023305, F/U 3 7041399, F/U 7 7059309, F/U 8 7059309 F/U 3 7065584, F/U 4 7065584, F/U 2 7073386	10-18-11
408	F/U 3 7039801, F/U 4 7041399, Initials 7062063, 7092606, F/U 2 7063793	11-8-1
409	Clin Info Amendment terminating Onward & Oracle Studies	11-10-11
410	Initial 7093624	11-15-11
411	Initial 7094333	11-21-11
412	F/U 4 7014718, F/U 9 7059309	12-5-11
413	F/U 9 7005088, F/U 5 7014718, F/U 1 7093624, F/U 1 7094333	12-7-11
414	F/U 6 7014718, F/U 7 7014718, F/U 3 7072634, F/U 2 7072634	12-21-11
415	F/U 10 7059309	12-27-11
416	F/U 2 7094333, F/U 1 7101799, F/U 2 7094333	12-30-11
417	F/U 5 7047972, Initial 7101970	1-5-12
418	F/U 1 7040290, F/U 4 7072634	1-18-12

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419	Initial 7108211	1-27-12
420	Initials 510002e09POL & 7108209, F/U 1 7101970, F/U 2 7045053	1-30-12
421	F/U 1 7108209, F/U 1 7108211	1-31-12
422	F/U 2 7101799	2-10-12
423	F/U 2 7101970, F/U 2 7108209	2-16-12
424	F/U 3 7101970	2-23-12
425	F/U 3 7060149, Initials 7113253 & 7113255, F/U 1 7113253	2-27-12
426	Premiere Protocol Amendment & revised ICF's	3-2-12
427	Initial 7115887	3-12-12
428	Initial 7047529	3-27-12
429	Premiere Amendment 1 Tracked Version	4-4-12
430	Initial 7121036, F/U 1 7121036	4-4-12
431	2 aCSRs – Oracle & Clarity Ext	4-6-12
432	F/U 5 510005E07USA	4-10-12
433	F/U 2 7057926	4-11-12
434	F/U 2 7093624	4-13-12
435	F/U 5 7023305 Initial 7125405	4-24-12
436	F/U 16 510004E09USA	4-26-12
437	F/U 17 510004E09USA F/U 3 7045053	5-1-12
438	F/U 11 7059309	5-23-12

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439	Initial 7133572	5-30-12
440	Initial 7133768 F/U 5 7016360	6-1-12
441	Initials 7134689, 7134687, 7135032	6-6-12
442	Initial 7135880, F/U 4 7043041 F/U 3 7094333	6-7-12
443	Annual Report	6-8-12
444	Initial 7138299	6-12-12
445	F/U 1 7138299 F/U 3 7017149	6-13-12
446	F/U 1 7016689	6-21-12
447	Initial 7134374	6-22-12
448	Initial 7142690	7-5-12
449	F/U 1 7142690 Initial 7145323	7-11-12
450	Initial 7144397 F/U 1 7144397 Movectro	7-12-12
451	Premiere Amendment 1, V3 & Rev. ICFs	7-30-12
452	Initial 7149516	8-8-12
453	Initial 7152077	8-13-12
454	F/U 1 7149516	8-14-12
455	Initial 7154094	8-23-12
456	F/U 4 7045053	9-6-12
457	F/U 2 7019448	9-26-12
458	Clarity Extension 120 Week Report	10-1-12

IND #74,634
Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
459	F/U 3 7019448	10-4-12
460	F/U 1 7076477, F/U 5 510004e09can, Initial 7166798 F/U 1 7154094, F/U 1 7166798	10-23-12
461	Initial 7172246	11-9-12
462	F/U 2 7154094	11-21-12
463	F/U 1 7172246	12-3-12
464	F/U 7 7017132 F/U 6 7047972	12-11-12
465	Cross Ref for Cladribine Ctrs 28821 & 26593	1-14-13
466	Initials 7187173 & 7187166	1-24-13
467	F/U 1 7187173	2-4-13
468	F/U 3 7154094	2-21-13
469	Initial 7197251	3-6-13
470	F/U 1 7197251, Initials 7197832 & 7197826	3-12-13
471	Initial 7197867, F/U 1 7197867	3-20-13
472	F/U 1 7187166, F/U 4 7094333	3-27-13
473	F/U 2 7197251	4-2-13
474	F/U 7152077	4-12-13
475	F/U 3 7197251	4-16-13
476	F/U 2 7187173, F/U 2 7197867	4-30-13
477	Initial 7207635	5-2-13
478	Initial 7211838	5-29-13

IND #74,634
Oral Cladribine
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SER – SEQ NO	CONTENT	DATE
479 - 436	Anual Report	6-5-13
480 – 437	Initial 7215739, F/U 1 7215739 F/U 1 7211838	6-11-13
481 - 438	F/U 2 7211838	6-25-13
482 – 439	Initial 7221576 F/U 1 7221576	7-11-13
483 – 440	F/U 2 7221576	8-2-13
484 - 441	F/U 4 510006E10USA	9-4-13
485 – 442	F/U 1 7207635	9-12-13
486 – 443	F/U 2 7207635	9-25-13
487 – 444	F/U 3 7221576	10-7-13
488 - 445	F/U 2 7215739	10-16-13
489 – 446	F/U 3 7152077 F/U 4 7152077	12-3-13
490 – 447	F/U 3 7197867	2-14-14
491 – 448	F/U 4 7197867	3-7-14
492 – 449	Annual Report	6-9-14
493 – 450	Initial 7310422	8-12-14
494 – 451	Initial 7310877 postmarketing australia	8-13-14
495 – 452	F/U 1 7310422	8-19-14
496 – 453	Initial 7315281	9-2-14
497 – 454	Initial 8006474	2-3-15
498 – 455	8006474-1	2-6-15

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Oral Cladribine
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SER – SEQ NO	CONTENT	DATE
499 – 456	7142690-2	3-11-15
500 – 457	7315281-1	3-17-15
501 – 458	8016716-0	3-31-15
502 – 459	7187173-3 7101970-4	5-14-15
503 – 460	Annual Report (2014-2015)	6-11-15
504 – 461	7315281-2	6-19-15
505 – 462	8016716-1	8-6-15
506 – 463	7187173-43	9-11-15
507 – 464	7154094-4	9-17-15
508 – 465	8045741-0	10-6-15
509 – 466	7108209-3	2-4-16
510 – 467	7197251-4 7144397-2	3-4-16
511 - 468	7142690-3 7315281-3	3-16-16
512 – 469	7207635-3	3-23-16
513 – 470	510009e09rus-7	3-30-16
514 – 471	7197832-1	4-1-16
515 – 472	510010e09rus-7 (late-was due 4-2; capa was sent)	4-4-16
516 - 473	7211838-3	4-7-16
517 – 474	8078649-0 8006474-2 71871735 7207635-4	4-13-16
518 – 475	7144397-3	4-20-16

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Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
519 – 476	7187173-6 015	5-11-16
520 – 477	8078649-1 012	5-13-16
521 – 478	Request for DSUR	6-6-16
522 – 479	7310877-1 postmarketing australia	7-13-16
523 – 480	DSUR 2015-2016	8-31-16
524 – 481	7310877-2 postmarketing australia	9-13-16
525-482	Protocol amendment	9-22
526-483	Request for revised DSUR due date	10-14
527-484	8045741-1 (012)	10-25
528-485	7207635-5 7154094-5 (012)	12-27
529-486	8147577-0 (27820)	3-17-17
530-487	8147577-1 (27820)	3-24-17
531-488	8147577-2 (27820)	4-18-17
532-489	Type C meeting requenst	5-15
533-490	8162959-0 (27820)	6-16
534-491	Change in contact – Lynne Baron	6-30
535-492	8045741-2 (012)	7-19
536-493	Request for proprietary name review	7-21
537-494	8162959-1	8-18
538-495	DSUR 2016-2017	9-1

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SER – SEQ NO	CONTENT	DATE
539-496	Info Amend: Clinical - IB update 1.0	9-21
540-497	PSP – pediatric study plan	11-1
541-498	8199968-0	11-17
542-499	8203690-0	11-22
543-500	8203487-0	11-29
544-501	8205831-0	11-30
545-502	8203690-1	12-15
546-503	**90003603-0**	**1-2-18**
547-504	9001728-0 9008213-0	1-31
548-505	9008718-0	2-6
549-506	9010286-0	2-15
550-507	9008718-1	2-23
551-508	9010286-1	2-26
552-509	9008718-2 9012465-0	2-28
553-510	9008718-3	3-12
554-511	General corres	3-20
555-512	9008213-1	3-20
556-513	9016723-0 9008718-4 9009984-0	3-23
557-514	9008213-2	3-28
558-515	Type B mtg request PPMS	4-4

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SER – SEQ NO	CONTENT	DATE
559-516	9016723-1	4-6
560-517	9016723-2	4-19
561-518	Briefing Book	4-23
562-519	Pediatric Study Plan - PSP	4-24
563-520	9023286-0	5-10
564-521	Revised PSP	5-14
565-522	9008213-3 9023286-1	5-16
566-523	9026775-0 90038366-0	5-18
567-524	90038366-1 90038366-2	6-1
568-525	9029591-0 90038366-3 9029837-0 9029831-0 9030166-0	6-12
569-526	9031080-0 9032015-0 9032873-0	6-29
570-527	9032987-0 90050647-0 9031080-1 9035563-0	7-17
571-528	9035496-0	7-25
572-529	Update module 3 & 4; chg in contact from Lynn B to Tammy S	7-31
573-530	9035563-1 9037212-0 9034720-0	8-1
574-531	9037212-1	8-8
575-532	9035636-0 9039790-0	8-21
576-533	9039995-0 9040223-0	8-28
577-534	009-9035636-1 9040223-1 PSP 90054939-0	8-30
578-535	DSUR 2017-2018	9-5

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Oral Cladribine
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SER – SEQ NO	CONTENT	DATE
579-536	9036764-0 9040223-2 9041724-0 9041833-0 90024448-0	9-7
580-537	9042393-0 9042178-0 9042546-0 90054939-1	9-14
581-538	9043767-0 9044115-0 9029837-1 9044324-0	9-25
582-539	9043919-0 9035636-2 9044992-0 9042546-1	10-3
583-540	9044324-1 9045939-0 9045721-0 9045719-0 9039790-1 9036764-1 9045753-0 9035636-3 9017898-0	10-9
584-541	9046711-0 9039931-0 90055540-0	10-11
585-542	9040223-3	10-12
586-543	9039995-1	10-17
587-544	9046995-0 9046966-0 9046675-0 9029837-2	10-19
588-545	9043767-1 9047436-0 9046711-1	10-23
589-546	9036764-2 9046571-0 9044449-0 9035636-4	10-31
590-547	8006474-0 9043767-2 9046995-1 9049467-0 9043762-2	11-5
591-548	9045376-0 9000101-1 9008718-5	11-7
592-549	Amendment non clinical	11-9
593-550	90356365 9050599-0 9050228-0 9032820-0	11-14
594-551	9045865-0 9044992-1 9043557-0	11-20
595-552	9052502-0 9012465-1 9046675-1 9045376-1 9046711-2 9035636-6	11-27
596-553	9009984-1 9029831-1 9054946-0 9050228-1	11-30
597-554	9042393-1 9032820-2	12-6
598-555	9052502-1 9057542-0 9046571-1 9046711-3 90065122-0	12-18

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Oral Cladribine
Serial Number Log

SER – SEQ NO	CONTENT	DATE
599-556	9058502-0 9059148-0 9057843-0 90065359-0	12-21-18
600-557	9053378-0 9056311-0 9055198-0	12-28-18
601-558	PSP request for feedback	**1-7-19**
602-559	9062762-0 9062762-1 9062255-0 9061546-0 9057542-1 9063072-0 9063208-0 9032987-1	1-17-19
603-560	9065109-0 9032987-1 9064142-0 9064183-0 9065064-0 9065022-0 9060359-0 9053378-1	1-24-19
604-561	9063208-1 9062762-2 9065795-0 90020189-0 9056500-0 9035659-0	1-29-19
605-562	9042546-2 90020189-1 9067688-0 9035636-7	2-5
606-563	9069368-0 9035636-8 9070247-0 9009984-2 9062255-1 90054939-2 9061546-1	2-15
607-564	9054192-6 9055198-1 9061546-2 9041193-0 9050228-2 9017898-1 9072028-0 9072025-0	2-22
608-565	9072945-0 9062104-0 9073084-0 9063358-0 9069368-1 9070247-1 9056311-1 9044115-1	3-1
609-566	9074360-0 9040223-4 9075013-0 9074964-0 9017898-2 9050228-3 9072025-1	3-8
610-567	9075013-1 9062104-1	3-15
611-568	9070552-0 9061546-3 9041193-1	3-22
612-569	90062992-0 9061546-4 9079022-0 9065637-1 9079698-0 9072028-1	3-27
613-570	CMC Amendment	4-1
614-571	9078568-1 9080621-0 90038366-4	4-5
615-572	9054753-0 9042178-1	4-12
616-573	9081819-0 9028817-0 90062992-1	4-17
617-574	9061546-5 - 0021	4-19

NDA 022561US Chronology

Date	Content
September 29, 2009	Application Dated
September 30, 2009	Application Received
October 13, 2009	FDA Acknowledgment of NDA receipt signed
November 19, 2009	Tradename submission
November 25, 2009	FDA Refuse to file Received
February 22, 2010	End-of-Review Meeting summary
March 25, 2010	Teleconference to discuss structure and content for NDA resubmission
April 27, 2010	Rolling submission Part 1/2
May 27, 2010	Rolling submission Part 2/2
May 28, 2010	Tradename resubmission
May 28, 2010	Response to FDA Information request
June 24, 2010	Response to FDA Information request
June 28, 2010	Response to FDA Information request
July 2, 2010	Response to FDA Information request
July 20, 2010	Response to FDA Information request
July 21, 2010	Response to FDA Information request (2)
July 30, 2010	Response to FDA Information request
August 16, 2010	Response to FDA Information request
August 18, 2010	Response to FDA Information request
September 1, 2010	Response to FDA Information request
September 2, 2010	Response to FDA Information request
September 8, 2010	Response to FDA Information request (2)
September 10, 2010	Response to FDA Information request
September 13, 2010	Response to FDA Information request
September 15, 2010	Response to FDA Information request
September 17, 2010	Response to FDA Information request (2)
September 22, 2010	Response to FDA Information request
September 23, 2010	Response to FDA Information request
September 29, 2010	Response to FDA Information request

Date	Content
September 30, 2010	Response to FDA Information request (2)
October 1, 2010	Response to FDA Information request
October 4, 2010	Response to FDA Information request
October 12, 2010	Response to FDA Information request
October 13, 2010	Response to FDA Information request (3)
October 18, 2010	Response to FDA Information request
October 28, 2010	Response to FDA Information request
November 1, 2010	Response to FDA Information request
November 5, 2010	Response to FDA Information request
November 9, 2010	Response to FDA Information request
November 10, 2010	Response to FDA Information request
December 1, 2010	Response to FDA Information request
February 28, 2011	Complete Response from FDA
March 3, 2011	Complete Response acknowledgment
June 8, 2011	End-of-Review Meeting summary
August 19, 2011	Application Withdrawn
August 22, 2011	FDA Acknowledgment of withdrawal signed
August 25, 2011	FDA Acknowledgment of withdrawal received
May 15, 2017	Type C meeting request submitted
May 26, 2017	Type C meeting request rejected
May 30, 2017	Teleconference to discuss resubmission
October 12, 2017	FDA Pre-submission Meeting
May 30, 2018	Application Dated
May 31, 2018	Application Received
June 3, 2018	FDA Acknowledgment of NDA receipt (including acknowledgment of response to all items listed in February 28, 2011, Complete Response letter) signed
August 10, 2018	Response to FDA Information request
August 28, 2018	Response to FDA Information request
November 6, 2018	Response to FDA Information request
November 9, 2018	Response to FDA Information request

Date	Content
December 5, 2018	Response to FDA Information request
December 12, 2018	Response to FDA Information request
December 19, 2018	Response to FDA Information request
January 10, 2019	Response to FDA Information request
January 25, 2019	Response to FDA Information request
January 30, 2019	Carton and container labeling submitted to FDA
February 8, 2019	Response to FDA Information request
February 19, 2019	Response to FDA Information request
March 1, 2019	Response to FDA Information request
March 5, 2019	Response to FDA Information request
March 14, 2019	Draft Label received
March 18, 2019	Response to FDA Information request
March 19, 2019	Timetable for study submitted to FDA
March 21, 2019	Timetable for study submitted to FDA
March 22, 2019	Draft Label received
March 25, 2019	Teleconference with FDA to discuss label
March 27, 2019	Draft Label received
March 28, 2019	Response to FDA Information request
March 29, 2019	NDA Approval signed

United States Patent and Trademark Office

- Sales Receipt -

06/07/2019 GARIAS 00000001 601920 11722018

01 FC:1457 1120.00 DA

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 06/07/2019

GARIAS SALE #00000001 Mailroom Dt: 05/24/2019 601920 11722018
01 FC : 1457 1,120.00 DA

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/722,018	06/18/2007	Giampiero De Luca	SER.125

CONFIRMATION NO. 5532

POWER OF ATTORNEY NOTICE

23557
SALIWANCHIK, LLOYD & EISENSCHENK
A PROFESSIONAL ASSOCIATION
PO Box 142950
GAINESVILLE, FL 32614
UNITED STATES OF AMERICA

OC000000108485257

Date Mailed: 05/29/2019

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/21/2019.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sibrahim/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/722,018	06/18/2007	Giampiero De Luca	000758US

CONFIRMATION NO. 5532

POA ACCEPTANCE LETTER

151167
Gruneberg and Myers PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

OC00000108485613

Date Mailed: 05/29/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/21/2019.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/sibrahim/

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

September 4, 2020

Attention: Beverly Friedman

The attached application for patent term extension of U.S. Patent No. 7,713,947 was filed on May 24, 2019, under 35 U.S.C. § 156.

The assistance of your Office is requested in confirming that the product identified in the application Mavenclad® (cladribine), has been subject to a regulatory review period within the meaning of 35 U.S.C. § 156(g) before its first commercial marketing or use and that the application for patent term extension was filed within the sixty-day period beginning on the date the product was approved. Since a determination has not been made whether the patent in question claims a product which has been subject to the Federal Food, Drug and Cosmetic Act, or a method of manufacturing or use of such a product, this communication is NOT to be considered as notice which may be made in the future pursuant to 35 U.S.C. § 156(d)(2)(A).

Our review of the application to date indicates that the subject patent would be eligible for extension of the patent term under 35 U.S.C. § 156.

Inquiries regarding this communication should be directed to the undersigned at (571) 272-0909 (telephone) or (571) 273-0909 (facsimile) or by e-mail at ali.salimi@uspto.gov.

/Ali Salimi/

Ali Salimi
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Dr. Kirsten Grüneberg
Grüneberg and Myers, PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

U.S. FOOD & DRUG ADMINISTRATION

Re: MAVENCLAD
Patent No. 7,713,947
Docket No. FDA-2020-E-1885

The Honorable Andrei Iancu
Under Secretary of Commerce for Intellectual Property
Director, United States Patent and Trademark Office
Mail Stop Hatch-Waxman PTE
P.O. Box 1450
Alexandria, VA 22313-1450

OCT 13 2020

Dear Director Iancu:

This is concerning the application for patent term extension for U.S. Patent No. 7,713,947 filed by Merck Serono SA, under 35 U.S.C. 156. The human drug product claimed by the patent is MAVENCLAD (cladribine), which was assigned new drug application (NDA) No. 22561.

A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. 156(a)(4). However, our records also indicate that MAVENCLAD (cladribine) does not represent the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1).

The active ingredient in MAVENCLAD, cladribine, has been previously approved for commercial marketing or use, in the following list[1] of prior NDA and abbreviated NDA (ANDA) approvals:

PRODUCT NAME (GENERIC NAME)	APPLICATION NUMBER	APPLICANT	APPROVAL DATE
LEUSTATIN (CLADRIBINE)	NDA 20229	Janssen Pharmaceuticals Inc.	2/26/1993
CLADRIBINE	ANDA 75405	West-Ward Pharmaceuticals International Ltd.	2/28/2000
CLADRIBINE	ANDA 76571	Fresenius Kabi USA LLC	4/22/2004
CLADRIBINE	ANDA 200510	Mylan Laboratories Ltd.	10/6/2011

[1] Not comprehensive.

U.S. Food and Drug Administration
10903 New Hampshire Avenue
WO Building 51, Room 6250
Silver Spring, MD 20993-0002
www.fda.gov

NDA 22561 was approved on March 29, 2019, which makes the submission of the patent term extension application on May 24, 2019, timely within the meaning of 35 U.S.C. 156(d)(1).

Should you conclude that the subject patent is eligible for patent term extension, please advise us accordingly. As required by 35 U.S.C. 156(d)(2)(A) we will then determine the applicable regulatory review period, publish the determination in the *Federal Register*, and notify you of our determination.

Please let me know if we can be of further assistance.

Sincerely yours,

Patrizia Cavazzoni

Patrizia Cavazzoni, M.D., Acting Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Dr. Kirsten Gruneberg
GRUNEBERG and MYERS, PLLC
1775 Tysons Blvd, 5th Floor
Tysons, VA 22102

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22314-1450
www.uspto.gov

Dr. Kirsten Gruneberg
Grüneberg and Myers, PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

In Re: Patent Term Extension
Application for
U.S. Patent No. 7,713,947

May 20, 2021

NOTICE OF DETERMINATION OF INELIGIBILITY

An application for extension of the patent term of U.S. Patent No. 7,713,947 (the '947 patent) under 35 U.S.C. § 156 was filed in the United States Patent and Trademark Office on May 24, 2019. The application was filed by Merck Serono SA. Extension is sought based upon the premarket review under § 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) of New Drug Application (NDA) 22561 for the human drug product known by the tradename Mavenclad® (cladribine) having the active ingredient cladribine. Mavenclad® (cladribine) was approved for commercial use and sale by the Food and Drug Administration (FDA) on April 1, 2019.

A determination has been made that U.S. Patent No. 7,713,947 is **NOT** eligible for patent term extension under 35 U.S.C. § 156 based upon the regulatory review period of Mavenclad® (cladribine) which is the subject of NDA 22561.

A single request for reconsideration of this FINAL DETERMINATION OF INELIGIBILITY may be made if filed by the applicant within TWO MONTHS of the mailing date of this letter. The period for response may be extended pursuant to 37 C.F.R. 1.136. See 37 C.F.R. 1.750. A failure to respond to this letter will result in the application papers being placed into the patent file with no further action taken on the application for patent term extension.

I. The Approval of Mavenclad® As Claimed In The '947 patent Fails to Comply with 35 U.S.C. § 156(a)(5)(A)

The FDA official records indicate that cladribine was previously approved for commercial marketing or use prior to the approval of Mavenclad® (cladribine). In a letter dated October 13, 2020, FDA stated:

> A review of the Food and Drug Administration's official records indicates that this product was subject to a regulatory review period before its commercial marketing or use, as required under 35 U.S.C. § 156(a)(4). However, our records also indicate that Mavenclad (cladribine) **does not** represent the first permitted commercial marketing or use of the product, as defined under 35 U.S.C. § 156(f)(1). The active ingredient in

Mavenclad, cladribine,[1] has been previously approved in the following list[2] of prior NDA, and abbreviated NDA (ANDA) approvals:

PRODUCT NAME (GENERIC NAME)	APPLICATION NUMBER	APPLICANT	APPROVAL DATE
LEUSTATIN (CLADRIBINE)	NDA 20229	Janssen Pharmaceuticals Inc.	2/26/1993
CLADRIBINE	ANDA 75405	West-Ward Pharmaceuticals International Ltd.	2/28/2000
CLADRIBINE	ANDA 76571	Fresenius Kabi USA LLC	4/22/2004
CLADRIBINE	ANDA 200510	Mylan Laboratories Ltd.	10/6/2011

Under 35 U.S.C. § 156(a) a term of a patent which claims a product shall be extended if, *inter alia*, the product has been subject to a regulatory review period before its commercial marketing or use. In addition, under § 156(a)(5)(A):

> the permission for the commercial marketing or use of the product . . . is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; (Emphasis added)

Thus, the determination of eligibility of U.S. Patent No. 7,713,947 turns on the provisions in § 156(a)(5)(A) that the permission for the commercial marketing or use is **the first** permitted commercial marketing or use of the product. The term "product" is defined in 35 U.S.C. § 156(f) as follows:

> (f) For purposes of this section:
> (1) The term "product" means:
> (A) A drug product . . .
> (2) The term "drug product" means the active ingredient of -
> (A) A new drug, antibiotic drug, or human biological product . . . .including any salt or ester of the active ingredient, as a single entity or in combination with another active ingredient. (Emphasis added.)

By the explicit terms of section 156(f)(2), the term "product" as it relates to a human drug product means the active ingredient of the new drug product. The active ingredient in the approved product, is cladribine. As noted in the above FDA letter, the active ingredient

[1] As per the October 13, 2020 letter, FDA has confirmed that the active ingredient in the product is cladribine alone.

[2] Not comprehensive

cladribine had been approved for commercial marketing and use prior to the approval of the applicant's product. Furthermore, the prior approval of the active ingredient cladribine by the Food and Drug Administration was under section 505 of the FFDCA, the same provision of law under which regulatory review of NDA 22561 for Mavenclad® (cladribine) occurred. Applying the definition of "product" provided in section 156(f) to the extension requirement of § 156(a)(5)(A), applicant's product, Mavenclad® (cladribine), does not qualify as the first permitted marketing or use of the active ingredient. Since the approval of Mavenclad® (cladribine) was not the first permitted marketing or use of the active ingredient thereof, cladribine, the patent is not eligible for patent term extension based upon the regulatory review of Mavenclad® (cladribine). See *In re Fisons Pharmaceuticals Limited*, 231 USPQ 305 (Comm'r Pats. 1986); aff'd, *Fisons plc v. Quigg*, 8 USPQ2d 1491 (DDC 1988); aff'd, 10 USPQ2d 1869 (Fed. Cir. 1988); *Glaxo Operations UK Ltd. v. Quigg*, 13 USPQ 1628 (Fed. Cir. 1990).

II. Conclusion

For the above-stated reason, the PTE application for the 7,713,947 patent is **DISMISSED**.

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-0909.

/Ali Salimi/

Ali Salimi
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: Mavenclad® (cladribine)
Docket No.: FDA-2020-E-1885

EXHIBIT H

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MAVENCLAD safely and effectively. See full prescribing information for MAVENCLAD.

MAVENCLAD® (cladribine) tablets, for oral use
Initial U.S. Approval: 1993

WARNING: MALIGNANCIES and RISK OF TERATOGENICITY
See full prescribing information for complete boxed warning.

- **Malignancies**

MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy. (5.1)

- **Risk of Teratogenicity**

MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the risk of fetal harm. (5.2)

----------INDICATIONS AND USAGE----------

MAVENCLAD is a purine antimetabolite indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS *[see Warnings and Precautions (5)]*. (1)

Limitations of Use

MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile *[see Warnings and Precautions (5)]*. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assessments are required prior to starting each MAVENCLAD treatment course. (2.1)
- Cumulative dosage of 3.5 mg/kg administered orally and divided into 2 treatment courses (1.75 mg/kg per treatment course). Each treatment course is divided into 2 treatment cycles. (2.2)
- MAVENCLAD is a cytotoxic drug. (2.4)
- Separate administration from any other oral drug by at least 3 hours. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 10 mg (3)

----------CONTRAINDICATIONS----------

- Patients with current malignancy. (4)
- Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. (4, 8.3)
- HIV infection. (4)
- Active chronic infections (e.g., hepatitis or tuberculosis). (4)
- History of hypersensitivity to cladribine. (4, 5.8)
- Women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose. (4, 8.2)

----------WARNINGS AND PRECAUTIONS----------

- Lymphopenia: Monitor lymphocyte counts before, during and after treatment. (5.3)
- Infections: Screen patients for latent infections; consider delaying treatment until infection is fully controlled. Vaccinate patients antibody-negative to varicella zoster virus prior to treatment. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter. Monitor for infections. (5.4)
- Hematologic toxicity: Measure complete blood count annually if clinically indicated after treatment. (5.5)
- Graft-versus-host-disease with blood transfusion: Irradiation of cellular blood components is recommended. (5.6)
- Liver injury: Obtain tests prior to treatment. Discontinue if clinically significant injury is suspected. (5.7)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext. 5563 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Immunosuppressive drugs: Consider overlapping effects on immune system, when used sequentially. Concomitant use not recommended. (7.1)
- Hematotoxic drugs: Monitor patients for additive effects on the hematological profile. (7.3)
- Antiviral and antiretroviral drugs: Avoid concomitant use. (7.4)
- BCRP or ENT/CNT inhibitors: May alter bioavailability of cladribine. Avoid concomitant use. (7.5)

See 17 for PATIENT COUNSELING INFORMATION **and Medication Guide.**

Revised: 3/2019

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FULL PRESCRIBING INFORMATION

WARNING: MALIGNANCIES AND RISK OF TERATOGENICITY

- **Malignancies**

Treatment with MAVENCLAD may increase the risk of malignancy. MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

- **Risk of Teratogenicity**

MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the potential for fetal harm. Malformations and embryolethality occurred in animals. Exclude pregnancy before the start of treatment with MAVENCLAD in females of reproductive potential. Advise females and males of reproductive potential to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. Stop MAVENCLAD if the patient becomes pregnant *[see Contraindications (4), Warnings and Precautions (5.2), and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

MAVENCLAD is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS *[see Warnings and Precautions (5)]*.

Limitations of Use

MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile *[see Warnings and Precautions (5)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to Starting Each MAVENCLAD Treatment Course

Cancer Screening

Follow standard cancer screening guidelines because of the risk of malignancies *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Pregnancy

Exclude pregnancy prior to treatment with MAVENCLAD in females of reproductive potential *[see Contraindications (4), Warnings and Precautions (5.2), and Use in Specific Populations (8.1, 8.3)]*.

Complete Blood Count (CBC)

Obtain a CBC with differential including lymphocyte count *[see Dosage and Administration (2.5) and Warnings and Precautions (5.3)]*. Lymphocytes must be:

- within normal limits before initiating the first treatment course
- at least 800 cells per microliter before initiating the second treatment course

If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with MAVENCLAD.

Infections *[see Warnings and Precautions (5.4)]*

- Exclude HIV infection.
- Perform tuberculosis screening.
- Screen for hepatitis B and C.
- Evaluate for acute infection. Consider a delay in MAVENCLAD treatment until any acute infection is fully controlled.
- Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of MAVENCLAD.
- Administer all immunizations according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

Liver Injury

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels *[see Warnings and Precautions (5.7)]*.

2.2 Recommended Dosage

The recommended cumulative dosage of MAVENCLAD is 3.5 mg per kg body weight administered orally and divided into 2 yearly treatment courses (1.75 mg per kg per treatment course) (see Table 1). Each treatment course is divided into 2 treatment cycles:

Administration of First Treatment Course

- First Course/First Cycle: start any time.
- First Course/Second Cycle: administer 23 to 27 days after the last dose of First Course/First Cycle.

Administration of Second Treatment Course

- Second Course/First Cycle: administer at least 43 weeks after the last dose of First Course/Second Cycle.
- Second Course/Second Cycle: administer 23 to 27 days after the last dose of Second Course/First Cycle.

Table 1 Dose of MAVENCLAD per Cycle by Patient Weight in Each Treatment Course

Weight Range	**Dose in mg (Number of 10 mg Tablets) per Cycle**	
kg	First Cycle	Second Cycle
40* to less than 50	40 mg (4 tablets)	40 mg (4 tablets)
50 to less than 60	50 mg (5 tablets)	50 mg (5 tablets)
60 to less than 70	60 mg (6 tablets)	60 mg (6 tablets)
70 to less than 80	70 mg (7 tablets)	70 mg (7 tablets)
80 to less than 90	80 mg (8 tablets)	70 mg (7 tablets)
90 to less than 100	90 mg (9 tablets)	80 mg (8 tablets)
100 to less than 110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

*The use of MAVENCLAD in patients weighing less than 40 kg has not been investigated.

Administer the cycle dosage as 1 or 2 tablets once daily over 4 or 5 consecutive days *[see How Supplied/Storage and Handling (16.1)]*. Do not administer more than 2 tablets daily.

Following the administration of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years. Treatment during these 2 years may further increase the risk of malignancy *[see Warnings and Precautions (5.1)]*. The safety and efficacy of reinitiating MAVENCLAD more than 2 years after completing 2 treatment courses has not been studied.

2.3 Missed Dose

If a dose is missed, patients should not take double or extra doses.

If a dose is not taken on the scheduled day, then the patient must take the missed dose on the following day and extend the number of days in that treatment cycle. If two consecutive doses are missed, the treatment cycle is extended by 2 days.

2.4 Administration

MAVENCLAD tablets are taken orally, with water, and swallowed whole without chewing. MAVENCLAD can be taken with or without food.

Separate administration of MAVENCLAD and any other oral drugs by at least 3 hours during the 4 to 5 day MAVENCLAD treatment cycles *[see Clinical Pharmacology (12.6)]*.

MAVENCLAD is a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]*. MAVENCLAD is an uncoated tablet and must be swallowed immediately once removed from the blister. If a tablet is left on a surface, or if a broken or fragmented tablet is released from the blister, the area must be thoroughly washed with water.

The patient's hands must be dry when handling the tablets and washed thoroughly afterwards. Avoid prolonged contact with skin.

2.5 Laboratory Testing and Monitoring to Assess Safety

Cancer Screening

Follow standard cancer screening guidelines in patients treated with MAVENCLAD *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

Complete Blood Count

Obtain complete blood count (CBC) with differential including lymphocyte count:

- before initiating the first treatment course of MAVENCLAD
- before initiating the second treatment course of MAVENCLAD
- 2 and 6 months after start of treatment in each treatment course; if the lymphocyte count at month 2 is below 200 cells per microliter, monitor monthly until month 6. *See Warnings and Precautions (5.3, 5.4)* for instructions based on the patient's lymphocyte counts and clinical status (e.g., infections). Hold MAVENCLAD therapy if the lymphocyte count is below 200 cells per microliter
- periodically thereafter and when clinically indicated *[see Warnings and Precautions (5.5)]*

2.6 Recommended Concomitant Medication

Herpes Prophylaxis

Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter *[see Warnings and Precautions (5.4)]*.

3 DOSAGE FORMS AND STRENGTHS

MAVENCLAD is available as 10 mg tablets. The tablets are uncoated, white, round, biconvex, and engraved with a "C" on one side and "10" on the other side.

4 CONTRAINDICATIONS

MAVENCLAD is contraindicated:

- in patients with current malignancy *[see Warnings and Precautions (5.1)]*.
- in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course. May cause fetal harm *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.
- in patients infected with the human immunodeficiency virus (HIV) *[see Warnings and Precautions (5.4)]*.
- in patients with active chronic infections (e.g., hepatitis or tuberculosis) *[see Warnings and Precautions (5.4)]*.
- in patients with a history of hypersensitivity to cladribine *[see Warnings and Precautions (5.8)]*.

- in women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose *[see Use in Specific Populations (8.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Malignancies

Treatment with MAVENCLAD may increase the risk of malignancy. In controlled and extension clinical studies worldwide, malignancies occurred more frequently in MAVENCLAD-treated patients [10 events in 3,754 patient-years (0.27 events per 100 patient-years)], compared to placebo patients [3 events in 2,275 patient-years (0.13 events per 100 patient-years)]. Malignancy cases in MAVENCLAD patients included metastatic pancreatic carcinoma, malignant melanoma (2 cases), ovarian cancer, compared to malignancy cases in placebo patients, all of which were curable by surgical resection [basal cell carcinoma, cervical carcinoma in situ (2 cases)]. The incidence of malignancies in United States MAVENCLAD clinical study patients was higher than the rest of the world [4 events in 189 patient-years (2.21 events per 100 patient-years) compared to 0 events in United States placebo patients]; however, the United States results were based on a limited amount of patient data.

After the completion of 2 treatment courses, do not administer additional MAVENCLAD treatment during the next 2 years *[see Dosage and Administration (2.2)]*. In clinical studies, patients who received additional MAVENCLAD treatment within 2 years after the first 2 treatment courses had an increased incidence of malignancy [7 events in 790 patient-years (0.91 events per 100 patient-years) calculated from the start of cladribine treatment in Year 3]. The risk of malignancy with reinitiating MAVENCLAD more than 2 years after the completion of 2 treatment courses has not been studied.

MAVENCLAD is contraindicated in patients with current malignancy. In patients with prior malignancy or with increased risk of malignancy, evaluate the benefits and risks of the use of MAVENCLAD on an individual patient basis. Follow standard cancer screening guidelines in patients treated with MAVENCLAD.

5.2 Risk of Teratogenicity

MAVENCLAD may cause fetal harm when administered to pregnant women. Malformations and embryolethality occurred in animals *[see Use in Specific Populations (8.1)]*. Advise women of the potential risk to a fetus during MAVENCLAD dosing and for 6 months after the last dose in each treatment course.

In females of reproductive potential, pregnancy should be excluded before initiation of each treatment course of MAVENCLAD and prevented by the use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose of each treatment course. Women who become pregnant during treatment with MAVENCLAD should discontinue treatment *[see Use in Specific Populations (8.1, 8.3)]*. MAVENCLAD is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception.

5.3 Lymphopenia

MAVENCLAD causes a dose-dependent reduction in lymphocyte count. In clinical studies, 87% of MAVENCLAD-treated patients experienced lymphopenia. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment course and were lower with each additional treatment course. In patients treated with a cumulative dose of MAVENCLAD 3.5 mg per kg over 2 courses as monotherapy, 26% and 1% had nadir absolute lymphocyte counts less than 500 and less than 200 cells per microliter, respectively. At the end of the second treatment course, 2% of clinical study patients had lymphocyte counts less than 500 cells per microliter; median time to recovery to at least 800 cells per microliter was approximately 28 weeks.

Additive hematological adverse reactions may be expected if MAVENCLAD is administered prior to or concomitantly with other drugs that affect the hematological profile *[see Drug Interactions (7.3)]*. The incidence of lymphopenia less than 500 cells per microliter was higher in patients who had used drugs to treat relapsing forms of MS prior to study entry (32.1%), compared to those with no prior use of these drugs (23.8%).

Obtain complete blood count (CBC) with differential including lymphocyte count prior to, during, and after treatment with MAVENCLAD. *See Dosage and Administration (2.1, 2.5) and Warnings and Precautions (5.4)* for timing of CBC measurements and additional instructions based on the patient's lymphocyte counts and clinical status (e.g., infections).

5.4 Infections

MAVENCLAD can reduce the body's immune defense and may increase the likelihood of infections. Infections occurred in 49% of MAVENCLAD-treated patients compared to 44% of placebo patients in clinical studies. The most frequent serious infections in MAVENCLAD-treated patients included herpes zoster and pyelonephritis *(see Herpes Virus Infections)*. Fungal infections were observed, including cases of coccidioidomycosis.

HIV infection, active tuberculosis, and active hepatitis must be excluded before initiation of each treatment course of MAVENCLAD *[see Contraindications (4)]*.

Consider a delay in initiation of MAVENCLAD in patients with an acute infection until the infection is fully controlled.

Initiation of MAVENCLAD in patients currently receiving immunosuppressive or myelosuppressive therapy is not recommended *[see Drug Interactions (7.1)]*. Concomitant use of MAVENCLAD with these therapies could increase the risk of immunosuppression.

Tuberculosis

Three of 1,976 (0.2%) cladribine-treated patients in the clinical program developed tuberculosis. All three cases occurred in regions where tuberculosis is endemic. One case of tuberculosis was fatal, and two cases resolved with treatment.

Perform tuberculosis screening prior to initiation of the first and second treatment course of MAVENCLAD. Latent tuberculosis infections may be activated with use of MAVENCLAD. In patients with tuberculosis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Hepatitis

One clinical study patient died from fulminant hepatitis B infection. Perform screening for hepatitis B and C prior to initiation of the first and second treatment course of MAVENCLAD. Latent hepatitis infections may be activated with use of MAVENCLAD. Patients who are carriers of hepatitis B or C virus may be at risk of irreversible liver damage caused by virus reactivation. In patients with hepatitis infection, delay initiation of MAVENCLAD until the infection has been adequately treated.

Herpes Virus Infections

In controlled clinical studies, 6% of MAVENCLAD-treated patients developed a herpes viral infection compared to 2% of placebo patients. The most frequent types of herpes viral infections were herpes zoster infections (2.0% vs. 0.2%) and oral herpes (2.6% vs. 1.2%). Serious herpes zoster infections occurred in 0.2% of MAVENCLAD-treated patients.

Vaccination of patients who are antibody-negative for varicella zoster virus is recommended prior to initiation of MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD.

The incidence of herpes zoster was higher during the period of absolute lymphocyte count less than 500 cells per microliter, compared to the time when the patients were not experiencing this degree of lymphopenia. Administer anti-herpes prophylaxis in patients with lymphocyte counts less than 200 cells per microliter.

Patients with lymphocyte counts below 500 cells per microliter should be monitored for signs and symptoms suggestive of infections, including herpes infections. If such signs and symptoms occur, initiate treatment as clinically indicated. Consider interruption or delay of MAVENCLAD until resolution of the infection.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is an opportunistic viral infection of the brain caused by the JC virus (JCV) that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes.

No case of PML has been reported in clinical studies of cladribine in patients with multiple sclerosis. In patients treated with parenteral cladribine for oncologic indications, cases of PML have been reported in the postmarketing setting.

Obtain a baseline (within 3 months) magnetic resonance imaging (MRI) before initiating the first treatment course of MAVENCLAD. At the first sign or symptom suggestive of PML, withhold MAVENCLAD and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms.

Vaccinations

Administer all immunizations according to immunization guidelines prior to starting MAVENCLAD. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting MAVENCLAD, because of a risk of active vaccine infection *(see Herpes Virus Infections)*. Avoid vaccination with live-attenuated or live vaccines during and after MAVENCLAD treatment while the patient's white blood cell counts are not within normal limits.

5.5 Hematologic Toxicity

In addition to lymphopenia *[see Warnings and Precautions (5.3)]*, decreases in other blood cells and hematological parameters have been reported with MAVENCLAD in clinical studies. Mild to moderate decreases in neutrophil counts (cell count between 1,000 cells per microliter and < lower limit of normal (LLN)) were observed in 27% of MAVENCLAD-treated patients, compared to 13% of placebo patients whereas severe decreases in neutrophil counts (cell count below 1,000 cells per microliter) were observed in 3.6% of MAVENCLAD-treated patients, compared to 2.8% of placebo patients. Decreases in hemoglobin levels, in general mild to moderate (hemoglobin 8.0 g per dL to < LLN), were observed in 26% of MAVENCLAD-treated patients, compared to 19% of placebo patients. Decreases in platelet counts were generally mild (cell count 75,000 cells per microliter to < LLN) and were observed in 11% of MAVENCLAD-treated patients, compared to 4% of placebo patients.

In clinical studies at dosages similar to or higher than the approved MAVENCLAD dosage, serious cases of thrombocytopenia, neutropenia, and pancytopenia (some with documented bone marrow hypoplasia) requiring transfusion and granulocyte-colony stimulating factor treatment have been reported *[see Warnings and Precautions (5.6)* for information regarding graft-versus-host disease with blood transfusion*]*.

Obtain complete blood count (CBC) with differential prior to, during, and after treatment with MAVENCLAD *[see Dosage and Administration (2.1, 2.5)]*.

5.6 Graft-Versus-Host Disease With Blood Transfusion

Transfusion-associated graft-versus-host disease has been observed rarely after transfusion of nonirradiated blood in patients treated with cladribine for non-MS treatment indications.

In patients who require blood transfusion, irradiation of cellular blood components is recommended prior to administration to decrease the risk of transfusion-related graft-versus-host disease. Consultation with a hematologist is advised.

5.7 Liver Injury

In clinical studies, 0.3% of MAVENCLAD-treated patients had liver injury (serious or causing treatment discontinuation) considered related to treatment, compared to 0 placebo patients. Onset has ranged from a few weeks to several months after initiation of treatment with MAVENCLAD. Signs and symptoms of liver injury, including elevation of serum aminotransferases to greater than 20-fold the upper limit of normal, have been observed. These abnormalities resolved upon treatment discontinuation.

Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to the first and second treatment course *[see Dosage and Administration (2.1)]*. If a patient develops clinical signs, including unexplained liver enzyme elevations or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with MAVENCLAD, as appropriate.

5.8 Hypersensitivity

In clinical studies, 11% of MAVENCLAD-treated patients had hypersensitivity reactions, compared to 7% of placebo patients. Hypersensitivity reactions that were serious and/or led to discontinuation of MAVENCLAD (e.g., dermatitis, pruritis) occurred in 0.5% of MAVENCLAD-treated patients, compared to 0.1% of placebo patients. One patient had a serious hypersensitivity reaction with rash, mucous membrane ulceration, throat swelling, vertigo, diplopia, and headache after the first dose of MAVENCLAD.

If a hypersensitivity reaction is suspected, discontinue MAVENCLAD therapy. Do not use MAVENCLAD in patients with a history of hypersensitivity to cladribine *[see Contraindications (4)]*.

5.9 Cardiac Failure

In clinical studies, one MAVENCLAD-treated patient experienced life-threatening acute cardiac failure with myocarditis, which improved after approximately one week. Cases of cardiac failure have also been reported with parenteral cladribine used for treatment indications other than multiple sclerosis.

Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling).

6 ADVERSE REACTIONS

The following serious adverse reactions and potential risks are discussed, or discussed in greater detail, in other sections of the labeling:

- Malignancies *[see Warnings and Precautions (5.1)]*
- Risk of Teratogenicity *[see Warnings and Precautions (5.2)]*
- Lymphopenia *[see Warnings and Precautions (5.3)]*
- Infections *[see Warnings and Precautions (5.4)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.5)]*
- Graft-Versus-Host Disease With Blood Transfusion *[see Warnings and Precautions (5.6)]*
- Liver Injury *[see Warnings and Precautions (5.7)]*
- Hypersensitivity *[see Warnings and Precautions (5.8)]*
- Cardiac Failure *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In the clinical trial program of cladribine in MS, 1,976 patients received cladribine for a total of 9,509 patient years. The mean time on study including follow-up was approximately 4.8 years, and approximately 24% of cladribine-treated patients had approximately 8 years of time on study including follow-up. Of these, 923 patients aged 18 to 66 years received MAVENCLAD as monotherapy at a cumulative dose of 3.5 mg per kg.

Table 2 shows adverse reactions in Study 1 *[see Clinical Studies (14)]* with an incidence of at least 5% for MAVENCLAD and higher than placebo. The most common (> 20%) adverse reactions reported in Study 1 are upper respiratory tract infection, headache, and lymphopenia.

Table 2 Adverse Reactions in Study 1 with an Incidence of at Least 5% for MAVENCLAD and Higher than Placebo

	MAVENCLAD (N=440) %	Placebo (N=435) %
Upper respiratory tract infection	38	32
Headache	25	19
Lymphopenia	24	2
Nausea	10	9
Back pain	8	6
Arthralgia and arthritis	7	5
Insomnia	6	4
Bronchitis	5	3
Hypertension	5	3
Fever	5	3
Depression	5	3

Hypersensitivity
In clinical studies, 11% of MAVENCLAD patients had hypersensitivity adverse reactions, compared to 7% of placebo patients *[see Warnings and Precautions (5.8)]*.

Alopecia
Alopecia occurred in 3% of MAVENCLAD-treated patients compared to 1% of placebo patients.

Myelodysplastic Syndrome
Cases of myelodysplastic syndrome have been reported in patients that had received parenteral cladribine at a higher dosage than that approved for MAVENCLAD. These cases occurred several years after treatment.

Herpes Meningoencephalitis
Fatal herpes meningoencephalitis occurred in one MAVENCLAD-treated patient, at a higher dosage and longer duration of therapy than the approved MAVENCLAD dosage and in combination with interferon beta-1a treatment.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
SJS and TEN are identified risks of parenteral cladribine for the treatment of oncologic indications.

Seizures
In clinical studies, serious events of seizure occurred in 0.3% of MAVENCLAD-treated patients compared to 0 placebo patients. Serious events included generalized tonic-clonic seizures and status epilepticus. It is unknown whether these events were related to the effects of multiple sclerosis alone, to MAVENCLAD, or to a combination of both.

7 DRUG INTERACTIONS

Table 3 Drug Interactions with MAVENCLAD

7.1 Immunomodulatory, Immunosuppressive, or Myelosuppressive Drugs	
Clinical Impact	Concomitant use of MAVENCLAD with immunomodulatory, immunosuppressive, or myelosuppressive drugs may increase the risk of adverse reactions because of the additive effects on the immune system *[see Warnings and Precautions (5.4)]*.
Prevention or Management	Concomitant use with myelosuppressive or other immunosuppressive drugs is not recommended. Acute short-term therapy with corticosteroids can be administered. In patients who have previously been treated with immunomodulatory or immunosuppressive drugs, consider potential additive effect, the mode of action, and duration of effect of the other drugs prior to initiation of MAVENCLAD.
7.2 Interferon-Beta	
Clinical Impact	Concomitant use of MAVENCLAD with interferon-beta did not change the exposure of cladribine to a clinically significant effect; however, lymphopenia risk may be increased *[see Warnings and Precautions (5.3)]*.
Prevention or Management	Concomitant use is not recommended.
7.3 Hematotoxic Drugs	
Clinical Impact	Concomitant use of MAVENCLAD with hematotoxic drugs may increase the risk of adverse reactions because of the additive hematological effects *[see Warnings and Precautions (5.5)]*.
Prevention or Management	Monitor hematological parameters.
7.4 Antiviral and Antiretroviral Drugs	
Clinical Impact	Compounds that require intracellular phosphorylation to become active (e.g., lamivudine, zalcitabine, ribavirin, stavudine, and zidovudine) could interfere with the intracellular phosphorylation and activity of cladribine.
Prevention or Management	Avoid concomitant use.

7.5 Potent ENT, CNT and BCRP Transporter Inhibitors	
Clinical Impact	Cladribine is a substrate of breast cancer resistance protein (BCRP), equilibrative nucleoside (ENT1), and concentrative nucleoside (CNT3) transport proteins. The bioavailability, intracellular distribution, and renal elimination of cladribine may be altered by potent ENT1, CNT3, and BCRP transporter inhibitors.
Prevention or Management	Avoid co-administration of potent ENT1, CNT3, or BCRP transporter inhibitors (e.g., ritonavir, eltrombopag, curcumin, cyclosporine, dilazep, nifedipine, nimodipine, cilostazol, sulindac, dipyridamole, or reserpine) during the 4 to 5 day MAVENCLAD treatment cycles. If this is not possible, consider selection of alternative concomitant drugs with no or minimal ENT1, CNT3, or BCRP transporter inhibiting properties. If this is not possible, dose reduction to the minimum mandatory dose of drugs containing these compounds, separation in the timing of administration, and careful patient monitoring is recommended.
7.6 Potent BCRP and P-gp Transporter Inducers	
Clinical Impact	Possible decrease in cladribine exposure if potent BCRP or P-gp transporter inducers are co-administered.
Prevention or Management	Consider a possible decrease in cladribine efficacy if potent BCRP (e.g., corticosteroids) or P-gp (e.g., rifampicin, St. John's Wort) transporter inducers are co-administered.
7.7 Hormonal Contraceptives	
Clinical Impact	It is currently unknown whether MAVENCLAD may reduce the effectiveness of systemically acting hormonal contraceptives.
Prevention or Management	Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

MAVENCLAD is contraindicated in pregnant women and in females and males of reproductive potential who do not plan to use effective contraception. There are no adequate data on the developmental risk associated with use of MAVENCLAD in pregnant women. Cladribine was embryolethal when administered to pregnant mice and produced malformations in mice and rabbits *[see Data]*. The observed developmental effects are consistent with the effects of cladribine on DNA *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The background risk of major birth defects and miscarriage for the indicated population is unknown.

Data

Animal Data
When cladribine was administered intravenously (0, 0.5, 1.5, or 3 mg/kg/day) to pregnant mice during the period of organogenesis, fetal growth retardation and malformations (including exencephaly and cleft palate) and embryofetal death were observed at the highest dose tested. An increase in skeletal variations was observed at all but the lowest dose tested. There was no evidence of maternal toxicity.

When cladribine was administered intravenously (0, 0.3, 1, and 3 mg/kg/day) to pregnant rabbits during the period of organogenesis, fetal growth retardation and a high incidence of craniofacial and limb malformations were observed at the highest dose tested, in the absence of maternal toxicity.

When cladribine was administered intravenously (0, 0.5, 1.5, or 3.0 mg/kg/day) to mice throughout pregnancy and lactation, skeletal anomalies and embryolethality were observed at all but the lowest dose tested.

8.2 Lactation

Risk Summary

MAVENCLAD is contraindicated in breastfeeding women because of the potential for serious adverse reactions in breastfed infants *[see Contraindications (4) and Warnings and Precautions (5)]*. Advise women not to breastfeed during dosing with MAVENCLAD and for 10 days after the last dose.

There are no data on the presence of cladribine in human milk, the effects on the breastfed infant, or the effects of the drug on milk production.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

In females of reproductive potential, pregnancy should be excluded before the initiation of each treatment course of MAVENCLAD *[see Use in Specific Populations (8.1)]*.

Contraception

Females
Females of reproductive potential should prevent pregnancy by use of effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course. It is unknown if MAVENCLAD may reduce the effectiveness of the systemically acting hormonal contraceptives. Women using systemically acting hormonal contraceptives should add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course. Women who become pregnant during MAVENCLAD therapy should discontinue treatment *[see Warnings and Precautions (5.2) and Drug Interactions (7.7)]*.

Males
As cladribine interferes with DNA synthesis, adverse effects on human gametogenesis could be expected. Therefore, male patients of reproductive potential should take precautions to prevent pregnancy of their partner during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course *[see Warnings and Precautions (5.2) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness in pediatric patients (below 18 years of age) have not been established. Use of MAVENCLAD is not recommended in pediatric patients because of the risk of malignancies *[see Warnings and Precautions (5.1)]*.

8.5 Geriatric Use

Clinical studies with MAVENCLAD did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution is recommended when MAVENCLAD is used in elderly patients, taking into account the potential greater frequency of decreased hepatic, renal, or cardiac function, concomitant diseases, and other drug therapy.

8.6 Patients with Renal Impairment

The concentration of cladribine is predicted to increase in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. No dosage adjustment is recommended in patients with mild renal impairment (creatinine clearance 60 to 89 mL per minute). MAVENCLAD is not recommended in patients with moderate to severe renal impairment (creatinine clearance below 60 mL per minute) *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown *[see Clinical Pharmacology (12.3)]*. No dosage adjustment is recommended in patients with mild hepatic impairment. MAVENCLAD is not recommended in patients with moderate to severe hepatic impairment (Child-Pugh score greater than 6) *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

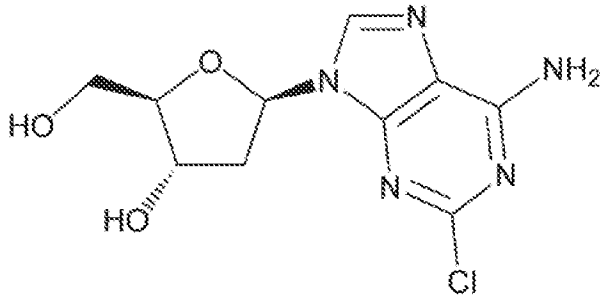
There is no experience with overdose of MAVENCLAD. Lymphopenia is known to be dose-dependent. Particularly close monitoring of hematological parameters is recommended in patients who have been exposed to an overdose of MAVENCLAD *[see Warnings and Precautions (5.3, 5.5)]*.

There is no known specific antidote to an overdose of MAVENCLAD. Treatment consists of careful observation and initiation of appropriate supportive measures. Discontinuation of MAVENCLAD may need to be considered. Because of the rapid and extensive intracellular and tissue distribution, hemodialysis is unlikely to eliminate cladribine to a significant extent.

11 DESCRIPTION

MAVENCLAD contains the nucleoside metabolic inhibitor cladribine, which is a white or almost white, non-hydroscopic, crystalline powder with the molecular formula $C_{10}H_{12}ClN_5O_3$ and molecular weight 285.69. It differs in structure from the naturally occurring nucleoside, deoxyadenosine, by the substitution of chlorine for hydrogen in the 2-position of the purine ring.

The chemical name of cladribine is 2-chloro-2'-deoxy-adenosine. The structural formula is shown below:



Cladribine is stable at slightly basic and at neutral pH. The main degradation pathway is hydrolysis and at acidic pH significant decomposition occurs with time. The ionization behavior of the molecule over the pH range 0 to 12 is characterized by a single pKa of approximately 1.21.

MAVENCLAD is provided as 10 mg tablets for oral use. Each MAVENCLAD 10 mg tablet contains cladribine as an active ingredient and hydroxypropyl betadex, magnesium stearate, and sorbitol as inactive ingredients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism by which cladribine exerts its therapeutic effects in patients with multiple sclerosis has not been fully elucidated but is thought to involve cytotoxic effects on B and T lymphocytes through impairment of DNA synthesis, resulting in depletion of lymphocytes.

12.2 Pharmacodynamics

MAVENCLAD causes a dose-dependent reduction in lymphocyte count. The lowest absolute lymphocyte counts occurred approximately 2 to 3 months after the start of each treatment cycle and were lower with each additional treatment cycle. At the end of Year 2, 2% of patients continued to have absolute lymphocyte counts less than 500 cells per microliter. The median time to recovery from lymphocyte counts less than 500 cells per microliter to at least 800 cells per microliter was approximately 28 weeks *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

Cladribine is a prodrug that becomes active upon phosphorylation to its 2-chlorodeoxyadenosine triphosphate (Cd-ATP) metabolite.

The pharmacokinetic parameters presented below were assessed following oral administration of cladribine 10 mg, unless otherwise specified. The cladribine mean maximum concentration (C_{max}) was in the range of 22 to 29 ng/ mL and corresponding mean AUC was in the range of 80 to 101 ng•h/mL.

The C_{max} and AUC of cladribine increased proportionally across a dose range from 3 to 20 mg.

No accumulation of cladribine concentration in plasma was observed after repeated dosing.

Absorption

The bioavailability of cladribine was approximately 40%. Following fasted administration of cladribine, the median time to maximum concentration (T_{max}) was 0.5 h (range 0.5 to 1.5 hours).

Effect of Food
Following administration of cladribine with a high fat meal, the geometric mean C_{max} decreased by 29% and AUC was unchanged. The T_{max} was prolonged to 1.5 hours (range 1 to 3 hours). This difference is not expected to be clinically significant.

Distribution

Cladribine mean apparent volume of distribution ranges from 480 to 490 liters. The plasma protein binding of cladribine is 20% and is independent of concentration, in vitro.

Intracellular concentrations of cladribine and/or its metabolites in human lymphocytes were approximately 30 to 40 times extracellular, in vitro.

Cladribine has the potential to penetrate the blood brain barrier. A cerebrospinal fluid/plasma concentration ratio of approximately 0.25 was observed in cancer patients.

Elimination

Cladribine estimated terminal half-life is approximately 1 day. The intracellular half-life of the cladribine phosphorylated metabolites cladribine monophosphate (Cd-AMP) is 15 hours and Cd-ATP is 10 hours. Cladribine estimated median apparent renal clearance is 22.2 liter per hour and non-renal clearance is 23.4 liter per hour.

Metabolism
Cladribine is a prodrug that is phosphorylated to Cd-AMP by deoxycytidine kinase (and also by deoxyguanosine kinase in the mitochondria) in lymphocytes. Cd-AMP is further phosphorylated to cladribine diphosphate (Cd-ADP) and the active moiety Cd-ATP. The dephosphorylation and deactivation of Cd-AMP is catalyzed by cytoplasmic 5'-nucleotidase (5'-NTase).

The metabolism of cladribine in whole blood has not been fully characterized. However, extensive whole blood and negligible hepatic enzyme metabolism was observed, in vitro.

Excretion
After administration of 10 mg oral cladribine in MS patients, 28.5 [20] (mean [SD]) percent of the dose was excreted unchanged via the renal route. Renal clearance exceeded the glomerular filtration rate, indicating active renal secretion of cladribine.

Specific Populations

No studies have been conducted to evaluate the pharmacokinetics of cladribine in elderly or in patients with renal or hepatic impairment.

There were no clinically significant differences in the pharmacokinetics of cladribine based on age (range 18 to 65 years) or gender. The effect of hepatic impairment on the pharmacokinetics of cladribine is unknown.

Patients with Renal Impairment
Renal clearance of cladribine was shown to be dependent on creatinine clearance (CL_{CR}). No dedicated studies have been conducted in patients with renal impairment, however patients with mild renal impairment (CL_{CR} of 60 mL to below 90 mL per minute) were included in Study 1. A pooled pharmacokinetic analysis estimated a decrease of 18% in total clearance in a typical subject with a CL_{CR} of 65 mL per minute leading to an increase in cladribine exposure of 25%. Clinical experience in patients with moderate to severe renal impairment (i.e., CL_{CR} below 60 mL per minute) is limited *[see Use in Specific Populations (8.6)]*.

Drug Interaction Studies

Clinical Studies
No clinically significant differences in cladribine pharmacokinetics were observed when used concomitantly with pantoprazole or interferon beta-1a.

In Vitro Studies
It has been reported that lamivudine can inhibit the phosphorylation of cladribine intracellularly. Potential competition for intracellular phosphorylation exists between cladribine and compounds that require intracellular phosphorylation to become active (e.g., lamivudine, zalcitabine, ribavirin, stavudine, and zidovudine).

Cytochrome P450 (CYP) Enzymes: Cladribine is not a substrate of cytochrome P450 enzymes and does not show significant potential to act as inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Cladribine has no clinically meaningful inductive effect on CYP1A2, CYP2B6 and CYP3A4 enzymes.

Transporter Systems: Cladribine is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), equilibrative nucleoside transporter 1 (ENT1) and concentrative nucleoside transporter 3 (CNT3). Inhibition of BCRP in the gastrointestinal tract may increase the oral bioavailability and systemic exposure of cladribine. Intracellular distribution and renal elimination of cladribine may be altered by potent ENT1, CNT3 transporter inhibitors.

12.6 Hydroxypropyl Betadex-Related Complex Formation

MAVENCLAD contains hydroxypropyl betadex that may be available for complex formation with the active ingredients of other drugs. Complex formation between free hydroxypropyl betadex, released from the cladribine tablet formulation, and concomitant ibuprofen, furosemide, and gabapentin was observed. Concomitant use with MAVENCLAD may increase the bioavailability of other drugs (especially agents with low solubility), which may increase the risk or severity of adverse reactions *[see Dosage and Administration (2.4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In mice administered cladribine (0, 0.1, 1, or 10 mg/kg) by subcutaneous injection intermittently (7 daily doses followed by 21 days of non-dosing per cycle) for 22 months, an increase in Harderian gland tumors (adenoma) was observed at the highest dose tested.

Mutagenesis

Cladribine was negative for mutagenicity in in vitro (reverse mutation in bacteria, CHO/HGPRT mammalian cell) assays.

Cladribine was positive for clastogenicity in an in vitro mammalian cell assay, in the absence and presence of metabolic activation, and in an in vivo mouse micronucleus assay.

Impairment of Fertility

When cladribine (0, 1, 5, 10, or 30 mg/kg/day) was administered by subcutaneous injection to male mice prior to and during mating to untreated females, no effects on fertility were observed. However, an increase in non-motile sperm was observed at the highest dose tested. In female mice, administration of cladribine (0, 1, 2, 4, or 8 mg/kg/day) by subcutaneous injection prior to and during mating to untreated males and continuing to gestation day 6 caused an increase in embryolethality at the highest dose tested.

In monkeys administered cladribine (0, 0.15, 0.3, or 1.0 mg/kg) by subcutaneous injection intermittently (7 consecutive daily doses followed by 21 days of non-dosing per cycle) for one year, testicular degeneration was observed at the highest dose tested.

14 CLINICAL STUDIES

The efficacy of MAVENCLAD was demonstrated in a 96-week randomized, double-blind, placebo-controlled clinical study in patients with relapsing forms of MS (Study 1; NCT00213135).

Patients were required to have at least 1 relapse in the previous 12 months. The median age was 39 years (range 18 to 65) and the female-to-male ratio was approximately 2:1. The mean duration of MS prior to study enrollment was 8.7 years, and the median baseline neurological disability based on Kurtzke Expanded Disability Status Scale (EDSS) score across all treatment groups was 3.0. Over two thirds of the study patients were treatment-naive for drugs used to treat relapsing forms of MS.

1,326 patients were randomized to receive either placebo (n = 437), or a cumulative oral dosage of MAVENCLAD 3.5 mg per kg (n = 433) or 5.25 mg per kg body weight (n = 456) over the 96-week study period in 2 treatment courses. Patients randomized to the 3.5 mg per kg cumulative dose received a first treatment course at Weeks 1 and 5 of the first year and a second treatment course at Weeks 1 and 5 of the second year *[see Dosage and Administration (2.2)]*. Patients randomized to the 5.25 mg per kg cumulative dose received additional treatment at Weeks 9 and 13 of the first year. Higher cumulative doses did not add any clinically meaningful benefit, but were associated with a higher incidence in grade 3 lymphopenia or higher (44.9% in the 5.25 mg per kg group vs. 25.6% in the 3.5 mg per kg group). Ninety-two percent of patients treated with MAVENCLAD 3.5 mg per kg and 87% of patients receiving placebo completed the full 96 weeks of the study.

The primary outcome of Study 1 was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the time to first qualifying relapse, the mean number of MRI T1 Gadolinium-enhancing (Gd+) lesions, and new or enlarging MRI T2 hyperintense lesions. Disability progression was measured in terms of a 3-month sustained change in EDSS score of at least one point, if baseline EDSS score was between 0.5 and 4.5 inclusively, or at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least 3 months.

MAVENCLAD 3.5 mg per kg significantly lowered the annualized relapse rate. The results from Study 1 are presented in Table 4.

Table 4 Clinical Outcomes in Study 1 (96 Weeks) - Primary and Secondary Endpoints

Endpoints	MAVENCLAD Cumulative Dose 3.5 mg per kg (n = 433)	Placebo (n = 437)
Clinical Endpoints		
Annualized relapse rate (ARR)	0.14*	0.33
Relative reduction in ARR	58%	
Proportion of patients without relapse	81%**	63%
Time to 3-month confirmed EDSS progression, HR	0.67**	
Proportion of patients with 3-month EDSS progression	13%	19%
MRI Endpoints		
Median Number of Active T1 Gd+ Lesions	0*	0.33
Median Number of Active T2 Lesions	0*	0.67

* $p < 0.001$ compared to placebo
** nominal $p < 0.05$ compared to placebo
HR: Hazard Ratio

15 REFERENCES

1 "OSHA Hazardous Drugs". OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MAVENCLAD tablets, 10 mg, are uncoated, white, round, biconvex, and engraved with a "C" on one side and "10" on the other side. Each tablet is packaged in a child-resistant day pack containing one or two tablets in a blister card.

Dispense one box for each treatment cycle with a Medication Guide *[see Dosage and Administration (2.2)]*.

Presentations

NDC 44087-400-11	Box of 1 tablet: One day pack containing one tablet.
NDC 44087-400-12	Box of 2 tablets: One day pack containing two tablets.
NDC 44087-400-04	Box of 4 tablets: Four day packs each containing one tablet.
NDC 44087-400-05	Box of 5 tablets: Five day packs each containing one tablet.
NDC 44087-400-06	Box of 6 tablets: One day pack containing two tablets. Four day packs each containing one tablet.
NDC 44087-400-07	Box of 7 tablets: Two day packs each containing two tablets. Three day packs each containing one tablet.
NDC 44087-400-08	Box of 8 tablets: Three day packs each containing two tablets. Two day packs each containing one tablet.
NDC 44087-400-09	Box of 9 tablets: Four day packs each containing two tablets. One day pack containing one tablet.
NDC 44087-400-10	Box of 10 tablets: Five day packs each containing two tablets.

16.2 Storage and Handling

Store at controlled room temperature, 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Store in original package in order to protect from moisture.

MAVENCLAD is a cytotoxic drug. Follow applicable special handling and disposal procedures *[see References (15)]*.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Malignancies

Inform patients that MAVENCLAD may increase their risk of malignancies. Instruct patients to follow standard cancer screening guidelines *[see Dosage and Administration (2) and Warnings and Precautions (5.1)]*.

Risk of Teratogenicity

Inform patients that MAVENCLAD may cause fetal harm. Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant. Before initiating each treatment course, inform patients about the potential risk to the fetus, if female patients or partners of male patients get pregnant during MAVENCLAD dosing or within 6 months after the last dose in each treatment course *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3)]*.

Instruct female patients of childbearing potential to use effective contraception during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course to avoid pregnancy. Advise women using systemically acting hormonal contraceptives to add a barrier method during MAVENCLAD dosing and for at least 4 weeks after the last dose in each treatment course because MAVENCLAD may reduce the effectiveness of the hormonal contraceptive *[see Drug Interactions (7.7)]*.

Instruct male patients to take precautions to prevent pregnancy of their partner during MAVENCLAD dosing and for at least 6 months after the last dose in each treatment course.

Advise patients that female patients or partners of male patients who get pregnant immediately inform their healthcare provider.

Lactation

Inform women that they cannot breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose *[see Use in Specific Populations (8.2)]*.

Lymphopenia and Other Hematologic Toxicity

Inform patients that MAVENCLAD may decrease lymphocyte counts and may also decrease counts of other blood cells. A blood test should be obtained before starting a treatment course, 2 and 6 months after start of treatment in each treatment course, periodically thereafter, and when clinically needed. Advise patients to keep all appointments for lymphocyte monitoring during and after MAVENCLAD treatment *[see Dosage and Administration (2.5) and Warnings and Precautions (5.3, 5.5)]*.

Infections

Inform patients that use of MAVENCLAD may increase the risk of infections. Instruct patients to notify their healthcare provider promptly if fever or other signs of infection such as aching, painful muscles, headache, generally feeling unwell or loss of appetite occur while on therapy or after a course of treatment *[see Warnings and Precautions (5.4)]*.

Advise patients that PML has happened with parenteral cladribine used in oncologic indications. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes *[see Warnings and Precautions (5.4)]*.

Liver Injury

Inform patients that MAVENCLAD may cause liver injury. Instruct patients treated with MAVENCLAD to report promptly any symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. A blood test should be obtained prior to each treatment course with MAVENCLAD and as clinically indicated thereafter *[see Warnings and Precautions (5.7)]*.

Hypersensitivity

Advise patients to seek immediate medical attention if they experience any symptoms of serious or severe hypersensitivity reactions, including skin reactions *[see Warnings and Precautions (5.8)]*.

Cardiac Failure

Advise patients that MAVENCLAD may cause cardiac failure. Instruct patients to seek medical advice if they experience symptoms of cardiac failure (e.g., shortness of breath, rapid or irregular heartbeat, swelling) *[see Warnings and Precautions (5.9)]*.

Treatment Handling and Administration

Instruct patients that MAVENCLAD is a cytotoxic drug and to use care when handling MAVENCLAD tablets, limit direct skin contact with the tablets, and wash exposed areas thoroughly. Advise patients to keep the tablets in the original package until just prior to each scheduled dose and consult their pharmacist on the proper disposal of unused tablets *[see Dosage and Administration (2.4) and How Supplied/Storage and Handling (16.2)]*.

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MEDICATION GUIDE
MAVENCLAD® (MAY-ven-klad)
(cladribine)
tablets, for oral use

What is the most important information I should know about MAVENCLAD?
MAVENCLAD can cause serious side effects, including:

- **Risk of cancer (malignancies).** Treatment with MAVENCLAD may increase your risk of developing cancer. Talk to your healthcare provider about your risk of developing cancer if you receive MAVENCLAD. You should follow your healthcare provider instructions about screening for cancer.
- **MAVENCLAD may cause birth defects if used during pregnancy. Females must not be pregnant when they start treatment with MAVENCLAD or become pregnant during MAVENCLAD dosing and within 6 months after the last dose of each yearly treatment course. Stop your treatment with MAVENCLAD and call your healthcare provider right away if you become pregnant during treatment with MAVENCLAD.**
  - For females who are able to become pregnant:
    - Your healthcare provider should order a pregnancy test for you before you begin your first and second yearly treatment course of MAVENCLAD to make sure that you are not pregnant. Your healthcare provider will decide when to do the test.
    - Use effective birth control (contraception) on the days on which you take MAVENCLAD and for at least 6 months after the last dose of each yearly treatment course.
      - Talk to your healthcare provider if you use oral contraceptives (the "pill").
      - You should use a second method of birth control on the days on which you take MAVENCLAD and for at least 4 weeks after your last dose of each yearly treatment course.
  - For males with female partners who are able to become pregnant:
    - Use effective birth control (contraception) during the days on which you take MAVENCLAD and for at least 6 months after the last dose of each yearly treatment course.

What is MAVENCLAD?
MAVENCLAD is a prescription medicine used to treat relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, MAVENCLAD is generally used in people who have tried another MS medicine that they could not tolerate or that has not worked well enough.

MAVENCLAD is not recommended for use in people with clinically isolated syndrome (CIS).

It is not known if MAVENCLAD is safe and effective in children under 18 years of age.

Do not take MAVENCLAD if you:

- have cancer (malignancy).
- are pregnant, plan to become pregnant, or are a woman of childbearing age or a man able to father a child and you are not using birth control. See "**What is the most important information I should know about MAVENCLAD?**"
- are human immunodeficiency virus (HIV) positive.
- have active infections, including tuberculosis (TB), hepatitis B or C.
- are allergic to cladribine.
- are breastfeeding. See "**Before you take MAVENCLAD, tell your healthcare provider about all of your medical conditions, including if you:**"

Before you take MAVENCLAD, tell your healthcare provider about all of your medical conditions, including if you:

- think you have an infection.
- have heart failure.
- have liver or kidney problems.
- have taken, take, or plan to take medicines that affect your immune system or your blood cells, or other treatments for MS. Certain medicines can increase your risk of getting an infection.
- have had a recent vaccination or are scheduled to receive any vaccinations. You should not receive live or live-attenuated vaccines within the 4 to 6 weeks preceding your treatment with MAVENCLAD. You should not receive these types of vaccines during your treatment with MAVENCLAD and until your healthcare provider tells you that your immune system is no longer weakened.
- have or have had cancer.
- are breastfeeding or plan to breastfeed. It is not known if MAVENCLAD passes into your breast milk. Do not breastfeed on the days, on which you take MAVENCLAD, and for 10 days after the last dose. See "**Do not** take

MAVENCLAD if you:"

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take MAVENCLAD?

- MAVENCLAD is given as two yearly treatment courses.
- Each yearly treatment course consists of 2 treatment weeks (also called cycles) that will be about a month apart. Your healthcare provider will tell you when you have to start your treatment weeks and how many tablets per week you need, depending on your weight. Each treatment week is 4 or 5 days.
- Your pharmacist will dispense a carton of MAVENCLAD for each treatment week. The prescribed number of tablets per day are provided in child resistant day packs.
- Take MAVENCLAD exactly as your healthcare provider tells you. Do not change your dose or stop taking MAVENCLAD unless your healthcare provider tells you to.
- Take MAVENCLAD with water and swallow whole without chewing. MAVENCLAD can be taken with or without food.
- Swallow MAVENCLAD right away after opening the blister pack.
- Your hands must be dry when handling MAVENCLAD and washed well with water afterwards.
- Limit contact with your skin. Avoid touching your nose, eyes and other parts of the body. If you get MAVENCLAD on your skin or on any surface, wash it right away with water.
- Take MAVENCLAD at least 3 hours apart from other medicines taken by mouth during the 4- to 5-day MAVENCLAD treatment week.
- If you miss a dose, take it as soon as you remember on the same day. If the whole day passes before you remember, take your missed dose the next day. **Do not take 2 doses at the same time**. Instead, you will extend the number of days in that treatment week.

Your healthcare provider will continue to monitor your health during the 2 yearly treatment courses, and for at least another 2 years during which you do not need to take MAVENCLAD. It is not known if MAVENCLAD is safe and effective in people who restart MAVENCLAD treatment more than 2 years after completing 2 yearly treatment courses.

What are the possible side effects of MAVENCLAD?

MAVENCLAD can cause serious side effects, including:

- See **"What is the most important information I should know about MAVENCLAD?"**
- **low blood cell counts.** Low blood cell counts have happened and can increase your risk of infections during your treatment with MAVENCLAD. Your healthcare provider will do blood tests before you start treatment with MAVENCLAD, during your treatment with MAVENCLAD, and afterward, as needed.
- **serious infections such as:**
  - **TB, hepatitis B or C, and shingles (herpes zoster).** Fatal cases of TB and hepatitis have happened with cladribine during clinical studies. Tell your healthcare provider right away if you get any symptoms of the following infection related problems or if any of the symptoms get worse, including:
    - fever
    - aching painful muscles
    - headache
    - feeling of being generally unwell
    - loss of appetite
    - burning, tingling, numbness or itchiness of the skin in the affected area
    - skin blotches, blistered rash and severe pain
  - **progressive multifocal leukoencephalopathy (PML).** PML is a rare brain infection that usually leads to death or severe disability. Although PML has not been seen in MS patients taking MAVENCLAD, it may happen in people with weakened immune systems. Symptoms of PML get worse over days to weeks. Call your healthcare provider right away if you have any new or worsening neurologic signs or symptoms of PML, that have lasted several days, including:
    - weakness on 1 side of your body
    - loss or coordination in your arms and legs
    - decreased strength
    - problems with balance
    - changes in your vision
    - changes in your thinking or memory
    - confusion
    - changes in your personality
- **liver problems.** MAVENCLAD may cause liver problems. Your healthcare provider should do blood tests to check your liver before you start taking MAVENCLAD. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - nausea
  - vomiting
  - stomach pain
  - tiredness
  - loss of appetite
  - your skin or the whites or your eyes turn yellow
  - dark urine

- **allergic reactions (hypersensitivities).** MAVENCLAD can cause serious allergic reactions. Stop your treatment with MAVENCLAD and go to the closest emergency room for medical help right away if you have any signs or symptoms of allergic reactions. Symptoms of an allergic reaction may include: skin rash, swelling or itching of the face, lips, tongue or throat, or trouble breathing.
- **heart failure.** MAVENCLAD may cause heart failure, which means your heart may not pump as well as it should. Call your healthcare provider or go to the closest emergency room for medical help right away if you have any signs or symptoms such as shortness of breath, a fast or irregular heart beat, or unusual swelling in your body.

Your healthcare provider may delay or completely stop treatment with MAVENCLAD if you have severe side effects.

The most common side effects of MAVENCLAD include:

- upper respiratory infection
- headache
- low white blood cell counts

These are not all the possible side effects of MAVENCLAD. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MAVENCLAD?

- MAVENCLAD comes in a child resistant package.
- Store MAVENCLAD at room temperature between 68°F and 77°F (20°C and 25°C).
- Store MAVENCLAD in the original package to protect from moisture.
- Ask your healthcare provider or pharmacist about how to safely throw away any unused or expired MAVENCLAD tablets and packaging.

Keep MAVENCLAD and all medicines out of the reach of children.

General information about the safe and effective use of MAVENCLAD

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use MAVENCLAD for a condition for which it was not prescribed. Do not give MAVENCLAD to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider for information about MAVENCLAD that is written for health professionals.

What are the ingredients in MAVENCLAD?

Active ingredient: cladribine

Inactive ingredients: hydroxypropyl betadex, magnesium stearate, and sorbitol.

Distributed by: EMD Serono, Inc., Rockland, MA 02370

MAVENCLAD is a registered trademark of Merck KGaA, Darmstadt, Germany.

For more information, call toll-free 1-877-447-3243 or go to www.mavenclad.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: 3/2019

EXHIBIT L

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TWEET (HTTPS://TWITTER.COM/INTENT/TWEET/?TEXT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&URL=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS&APPLNO=020229)

EMAIL (MAILTO:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS&APPLNO=020229)

Home (index.cfm) | Previous Page

New Drug Application (NDA): 020229
Company: JANSSEN PHARMS

EMAIL (MAILTO:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTP://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS%26VARAPPLNO=020229)

Products on NDA 020229

CSV | Excel | Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
LEUSTATIN	CLADRIBINE	1MG/ML **Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons**	INJECTABLE;INJECTION	Discontinued	None	Yes	No

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for NDA 020229

Original Approvals or Tentative Approvals

CSV | Excel | Print

Action Date	Submission	Action Type	Submission Classification	Review Priority; Orphan Status	Letters, Reviews, Labels, Patient Package Insert	Notes
02/26/1993	ORIG-1	Approval	Type 1 - New Molecular Entity	STANDARD		Withdrawn FR Effective 11/03/2016 Label is not available on this site.

Showing 1 to 1 of 1 entries

Supplements

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Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert
08/02/2012	SUPPL-34		**Label (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020 Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/**
06/29/2006	SUPPL-30		**Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/**

Action Date	Submission	Supplement Categories or Approval Type	Letters, Reviews, Labels, Patient Package Insert
08/22/2002	SUPPL-21		Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/
08/20/2002	SUPPL-7		Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/
08/20/2002	SUPPL-4		Letter (PDF) (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2002/

Showing 1 to 5 of 5 entries

Labels for NDA 020229

LEUSTATIN® (cladribine)
Injection
For Intravenous Infusion Only

WARNING

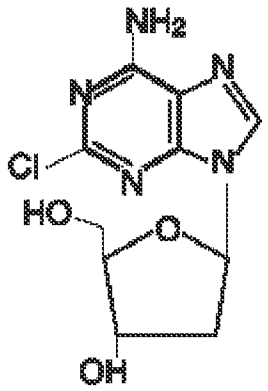
LEUSTATIN (cladribine) Injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Serious neurological toxicity (including irreversible paraparesis and quadraparesis) has been reported in patients who received LEUSTATIN Injection by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Acute nephrotoxicity has been observed with high doses of LEUSTATIN (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.

DESCRIPTION

LEUSTATIN (cladribine) Injection (also commonly known as 2-chloro-2′-deoxy-β-D-adenosine) is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. LEUSTATIN Injection is available in single-use vials containing 10 mg (1 mg/mL) of cladribine, a chlorinated purine nucleoside analog. Each milliliter of LEUSTATIN Injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3±0.3.

The chemical name for cladribine is 2-chloro-6-amino-9-(2-deoxy-β-D-erythropento-furanosyl) purine and the structure is represented below:



cladribine MW 285.7

CLINICAL PHARMACOLOGY

Cellular Resistance and Sensitivity:

The selective toxicity of 2-chloro-2′-deoxy-β-D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2′-deoxy- β -D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2′-deoxy- β -D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2′-deoxy- β -D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2′-deoxy- β -D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2′-deoxy- β -D-adenosine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

Reference ID: 3168717

Pharmacokinetics

In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of LEUSTATIN Injection (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with an estimated systemic clearance of 663.5 mL/h/kg when LEUSTATIN was given by continuous infusion over 7 days. In Hairy Cell Leukemia patients, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome.

In another study, 8 patients with hematologic malignancies received a two (2) hour infusion of LEUSTATIN Injection (0.12 mg/kg). The mean end-of-infusion plasma LEUSTATIN concentration was 48±19 ng/mL. For 5 of these patients, the disappearance of LEUSTATIN could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were 978±422 mL/h/kg and 4.5±2.8 L/kg, respectively.

Cladribine plasma concentration after intravenous administration declines multi-exponentially with an average half-life of 6.7 +/- 2.5 hours. In general, the apparent volume of distribution of cladribine is approximately 9 L/kg, indicating an extensive distribution in body tissues.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 25% of those in plasma.

LEUSTATIN is bound approximately 20% to plasma proteins.

Except for some understanding of the mechanism of cellular toxicity, no other information is available on the metabolism of LEUSTATIN in humans. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5-day continuous intravenous infusion of 3.5-8.1 mg/m^2/day of LEUSTATIN. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

CLINICAL STUDIES

Two single-center open label studies of LEUSTATIN (cladribine) have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 89 patients were treated with a single course of LEUSTATIN Injection given by continuous intravenous infusion for 7 days at a dose of

0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7-day continuous intravenous infusion of LEUSTATIN Injection at a comparable dose of 3.6 mg/m^2/day. A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the hemoglobin to 12 g/dL, platelet count to 100 x 10^9/L, and absolute neutrophil count to 1500 x 10^6/L. A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells remain in the bone marrow. A partial response (PR) required that hairy cells in the bone marrow be decreased by at least 50% from baseline and the same response for hematologic parameters as for complete response. A pathologic relapse was defined as an increase in bone marrow hairy cells to 25% of pretreatment levels. A clinical relapse was defined as the recurrence of cytopenias, specifically, decreases in hemoglobin $\geq$ 2 g/dL, ANC $\geq$ 25% or platelet counts $\geq$ 50,000. Patients who met the criteria for a complete response but subsequently were found to have evidence of bone marrow hairy cells (< 25% of pretreatment levels) were reclassified as partial responses and were not considered to be complete responses with relapse.

Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria described above, the complete response rates in patients treated with LEUSTATIN Injection were 65% and 68% for Study A and Study B, respectively, yielding a combined complete response rate of 66%. Overall response rates (i.e., Complete plus Good Partial plus Partial Responses) were 89% and 86% in Study A and Study B, respectively, for a combined overall response rate of 88% in evaluable patients treated with LEUSTATIN Injection.

Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and $\leq$ 13 cm on CT scan), the complete response rates for Study A and Study B were 54% and 53%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for Studies A and B, respectively, yielding a combined overall response rate of 89%.

RESPONSE RATES TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	CR	Overall
Evaluable Patients N=106	66%	88%
Intent-to-treat Population N=123	54%	89%

In these studies, 60% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving

LEUSTATIN as a first-line treatment. The remaining 40% of the patients received LEUSTATIN as a second-line treatment, having been treated previously with other agents, including α-interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 92%, compared with 84% for previously treated patients. LEUSTATIN is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to α-interferon.

OVERALL RESPONSE RATES (CR + GPR + PR) TO LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	OVERALL RESPONSE (N = 123)	NR + RELAPSE
No Prior Chemotherapy	68/74	6 + 4
	92%	14%
Any Prior Chemotherapy	41/49	8 + 3
	84%	22%
Previous Splenectomy	32/41*	9 + 1
	78%	24%
Previous Interferon	40/48	8 + 3
	83%	23%
Interferon Refractory	6/11*	5 + 2
	55%	64%
Previous Deoxycoformycin	3/6*	3 + 1
	50%	66%

NR = No Response
* $P < 0.05$

After a reversible decline, normalization of peripheral blood counts (Hemoglobin >12.0 g/dL, Platelets >100 x 10^9/L, Absolute Neutrophil Count (ANC) >1500 x 10^6/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 9 weeks from the start of treatment (Range: 2 to 72). The median time to normalization of Platelet Count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with complete response. Platelet recovery may be delayed in a minority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding LEUSTATIN therapy. (see also WARNINGS, PRECAUTIONS and ADVERSE REACTIONS)

LEUSTATIN TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA TIME TO NORMALIZATION OF PERIPHERAL BLOOD COUNTS

Parameter	Median Time to Normalization of Count*
Platelet Count	2 weeks
Absolute Neutrophil Count	5 weeks
Hemoglobin	8 weeks
ANC, Hemoglobin and Platelet Count	9 weeks

* Day 1 = First day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of data cut-off, the median duration of complete response was greater than 8 months and ranged to 25+ months. Among 93 responding patients, seven had shown evidence of disease progression at the time of the data cut-off. In four of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in three patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of LEUSTATIN received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

INDICATIONS FOR USE

LEUSTATIN Injection is indicated for the treatment of active Hairy Cell Leukemia as defined by clinically significant anemia, neutropenia, thrombocytopenia or disease-related symptoms.

CONTRAINDICATIONS

LEUSTATIN Injection is contraindicated in those patients who are hypersensitive to this drug or any of its components.

WARNINGS

Due to increased risk of infection in the setting of immunosuppression with chemotherapy including LEUSTATIN, it is recommended not to administer live attenuated vaccines to patients receiving LEUSTATIN Injection.

Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with LEUSTATIN, especially at high doses. At initiation of treatment, most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell

Leukemia. Following treatment with LEUSTATIN, further hematologic impairment occurred before recovery of peripheral blood counts began. During the first two weeks after treatment initiation, mean Platelet Count, ANC, and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 5 and Week 8, respectively. The myelosuppressive effects of LEUSTATIN were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring, especially during the first 4 to 8 weeks after treatment with LEUSTATIN Injection, is recommended (see PRECAUTIONS).

Fever ($T \geq 100°F$) was associated with the use of LEUSTATIN in approximately two-thirds of patients (131/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics. Overall, 47% (93/196) of all patients had fever in the setting of neutropenia ($ANC \leq 1000$), including 62 patients (32%) with severe neutropenia (i.e., $ANC \leq 500$).

In a Phase I investigational study using LEUSTATIN in high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. Thirty-one (31) poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins Lymphoma (2 cases) received LEUSTATIN for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with LEUSTATIN, 6 patients (19%) developed manifestations of renal dysfunction (e.g., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven (11) patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadriparesis) of the upper and/or lower extremities, first noted 35 to 84 days after starting high dose therapy with LEUSTATIN. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease. Severe neurologic toxicity has also been noted with high doses of another drug in this class.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

In patients with Hairy Cell Leukemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of nephrologic toxicities.

Serious (e.g. respiratory infection, pneumonia and viral skin infections), including fatal infections (e.g. sepsis) were reported (see ADVERSE REACTIONS).

Of the 196 Hairy Cell Leukemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following LEUSTATIN therapy. Of the 8 deaths, 6 occurred in previously treated patients who were refractory to α interferon.

Benzyl alcohol is a constituent of the recommended diluent for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. (see DOSAGE AND ADMINISTRATION)

Pregnancy Category D:

LEUSTATIN can cause fetal harm when administered to a pregnant woman. Although there is no evidence of teratogenicity in humans due to LEUSTATIN, other drugs which inhibit DNA synthesis have been reported to be teratogenic in humans. Cladribine is teratogenic in animals. Advise females of reproductive potential to use highly effective contraception during treatment with LEUSTATIN. If LEUSTATIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m^2) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3.0 mg/kg/day (9 mg/m^2). Fetal death and malformations were observed in rabbits that received 3.0 mg/kg/day (33.0 mg/m^2). No fetal effects were seen in mice at 0.5 mg/kg/day (1.5 mg/m^2) or in rabbits at 1.0 mg/kg/day (11.0 mg/m^2).

PRECAUTIONS

General:

LEUSTATIN Injection is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment of peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g., infection or bleeding). As with other potent chemotherapeutic agents, monitoring of renal and hepatic function is also recommended, especially in patients with underlying kidney or liver dysfunction (see WARNINGS and ADVERSE REACTIONS).

Fever was a frequently observed side effect during the first month on study. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated. Although 69% of patients developed fevers, less than 1/3 of febrile events were associated with documented infection. Given the known myelosuppressive effects of LEUSTATIN, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections (see WARNINGS and ADVERSE REACTIONS).

There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of LEUSTATIN has been described. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency (see WARNINGS).

Rare cases of tumor lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden.

LEUSTATIN Injection must be diluted in designated intravenous solutions prior to administration (see DOSAGE AND ADMINISTRATION).

Laboratory Tests:

During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached 100 x 10^9/L by Day 12, the mean Absolute Neutrophil Count reached 1500 x 10^6/L by Week 5 and the mean Hemoglobin reached 12 g/dL by Week 8.

Reference ID: 3168717

After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with LEUSTATIN. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

Drug Interactions:

There are no known drug interactions with LEUSTATIN Injection. Caution should be exercised if LEUSTATIN Injection is administered before, after, or in conjunction with other drugs known to cause immunosuppression or myelosuppression. (see WARNINGS)

Carcinogenesis:

No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

Mutagenesis:

As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test).

Impairment of Fertility:

The effect on human fertility is unknown. When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells.

Pregnancy:

Pregnancy Category D: (see WARNINGS).

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving patients 1-21 years old with relapsed acute leukemia, LEUSTATIN was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m^2/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m^2/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study [(1)] (see WARNINGS and ADVERSE REACTIONS).

Geriatric Use

Clinical studies of LEUSTATIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients.

ADVERSE REACTIONS

Clinical Trials Experience

Adverse drug reactions reported by ≥ 1% of LEUSTATIN-treated patients with HCL noted in the HCL clinical dataset (studies K90-091 and L91-048, n=576) are shown in the table below.

Adverse Drug Reactions in ≥ 1% of Patients Treated With LEUSTATIN in HCL Clinical Trials	
System Organ Class Preferred Term	**LEUSTATIN (n=576)** **%**
Blood and Lymphatic System Disorder (see also sections WARNINGS and PRECAUTIONS)	
Anemia	1
Febrile neutropenia	8
Psychiatric Disorders	
Anxiety	1
Insomnia	3
Nervous System Disorders	
Dizziness	6
Headache	14
Cardiac Disorders	
Tachycardia	2
Respiratory, Thoracic and Mediastinal Disorders	
Breath sounds abnormal	4
Cough	7
Dyspnea*	5
Rales	1
Gastrointestinal Disorders	
Abdominal pain**	4

Constipation	4
Diarrhea	7
Flatulence	1
Nausea	22
Vomiting	9
Skin and Subcutaneous Tissue Disorders	
Ecchymosis	2
Hyperhidrosis	3
Petechiae	2
Pruritus	2
Rash***	16
Musculoskeletal, Connective Tissue, and Bone Disorders	
Arthralgia	3
Myalgia	6
Pain****	6
General Disorders and Administration Site Conditions (see also sections WARNINGS and PRECAUTIONS)	
Administration site reaction*****	11
Asthenia	6
Chills	2
Decreased appetite	8
Fatigue	31
Malaise	5
Muscular weakness	1
Edema peripheral	2
Pyrexia	33
Injury, Poisoning and Procedural Complications	
Contusion	1

* Dyspnea includes dyspnea, dyspnea exertional, and wheezing
** Abdominal pain includes abdominal discomfort, abdominal pain, and abdominal pain (lower and upper)
*** Rash includes erythema, rash, and rash (macular, macula-papular, papular, pruritic, pustular and erythematous)
**** Pain includes pain, back pain, chest pain, arthritis pain, bone pain, and pain in extremity
***** Administration site reaction includes administration site reaction, catheter site (cellulitis, erythema, hemorrhage, and pain), and infusion site reaction(erythema, edema, and pain)

The following safety data are based on 196 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus an additional 72 patients enrolled at the same two centers after the original enrollment cutoff. In Month 1 of the Hairy Cell Leukemia clinical trials, severe neutropenia was noted in 70% of patients, fever in 69%, and infection was documented in 28%. Most non-hematologic adverse experiences were mild to moderate in severity.

Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC < 500 x 10^6/L) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (Hemoglobin < 8.5 g/dL) developed in 37% of patients, compared with 10% initially and thrombocytopenia (Platelets < 20 x 10^9/L) developed in 12% of patients, compared to 4% in whom it was noted initially.

During the first month, 54 of 196 patients (28%) exhibited documented evidence of infection. Serious infections (e.g., septicemia, pneumonia) were reported in 6% of all

patients; the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 6%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding LEUSTATIN therapy.

During the first month, 11% of patients experienced severe fever (i.e., ≥104°F). Documented infections were noted in fewer than one-third of febrile episodes. Of the 196 patients studied, 19 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven (7) of 8 documented episodes of herpes zoster occurred during the month following treatment. Fourteen (14) of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics. (see WARNINGS and PRECAUTIONS)

Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts. Prior to treatment, the mean CD4 count was 766/μL. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/μL. Fifteen (15) months after treatment, mean CD4 counts remained below 500/μL. CD8 counts behaved similarly, though increasing counts were observed after 9 months. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow cellularity of < 35% was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as day 1010. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

The vast majority of rashes were mild. Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine.

When used in other clinical settings the following ADRs were reported: bacteremia, cellulitis, localized infection, pneumonia, anemia, thrombocytopenia (with bleeding or petechiae), phlebitis, purpura, crepitations, localized edema and edema.

For a description of adverse reactions associated with use of high doses in non-Hairy Cell Leukemia patients, see WARNINGS.

Postmarketing Experience

The following additional adverse reactions have been reported since the drug became commercially available. These adverse reactions have been reported primarily in patients who received multiple courses of LEUSTATIN Injection:

Infections and infestations: Septic shock. Opportunistic infections have occurred in the acute phase of treatment.

Blood and lymphatic system disorders: Bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia; hemolytic anemia (including autoimmune hemolytic anemia), which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment. Rare cases of myelodysplastic syndrome have been reported.

Immune system disorders: Hypersensitivity.

Metabolism and nutrition disorders: Tumor lysis syndrome.

Psychiatric disorders: Confusion (including disorientation).

Hepatobiliary disorders: Reversible, generally mild increases in bilirubin (uncommon) and transaminases.

Nervous System disorders: Depressed level of consciousness, neurological toxicity (including peripheral sensory neuropathy, motor neuropathy (paralysis), polyneuropathy, paraparesis); however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Eye disorders: Conjunctivitis.

Respiratory, thoracic and mediastinal disorders: Pulmonary interstitial infiltrates (including lung infiltration, interstitial lung disease, pneumonitis and pulmonary fibrosis); in most cases, an infectious etiology was identified.

Skin and tissue disorders: Urticaria, hypereosinophilia; Stevens-Johnson. In isolated cases toxic epidermal necrolysis has been reported in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause these syndromes.

Renal and urinary disorders: Renal failure (including renal failure acute, renal impairment).

OVERDOSAGE

High doses of LEUSTATIN have been associated with: irreversible neurologic toxicity (paraparesis/quadriparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia (see WARNINGS). There is no known specific antidote to overdosage. Treatment of overdosage consists of discontinuation of LEUSTATIN, careful observation and appropriate supportive measures. It is not known whether the drug can be removed from the circulation by dialysis or hemofiltration.

DOSAGE AND ADMINISTRATION

Usual Dose:

The recommended dose and schedule of LEUSTATIN Injection for active Hairy Cell Leukemia is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of LEUSTATIN Injection for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs (see WARNINGS).

Specific risk factors predisposing to increased toxicity from LEUSTATIN have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic and non-hematologic toxicity (see WARNINGS and PRECAUTIONS).

Preparation and Administration of Intravenous Solutions:

LEUSTATIN Injection must be diluted with the designated diluent prior to administration. Since the drug product does not contain any anti-microbial preservative or bacteriostatic agent, **aseptic technique and proper environmental precautions must be observed in preparation of LEUSTATIN Injection solutions.**

To prepare a single daily dose:

LEUSTATIN Injection should be passed through a sterile 0.22µm disposable hydrophilic syringe filter prior to introduction into the infusion bag, prior to each daily infusion. Add the calculated dose (0.09 mg/kg or 0.09 mL/kg) of LEUSTATIN Injection through the sterile filter to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days. **The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.** Admixtures of

LEUSTATIN Injection are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex®† PVC infusion containers. **Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.**

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
24-hour infusion method	1(day) x 0.09 mg/kg	0.9% Sodium Chloride Injection, USP	500 mL

To prepare a 7-day infusion:

The 7-day infusion solution should only be prepared with Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved). In order to minimize the risk of microbial contamination, both LEUSTATIN Injection and the diluent should be passed through a sterile 0.22 µm disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of LEUSTATIN Injection (7 days x 0.09 mg/kg or mL/kg) to the infusion reservoir through the sterile filter.

Then add a calculated amount of Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol preserved) also through the filter to bring the total volume of the solution to 100 mL. After completing solution preparation, clamp off the line, disconnect and discard the filter. Aseptically aspirate air bubbles from the reservoir as necessary using the syringe and a dry second sterile filter or a sterile vent filter assembly. Reclamp the line and discard the syringe and filter assembly. Infuse continuously over 7 days. Solutions prepared with Bacteriostatic Sodium Chloride Injection for individuals weighing more than 85 kg may have reduced preservative effectiveness due to greater dilution of the benzyl alcohol preservative. Admixtures for the 7-day infusion have demonstrated acceptable chemical and physical stability for at least 7 days in the SIMS Deltec MEDICATION CASSETTE™ Reservoir‡.

	Dose of LEUSTATIN Injection	Recommended Diluent	Quantity of Diluent
7-day infusion method (use sterile 0.22µ filter when preparing infusion solution)	7 (days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection, USP (0.9% benzyl alcohol)	q.s. to 100 mL

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing LEUSTATIN Injection should not be mixed with other intravenous drugs or additives or infused

simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates (see WARNINGS).

Care must be taken to assure the sterility of prepared solutions. Once diluted, solutions of LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to start of administration. Vials of LEUSTATIN Injection are for single-use only. Any unused portion should be discarded in an appropriate manner (see Handling and Disposal).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of LEUSTATIN Injection to low temperatures; it may be resolubilized by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

Chemical Stability of Vials:

When stored in refrigerated conditions between 2° to 8°C (36° to 46°F) protected from light, unopened vials of LEUSTATIN Injection are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of LEUSTATIN Injection is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing LEUSTATIN Injection should be administered promptly or stored in the refrigerator (2° to 8°C) for no more than 8 hours prior to administration.

Handling and Disposal:

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering LEUSTATIN Injection. The use of disposable gloves and protective garments is recommended. If LEUSTATIN Injection contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published.[2-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your Institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

HOW SUPPLIED

LEUSTATIN Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine as 10 mL filled into a single-use clear flint

glass 20 mL vial. LEUSTATIN Injection is supplied in 10 mL (1 mg/mL) single-use vials (NDC 59676-201-01) available in a treatment set (case) of seven vials.

Store refrigerated 2° to 8°C (36° to 46°F). Protect from light during storage.

REFERENCES:

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2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C. 20402.

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4. National Study Commission on Cytotoxic Exposure--Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

5. Clinical Oncological Society of Australia: Guidelines and Recommendations for Safe Handling of Antineoplastic Agents, Med. J. Australia **1**:425 (1983).

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7. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic Drugs in Hospitals. Am. J. Hosp. Pharm., **42**:131 (1985).

8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (antineoplastic) Drugs. Am. J. Hosp. Pharm., **43**:1193 (1986).

† Viaflex® containers, manufactured by Baxter Healthcare Corporation - Code No. 2B8013 (tested in 1991)

‡ MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 602100A (tested in 1991)

Centocor Ortho Biotech Products, L.P. [new code]
Raritan, NJ 08869 Revised July 2012
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EXHIBIT T

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75405

DRAFT FINAL PRINTED LABELING

CLADRIBINE INJECTION

Rx ONLY

For Intravenous Infusion Only

WARNINGS

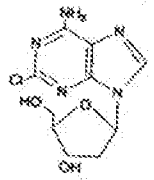
Cladribine injection should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. Suppression of bone marrow function should be anticipated. This is usually reversible and appears to be dose dependent. Serious neurological toxicity (including irreversible paraparesis and quadriparesis) has been reported in patients who received cladribine injection by continuous infusion at high doses (4 to 9 times the recommended dose for Hairy Cell Leukemia). Neurologic toxicity appears to demonstrate a dose relationship; however, severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Acute nephrotoxicity has been observed with high doses of cladribine (4 to 9 times the recommended dose for Hairy Cell Leukemia), especially when given concomitantly with other nephrotoxic agents/therapies.

DESCRIPTION

Cladribine injection (also commonly known as 2-chloro-2'-deoxy-β-D-adenosine) is a synthetic antineoplastic agent for continuous intravenous infusion. It is a clear, colorless, sterile, preservative-free, isotonic solution. Cladribine injection is available in single-use vials containing 10 mg (1 mg/mL) of cladribine, a chlorinated purine nucleoside analog. Each mL of cladribine injection contains 1 mg of the active ingredient and 9 mg (0.15 mEq) of sodium chloride as an inactive ingredient. The solution has a pH range of 5.5 to 8.0. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH to 6.3 ± 0.3.

The chemical name for cladribine is 2-chloro-6-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine and the structure is represented below:



Molecular Formula = $C_{10}H_{12}ClN_5O_3$ Molecular Weight = 285.69

CLINICAL PHARMACOLOGY

Cellular Resistance and Sensitivity:

The selective toxicity of 2-chloro-2'-deoxy-β-D-adenosine towards certain normal and malignant lymphocyte and monocyte populations is based on the relative activities of deoxycytidine kinase and deoxynucleotidase. Cladribine passively crosses the cell membrane. In cells with a high ratio of deoxycytidine kinase to deoxynucleotidase, it is phosphorylated by deoxycytidine kinase to 2-chloro-2'-deoxy-β-D-adenosine monophosphate (2-CdAMP). Since 2-chloro-2'-deoxy-β-D-adenosine is resistant to deamination by adenosine deaminase and there is little deoxynucleotide deaminase in lymphocytes and monocytes, 2-CdAMP accumulates intracellularly and is subsequently converted into the active triphosphate deoxynucleotide, 2-chloro-2'-deoxy-β-D-adenosine triphosphate (2-CdATP). It is postulated that cells with high deoxycytidine kinase and low deoxynucleotidase activities will be selectively killed by 2-chloro-2'-deoxy-β-D-adenosine as toxic deoxynucleotides accumulate intracellularly.

Cells containing high concentrations of deoxynucleotides are unable to properly repair single-strand DNA breaks. The broken ends of DNA activate the enzyme poly (ADP-ribose) polymerase resulting in NAD and ATP depletion and disruption of cellular metabolism. There is evidence, also, that 2-CdATP is incorporated into the DNA of dividing cells, resulting in impairment of DNA synthesis. Thus, 2-chloro-2'-deoxy-β-D-adenosine can be distinguished from other chemotherapeutic agents affecting purine metabolism in that it is cytotoxic to both actively dividing and quiescent lymphocytes and monocytes, inhibiting both DNA synthesis and repair.

HUMAN PHARMACOLOGY

In a clinical investigation, 17 patients with Hairy Cell Leukemia and normal renal function were treated for 7 days with the recommended treatment regimen of cladribine (0.09 mg/kg/day) by continuous intravenous infusion. The mean steady-state serum concentration was estimated to be 5.7 ng/mL with an estimated systemic clearance of 663.5 mL/h/kg when cladribine was given by continuous infusion over 7 days. In Hairy Cell Leukemia patients, there does not appear to be a relationship between serum concentrations and ultimate clinical outcome.

In another study, 8 patients with hematologic malignancies received a bolus (2) hour infusion of cladribine (0.12 mg/kg). The mean end-of-infusion plasma cladribine concentration was 48 ± 19 ng/mL. For 5 of these patients, the disappearance of cladribine could be described by either a biphasic or triphasic decline. For these patients with normal renal function, the mean terminal half-life was 5.4 hours. Mean values for clearance and steady-state volume of distribution were 978 ± 422 mL/h/kg and 4.5 ± 2.8 L/kg, respectively.

Plasma concentrations are reported to decline multi-exponentially after intravenous infusions with terminal half-lives ranging from approximately 3 to 22 hours. In general, the apparent volume of distribution of cladribine is very large (mean approximately 9 L/kg), indicating an extensive distribution of cladribine in body tissues. The mean half-life of cladribine in leukemic cells has been reported to be 23 hours.

Cladribine penetrates into cerebrospinal fluid. One report indicates that concentrations are approximately 20% of those in plasma.

Cladribine is bound approximately 20% to plasma proteins.

Except for some understanding of the mechanism of cellular toxicity, no other information is available on the metabolism of cladribine in humans. An average of 18% of the administered dose has been reported to be excreted in urine of patients with solid tumors during a 5-day continuous intravenous infusion of 3.5 to 8.1 mg/m²/day of cladribine. The effect of renal and hepatic impairment on the elimination of cladribine has not been investigated in humans.

Two single-center open label studies of cladribine have been conducted in patients with Hairy Cell Leukemia with evidence of active disease requiring therapy. In the study conducted at the Scripps Clinic and Research Foundation (Study A), 68 patients were treated with a single course of cladribine given by continuous intravenous infusion for 7 days at a dose of 0.09 mg/kg/day. In the study conducted at the M.D. Anderson Cancer Center (Study B), 35 patients were treated with a 7 day continuous intravenous infusion of cladribine at a comparable dose of 3.5 mg/m²/day. A complete response (CR) required clearing of the peripheral blood and bone marrow of hairy cells and recovery of the hemoglobin to 12 g/dL, platelet count to 100 x 10⁹/L, and absolute neutrophil count to 1500 x 10⁹/L. A good partial response (GPR) required the same hematologic parameters as a complete response, and that fewer than 5% hairy cells remain in the bone marrow. A partial response (PR) required that hairy cells in the bone marrow be decreased by at least 50% from baseline and the same response for hematologic parameters as for complete response. A pathologic relapse was defined as an increase in bone marrow hairy cells to 25% of pretreatment levels. A clinical relapse was defined as the recurrence of cytopenias, specifically, decreases in hemoglobin ≥ 2 g/dL, ANC ≤ 25% or platelet counts ≤ 50,000. Patients who met the criteria for a complete response but subsequently were found to have evidence of bone marrow hairy cells (>25% of pretreatment levels) were reclassified as partial responders and were not considered to be complete responses with relapse.

Among patients evaluable for efficacy (N=106), using the hematologic and bone marrow response criteria described above, the complete response rates in patients treated with cladribine were 65% and 68% for Study A and Study B, respectively, yielding a combined complete response rate of 66%. Overall response rates (i.e., Complete plus Good Partial plus Partial Responses) were 89% and 90% in Study A and Study B, respectively, for a combined overall response rate of 89% in evaluable patients treated with cladribine.

Using an intent-to-treat analysis (N=123) and further requiring no evidence of splenomegaly as a criterion for CR (i.e., no palpable spleen on physical examination and ≤ 13 cm on CT scan), the complete response rates for Study A and Study B were 54% and 52%, respectively, giving a combined CR rate of 54%. The overall response rates (CR + GPR + PR) were 90% and 85%, for Studies A and B, respectively, yielding a combined overall response rate of 89%.

RESPONSE RATES TO CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	CR	Overall
Evaluable Patients: N=106	66%	89%
Intent-to-treat Population: N=123	54%	89%

In these studies, 60% of the patients had not received prior chemotherapy for Hairy Cell Leukemia or had undergone splenectomy as the only prior treatment and were receiving cladribine as a first-line treatment. The remaining 40% of the patients received cladribine as a second-line treatment, having been treated previously with other agents, including α-interferon and/or deoxycoformycin. The overall response rate for patients without prior chemotherapy was 90%, compared with 84% for previously treated patients. Cladribine is active in previously treated patients; however, retrospective analysis suggests that the overall response rate is decreased in patients previously treated with splenectomy or deoxycoformycin and in patients refractory to α-interferon.

OVERALL RESPONSE RATES (CR + CP + PR) TO CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA

	OVERALL RESPONSE (N=123)	NR + RELAPSE
No Prior Chemotherapy	68/74 92%	6 + 4 14%
Any Prior Chemotherapy	41/49 84%	8 + 3 22%
Previous Splenectomy	32/41* 78%	9 + 1 28%
Previous Interferon	40/48 83%	8 + 3 23%
Interferon Refractory	6/11* 55%	3 + 2 64%
Previous Deoxycoformycin	3/5* 60%	2 + 1 66%

NR = No Response
*P<0.05

After reversible decline, normalization of peripheral blood counts (Hemoglobin >12 g/dL, Platelets >100 x 10⁹/L, Absolute Neutrophil Count (ANC) >1500 x 10⁶/L) was achieved by 92% of evaluable patients. The median time to normalization of peripheral counts was 8 weeks from the start of treatment (Range: 2 to 72). The median time to normalization of Platelet Count was 2 weeks, the median time to normalization of ANC was 5 weeks and the median time to normalization of Hemoglobin was 8 weeks. With normalization of Platelet Count and Hemoglobin, requirements for platelet and RBC transfusions were abolished after Months 1 and 2, respectively, in those patients with complete response. Platelet recovery may be delayed in a majority of patients with severe baseline thrombocytopenia. Corresponding to normalization of ANC, a trend toward a reduced incidence of infection was seen after the third month, when compared to the months immediately preceding cladribine therapy. See also **WARNINGS, PRECAUTIONS** and **ADVERSE REACTIONS.**

CLADRIBINE TREATMENT IN PATIENTS WITH HAIRY CELL LEUKEMIA TIME TO NORMALIZATION OF PERIPHERAL BLOOD COUNTS

Parameter	Median Time to Normalization of Count*
Platelet Count	2 weeks
Absolute Neutrophil Count	5 weeks
Hemoglobin	8 weeks
ANC, Hemoglobin and Platelet Count	9 weeks

*Day 1 = First day of infusion

For patients achieving a complete response, the median time to response (i.e., absence of hairy cells in bone marrow and peripheral blood together with normalization of peripheral blood parameters), measured from treatment start, was approximately 4 months. Since bone marrow aspiration and biopsy were frequently not performed at the time of peripheral blood normalization, the median time to complete response may actually be shorter than that which was recorded. At the time of data cut-off, the median duration of complete response was greater than 8 months and ranged to 21+ months. Among 93 responding patients, seven had shown evidence of disease progression at the time of the data cut-off. In five of these patients, disease was limited to the bone marrow without peripheral blood abnormalities (pathologic progression), while in three patients there were also peripheral blood abnormalities (clinical progression). Seven patients who did not respond to a first course of cladribine received a second course of therapy. In the five patients who had adequate follow-up, additional courses did not appear to improve their overall response.

INDICATIONS AND USAGE

Cladribine is indicated for the treatment of active Hairy Cell Leukemia as defined by clinically significant anemia, neutropenia, thrombocytopenia or disease-related symptoms.

CONTRAINDICATIONS

Cladribine is contraindicated in those patients who are hypersensitive to this drug or any of its components.

WARNINGS

Severe bone marrow suppression, including neutropenia, anemia and thrombocytopenia, has been commonly observed in patients treated with cladribine, especially at high doses. At initiation of treatment, most patients in the clinical studies had hematologic impairment as a manifestation of active Hairy Cell Leukemia. Following treatment with cladribine, further hematologic impairment occurred before recovery of peripheral blood counts began. During the first two weeks after treatment initiation, mean Platelet Count, ANC, and Hemoglobin concentration declined and subsequently increased with normalization of mean counts by Day 12, Week 3 and Week 8, respectively. The myelosuppressive effects of cladribine were most notable during the first month following treatment. Forty-four percent (44%) of patients received transfusions with RBCs and 14% received transfusions with platelets during Month 1. Careful hematologic monitoring, especially during the first 4 to 8 weeks after treatment with cladribine, is recommended. See **PRECAUTIONS.**

Fever (T ≥ 100.8) was associated with the use of cladribine in approximately two-thirds of patients (131/196) in the first month of therapy. Virtually all of these patients were treated empirically with parenteral antibiotics. Overall, 47% (93/196) of all patients had fever in the setting of neutropenia (ANC ≤ 1000), including 62 patients (32%) with severe neutropenia (i.e., ANC ≤ 500).

In a Phase I investigational study using cladribine in high doses (4 to 6 times the recommended dose for Hairy Cell Leukemia) as part of a bone marrow transplant conditioning regimen, which also included high dose cyclophosphamide and total body irradiation, acute nephrotoxicity and delayed onset neurotoxicity were observed. Thirty-one (31) poor-risk patients with drug-resistant acute leukemia in relapse (29 cases) or non-Hodgkins Lymphoma (2 cases) received cladribine for 7 to 14 days prior to bone marrow transplantation. During infusion, 8 patients experienced gastrointestinal symptoms. While the bone marrow was initially cleared of all hematopoietic elements, including tumor cells, leukemia eventually recurred in all treated patients. Within 7 to 13 days after starting treatment with cladribine, 6 patients (19%) developed manifestations of renal dysfunction (e.g., acidosis, anuria, elevated serum creatinine, etc.) and 5 required dialysis. Several of these patients were also being treated with other medications having known nephrotoxic potential. Renal dysfunction was reversible in 2 of these patients. In the 4 patients whose renal function had not recovered at the time of death, autopsies were performed; in 2 of these, evidence of tubular damage was noted. Eleven (11) patients (35%) experienced delayed onset neurologic toxicity. In the majority, this was characterized by progressive irreversible motor weakness (paraparesis/quadriparesis), of the upper and/or lower extremities. Onset noted 33 to 84 days after starting high dose therapy with cladribine. Non-invasive testing (electromyography and nerve conduction studies) was consistent with demyelinating disease. Severe neurologic toxicity has also been noted with high doses of another drug in this class.

Axonal peripheral polyneuropathy was observed in a dose escalation study at the highest dose levels (approximately 4 times the recommended dose for Hairy Cell Leukemia) in patients not receiving cyclophosphamide or total body irradiation. Severe neurological toxicity has been reported rarely following treatment with standard cladribine dosing regimens.

In patients with Hairy Cell Leukemia treated with the recommended treatment regimen (0.09 mg/kg/day for 7 consecutive days), there have been no reports of neurologic toxicities.

Of the 196 Hairy Cell Leukemia patients entered in the two trials, there were 8 deaths following treatment. Of these, 6 were of infectious etiology, including 3 pneumonias, and 2 occurred in the first month following cladribine therapy. Of the 8 deaths, 6 occurred in previously treated patients who were Refractory to α-interferon.

Benzyl alcohol is a constituent of the recommended diluents for the 7-day infusion solution. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. See **DOSAGE AND ADMINISTRATION.**

Pregnancy Category D: Cladribine should not be given during pregnancy.

Cladribine is teratogenic in mice and rabbits and consequently has the potential to cause fetal harm when administered to a pregnant woman. A significant increase in fetal variations was observed in mice receiving 1.5 mg/kg/day (4.5 mg/m²) and increased resorptions, reduced litter size and increased fetal malformations were observed when mice received 3 mg/kg/day (9 mg/m²). Fetal death and malformations were observed in rabbits that received 3 mg/kg/day

(33 mg/m²). No fetal effects were seen in mice at 0.5 mg/kg/day (3.5 mg/m²) or in rabbits at 1 mg/kg/day (11 mg/m²).

Although there is no evidence of teratogenicity in humans due to cladribine, other drugs which inhibit DNA synthesis (e.g., methotrexate and aminopterin) have been reported to be teratogenic in humans. Cladribine has been shown to be embryotoxic in mice when given at doses equivalent to the recommended dose.

There are no adequate and well controlled studies in pregnant women. If cladribine is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should be advised to avoid becoming pregnant.

PRECAUTIONS

General: Cladribine is a potent antineoplastic agent with potentially significant toxic side effects. It should be administered only under the supervision of a physician experienced with the use of cancer chemotherapeutic agents. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment of peripheral blood counts, particularly during the first 4 to 8 weeks post-treatment, is recommended to detect the development of anemia, neutropenia and thrombocytopenia and for early detection of any potential sequelae (e.g., infection or bleeding). As with other potent chemotherapeutic agents, monitoring of renal and hepatic function is also recommended, especially in patients with underlying kidney or liver dysfunction. See **WARNINGS** and **ADVERSE REACTIONS**.

Fever was a frequently observed side effect during the first month on study. Since the majority of fevers occurred in neutropenic patients, patients should be closely monitored during the first month of treatment and empiric antibiotics should be initiated as clinically indicated. Although 69% of patients developed fevers, less the 1/3 of febrile events were associated with documented infection.

Given the known myelosuppressive effects of cladribine, practitioners should carefully evaluate the risks and benefits of administering this drug to patients with active infections. See **WARNINGS** and **ADVERSE REACTIONS**.

There are inadequate data on dosing of patients with renal or hepatic insufficiency. Development of acute renal insufficiency in some patients receiving high doses of cladribine has been described. Until more information is available, caution is advised when administering the drug to patients with known or suspected renal or hepatic insufficiency. See **WARNINGS**.

Rare cases of tumor lysis syndrome have been reported in patients treated with cladribine with other hematologic malignancies having a high tumor burden.

Cladribine must be diluted in designated intravenous solutions prior to administration. See **DOSAGE AND ADMINISTRATION**.

Laboratory Tests: During and following treatment, the patient's hematologic profile should be monitored regularly to determine the degree of hematopoietic suppression. In the clinical studies, following reversible declines in all cell counts, the mean Platelet Count reached 100 x 10⁹/L by Day 12, the mean Absolute Neutrophil Count reached 1500 x 10⁶/L by Week 5 and the mean Hemoglobin reached 12 g/dL by Week 8. After peripheral counts have normalized, bone marrow aspiration and biopsy should be performed to confirm response to treatment with cladribine. Febrile events should be investigated with appropriate laboratory and radiologic studies. Periodic assessment of renal function and hepatic function should be performed as clinically indicated.

Drug Interactions: There are no known drug interactions with cladribine. Caution should be exercised if cladribine is administered before, after, or in conjunction with other drugs known to cause immunosuppression or myelosuppression. See **WARNINGS**.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No animal carcinogenicity studies have been conducted with cladribine. However, its carcinogenic potential cannot be excluded based on demonstrated genotoxicity of cladribine.

As expected for compounds in this class, the actions of cladribine yield DNA damage. In mammalian cells in culture, cladribine caused the accumulation of DNA strand breaks. Cladribine was also incorporated into DNA of human lymphoblastic leukemia cells. Cladribine was not mutagenic *in vitro* (Ames and Chinese hamster ovary cell gene mutation tests) and did not induce unscheduled DNA synthesis in primary rat hepatocyte cultures. However, cladribine was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (mouse bone marrow micronucleus test).

When administered intravenously to Cynomolgus monkeys, cladribine has been shown to cause suppression of rapidly generating cells, including testicular cells. The effect on human fertility is unknown.

Pregnancy: Teratogenic Effects: Pregnancy Category D. See **WARNINGS**.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from cladribine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug for the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established. In a Phase I study involving patients 1 to 21 years old with relapsed acute leukemia, cladribine was given by continuous intravenous infusion in doses ranging from 3 to 10.7 mg/m²/day for 5 days (one-half to twice the dose recommended in Hairy Cell Leukemia). In this study, the dose-limiting toxicity was severe myelosuppression with profound neutropenia and thrombocytopenia. At the highest dose (10.7 mg/m²/day), 3 of 7 patients developed irreversible myelosuppression and fatal systemic bacterial or fungal infections. No unique toxicities were noted in this study. See **WARNINGS** and **ADVERSE REACTIONS**.

ADVERSE REACTIONS

Safety data are based on 196 patients with Hairy Cell Leukemia: the original cohort of 124 patients plus additional 72 patients enrolled at the same two centers after the original enrollment cutoff. In Month 1 of the Hairy Cell Leukemia clinical trials, severe neutropenia was noted in 70% of patients, fever in 69%, and infection was documented in 28%. Other adverse experiences reported frequently during the first 14 days after initiating treatment included: fatigue (45%), rashes (28%), rash (27%), headache (22%) and injection site reactions (19%). Most non-hematologic adverse experiences were mild to moderate in severity.

Myelosuppression was frequently observed during the first month after starting treatment. Neutropenia (ANC < 500 x 10⁶/L) was noted in 70% of patients, compared with 26% in whom it was present initially. Severe anemia (hemoglobin <8.5 g/dL) developed in 37% of patients, compared with 10% initially and thrombocytopenia (Platelets < 20 x 10⁹/L) developed in 12% of patients, compared to 4% in whom it was noted initially.

During the first month, 54 of 196 patients (28%) exhibited documented evidence of infection. Serious infections (e.g., septicemia, pneumonia) were reported in 8% of all patients; the remainder were mild or moderate. Several deaths were attributable to infection and/or complications related to the underlying disease. During the second month, the overall rate of documented infection was 8%; these infections were mild to moderate and no severe systemic infections were seen. After the third month, the monthly incidence of infection was either less than or equal to that of the months immediately preceding cladribine therapy.

During the first month, 11% of patients experienced severe fever (i.e., ≥39.4°F). Documented infections were noted in fewer than one-third of febrile episodes. Of the 196 patients studied, 18 were noted to have a documented infection in the month prior to treatment. In the month following treatment, there were 54 episodes of documented infection: 23 (42%) were bacterial, 11 (20%) were viral and 11 (20%) were fungal. Seven (7) of 8 documented episodes of herpes zoster occurred during the month following treatment. Fourteen (14) of 16 episodes of documented fungal infections occurred in the first two months following treatment. Virtually all of these patients were treated empirically with antibiotics. See **WARNINGS** and **PRECAUTIONS**.

Analysis of lymphocyte subsets indicates that treatment with cladribine is associated with prolonged depression of the CD4 counts. Prior to treatment, the mean CD4 count was 756/µL. The mean CD4 count nadir, which occurred 4 to 6 months following treatment, was 272/µL. Fifteen (15) months after treatment, mean CD4 counts remained below 500/µL. CD8 counts behaved similarly, though increasing counts were observed after 9 months. The clinical significance of the prolonged CD4 lymphopenia is unclear.

Another event of unknown clinical significance includes the observation of prolonged bone marrow hypocellularity. Bone marrow cellularity of <20% was noted after 4 months in 42 of 124 patients (34%) treated in the two pivotal trials. This hypocellularity was noted as late as day 1010. It is not known whether the hypocellularity is the result of disease related marrow fibrosis or if it is the result of cladribine toxicity. There was no apparent clinical effect on the peripheral blood counts.

The vast majority of rashes were mild and occurred in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause rash.

Most episodes of nausea were mild, not accompanied by vomiting, and did not require treatment with antiemetics. In patients requiring antiemetics, nausea was easily controlled, most frequently with chlorpromazine.

Adverse reactions reported during the first 2 weeks following treatment initiation (regardless of relationship to drug) by >5% of patients included:

Body as a Whole: fever (69%), fatigue (45%), chills (9%), asthenia (9%), diaphoresis (9%), malaise (7%), trunk pain (6%)

Gastrointestinal: nausea (28%), decreased appetite (17%), vomiting (13%), diarrhea (10%), constipation (9%), abdominal pain (6%)

Hemic/Lymphatic: purpura (10%), petechiae (8%), epistaxis (3%)

Nervous System: headache (22%), dizziness (9%), insomnia (7%)

Cardiovascular System: edema (6%), tachycardia (6%)

Respiratory System: abnormal breath sounds (11%), cough (10%), abnormal chest sounds (9%), shortness of breath (7%)

Skin/Subcutaneous Tissue: rash (27%), injection site reactions (19%), pruritis (6%), pain (6%), erythema (6%)

Musculoskeletal System: myalgia (7%), arthralgia (5%)

Adverse experiences related to intravenous administration included: injection site reactions (9%) (i.e., redness, swelling, pain), thrombosis (2%), phlebitis (2%) and a broken catheter (1%).

These appear to be related to the infusion procedure and/or indwelling catheter, rather than the medication or the vehicle. From Day 15 to the last follow-up visit, the only events reported by >5% of patients were: fatigue (11%), rash (10%), headache (7%), cough (7%), and malaise (5%).

For a description of adverse reactions associated with use of high doses in non-Hairy Cell Leukemia patients, see **WARNINGS**.

The following additional adverse events have been reported since the drug became commercially available. These adverse events have been reported primarily in patients who received multiple courses of cladribine:

Hematologic: bone marrow suppression with prolonged pancytopenia, including some reports of aplastic anemia, hemolytic anemia, which was reported in patients with lymphoid malignancies, occurring within the first few weeks following treatment.

Hepatic: reversible, generally mild increases in bilirubin and transaminases.

Nervous System: Neurological toxicity, however, severe neurotoxicity has been reported rarely following treatment with standard cladribine dosing regimens.

Respiratory System: pulmonary interstitial infiltrates, in most cases, an infectious etiology was identified.

Skin/Subcutaneous: urticaria, hypercalcinosis. In isolated cases Stevens-Johnson and toxic epidermal necrolysis have been reported in patients who were receiving or had recently been treated with other medications (e.g., allopurinol or antibiotics) known to cause these syndromes.

Opportunistic infections have occurred in the acute phase of treatment due to the immunosuppression mediated by cladribine.

OVERDOSAGE

High doses of cladribine have been associated with: irreversible neurologic toxicity (paraparesis/quadriparesis), acute nephrotoxicity, and severe bone marrow suppression resulting in neutropenia, anemia and thrombocytopenia. See **WARNINGS**. There is no known specific antidote for overdosage. Treatment of overdosage consists of discontinuation of cladribine, careful observation and appropriate supportive measures. It is not known whether the drug can be removed from the circulation by dialysis or hemofiltration.

DOSAGE AND ADMINISTRATION

Usual Dose:

The recommended dose and schedule of cladribine for active Hairy Cell Leukemia is as a single course given by continuous infusion for 7 consecutive days at a dose of 0.09 mg/kg/day. Deviations from this dosage regimen are not advised. If the patient does not respond to the initial course of cladribine for Hairy Cell Leukemia, it is unlikely that they will benefit from additional courses. Physicians should consider delaying or discontinuing the drug if neurotoxicity or renal toxicity occurs. See **WARNINGS**.

Specific risk factors predisposing to increased toxicity from cladribine have not been defined. In view of the known toxicities of agents of this class, it would be prudent to proceed carefully in patients with known or suspected renal insufficiency or severe bone marrow impairment of any etiology. Patients should be monitored closely for hematologic and non-hematologic toxicity. See **WARNINGS** and **PRECAUTIONS**.

Preparation and Administration of Intravenous Solutions:

Cladribine must be diluted with the designated diluent prior to administration. Since the drug product does not contain any antimicrobial preservative or bacteriostatic agent, **aseptic technique and proper environmental precautions must be observed in preparation of cladribine solutions.**

To prepare a single daily dose: Add the calculated dose (0.09 mg/kg or 0.06 mL/kg) of cladribine to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection. Infuse continuously over 24 hours. Repeat daily for a total of 7 consecutive days. **The use of 5% dextrose as a diluent is not recommended because of increased degradation of cladribine.** Admixtures of cladribine are chemically and physically stable for at least 24 hours at room temperature under normal room fluorescent light in Baxter Viaflex® PVC infusion containers. **Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised.**

	Dose of Cladribine Injection	Recommended Diluent	Quantity of Diluent
24 hour infusion method	1 (day) x 0.09 mg/kg	0.9% Sodium Chloride Injection	500 mL

To prepare a 7 day infusion: The 7 day infusion solution should only be prepared with Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol preserved). In order to minimize the risk of microbial contamination, both cladribine injection and the diluent should be passed through a sterile 0.22µ disposable hydrophilic syringe filter as each solution is being introduced into the infusion reservoir. First add the calculated dose of cladribine (7 days x 0.09 mg/kg or mL/kg) to the infusion reservoir through the sterile filter. Then add a calculated amount of Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol preserved) also through the filter to bring the total volume of the solution to 100 mL. After completing solution preparation, clamp off the line, disconnect and discard the filter. Aseptically aspirate air bubbles from the reservoir as necessary using the syringe and a dry second sterile filter or a sterile vent filter assembly. Reclamp the line and discard the syringe and filter assembly. Infuse continuously over 7 days. Solutions prepared with Bacteriostatic Sodium Chloride Injection for individuals weighing more than 85 kg may have reduced preservative effectiveness due to greater dilution of the benzyl alcohol preservative. Admixtures for the 7 day infusion have demonstrated acceptable chemical and physical stability for at least 7 days in the SIMS Deltec MEDICATION CASSETTE™ Reservoir 1.

	Dose of Cladribine Injection	Recommended Diluent	Quantity of Diluent
7 day infusion method (use sterile 0.22µ filter when preparing infusion solution)	7 (days) x 0.09 mg/kg	Bacteriostatic 0.9% Sodium Chloride Injection (0.9% benzyl alcohol)	q.s. to 100 mL

Since limited compatibility data are available, adherence to the recommended diluents and infusion systems is advised. Solutions containing cladribine should not be mixed with other intravenous drugs or additives or infused simultaneously via a common intravenous line, since compatibility testing has not been performed. Preparations containing benzyl alcohol should not be used in neonates. See **WARNINGS**.

Care must be taken to assure the stability of prepared solutions. Once diluted, solutions of cladribine should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to start of administration. Vials of cladribine are for single-use only. Any unused portion should be discarded in an appropriate manner. See **Handling and Disposal**.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. A precipitate may occur during the exposure of cladribine to low temperatures; it may be redissolved by allowing the solution to warm naturally to room temperature and by shaking vigorously. **DO NOT HEAT OR MICROWAVE.**

Chemical Stability of Vials:

When stored in refrigerated conditions between 2° to 8° C (36° to 46° F) protected from light, unopened vials of cladribine are stable until the expiration date indicated on the package. Freezing does not adversely affect the solution. If freezing occurs, thaw naturally to room temperature. DO NOT heat or microwave. Once thawed, the vial of cladribine is stable until expiry if refrigerated. DO NOT refreeze. Once diluted, solutions containing cladribine should be administered promptly or stored in the refrigerator (2° to 8° C) for no more than 8 hours prior to administration.

Handling and Disposal:

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken when handling, preparing, and administering cladribine. The use of disposable gloves and protective garments is recommended. If cladribine contacts the skin or mucous membranes, wash the involved surface immediately with copious amounts of water. Several guidelines on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Refer to your institution's guidelines and all applicable state/local regulations for disposal of cytotoxic waste.

HOW SUPPLIED

Cladribine Injection is supplied as a sterile, preservative-free, isotonic solution containing 10 mg (1 mg/mL) of cladribine at 10 mL filled into a single-use clear flint glass 20 mL vial, individually boxed. **NDC 55390-124-01**

Store refrigerated 2° to 8° C (36° to 46° F). Protect from light during storage.

REFERENCES

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2. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs. NIH Publication No. 83-2621. For sale by the Superintendent of Documents, US Government Printing Office, Washington, DC 20402.
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8. OSHA Work-Practice Guidelines for Personnel Dealing with Cytotoxic (Antineoplastic) Drugs. *Am J Hosp Pharm* 1986; 43:1193-1204.
9. Viaflex® containers, manufactured by Baxter Healthcare Corporation - Code No. 2B8013 (tested in 1991)
10. MEDICATION CASSETTE™ Reservoir, manufactured by SIMS Deltec, Inc. - Reorder No. 6021/60A (tested in 1991)

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146
January 2000

Manufactured for:
Bedford Laboratories™
Bedford, OH 44146
CLD-P09

BEN VENUE
021-26-02
PRINTED SIDE

Each mL contains 1 mg of cladribine and 9 mg of sodium chloride. Phosphoric acid and/or dibasic sodium phosphate may have been added to adjust the pH. pH approximately 6.3.

Manufactured by:
Ben Venue Labs, Inc.,
Bedford, OH 44146

Manufactured for:
Bedford Laboratories™,
Bedford, OH 44146

NDC 55390-124-01
10 mL single-dose vial

CLADRIBINE
INJECTION

MUST BE DILUTED PRIOR TO IV INFUSION

10 mg

(1 mg/mL)

Rx ONLY.

55390-124-01

LOT
EXP

Directions for Use:
Single-dose vial. Not for direct infusion. For the preparation of intravenous solutions and usual dosage: See package insert.

Store in refrigerator at 2° to 8°C (36° to 46°F).

PROTECT FROM LIGHT. Retain in carton until time of use.

NDC 55390-124-01
10 mL single-dose vial

CLADRIBINE
INJECTION

MUST BE DILUTED PRIOR TO IV INFUSION

10 mg

(1 mg/mL)

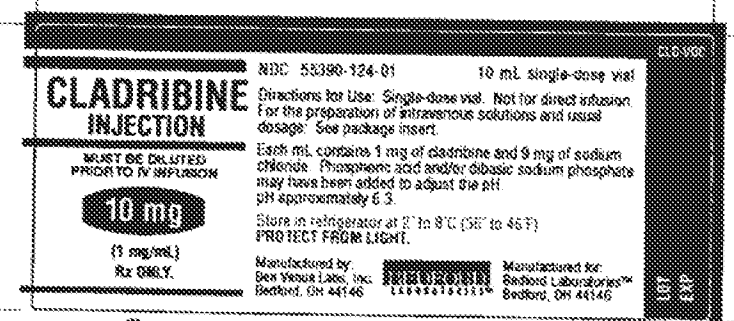
Rx ONLY.

CLD-COO

Format Number: 71939 #014A
Black
3292 Green
032 Red

Prepared by
Mark Zarnstorff
Checked by

Note: Keyline does not print.



Format: 71940 #037
1.5" x 3.5"
PMS Black, PMS 032 Red, PMS 3292 Green

EXHIBIT U

Drugs@FDA: FDA-Approved Drugs

SHARE (HTTPS://WWW.FACEBOOK.COM/SHARER/SHARER.PHP?U=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=BASICSEARCH.PROCESS)

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PIN IT (HTTPS://WWW.PINTEREST.COM/PIN/CREATE/BUTTON/?URL=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=BASICSEARCH.PROCESS&DESCRIPTION=DRUGS@FDA: FDA-APPROVED DRUGS)

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Abbreviated New Drug Application (ANDA): 076571
Company: FRESENIUS KABI USA

EMAIL (MAILTO:?SUBJECT=DRUGS@FDA: FDA APPROVED DRUG PRODUCTS&BODY=HTTP://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=OVERVIEW.PROCESS%26VARAPPLNO=076571)

Products on ANDA 076571

CSV | Excel | Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	AP	No	Yes

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for ANDA 076571

Therapeutic Equivalents for ANDA 076571

CLADRIBINE

INJECTABLE;INJECTION; 1MG/ML
TE Code = AP

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE Code	Application No.
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	076571
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	210856 (/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	200510 (/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	075405 (/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=

Showing 1 to 4 of 4 entries

EXHIBIT V

Drugs@FDA: FDA-Approved Drugs

SHARE (HTTPS://WWW.FACEBOOK.COM/SHARER/SHARER.PHP?U=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=BASICSEARCH.PROCESS&APPLNO=200510)

TWEET (HTTPS://TWITTER.COM/INTENT/TWEET/?TEXT=DRUGS@FDA: FDA-APPROVED DRUGS&URL=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=BASICSEARCH.PROCESS&APPLNO=200510)

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PIN IT (HTTPS://WWW.PINTEREST.COM/PIN/CREATE/BUTTON/?URL=HTTPS://WWW.ACCESSDATA.FDA.GOV/SCRIPTS/CDER/DAF/INDEX.CFM?EVENT=BASICSEARCH.PROCESS&APPLNO=200510&DESCRIPTION=DRUGS@FDA: FDA-APPROVED DRUGS)

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Abbreviated New Drug Application (ANDA): 200510
Company: MYLAN LABS LTD

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Products on ANDA 200510

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	TE Code	RLD	RS
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	AP	No	No

Showing 1 to 1 of 1 entries

Approval Date(s) and History, Letters, Labels, Reviews for ANDA 200510

Therapeutic Equivalents for ANDA 200510

CLADRIBINE

INJECTABLE;INJECTION; 1MG/ML
TE Code = AP

CSV Excel Print

Drug Name	Active Ingredients	Strength	Dosage Form/Route	Marketing Status	RLD	TE Code	Application No.
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	076571 (/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	210856 (/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=
CLADRIBINE	**CLADRIBINE**	**1MG/ML**	**INJECTABLE;INJECTION**	**Prescription**	**No**	**AP**	**200510**
CLADRIBINE	CLADRIBINE	1MG/ML	INJECTABLE;INJECTION	Prescription	No	AP	075405 (/scripts/cder/daf/index.cfm?event=BasicSearch.process&ApplNo=

Showing 1 to 4 of 4 entries

Electronic Patent Application Fee Transmittal

Application Number:	11722018
Filing Date:	18-Jun-2007
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Filer:	Eric J.I. Myers/Malika Ash Shakur
Attorney Docket Number:	000758US

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 5 months with $0 paid	1255	1	3160	3160
Miscellaneous:				
			Total in USD ($)	**3160**

Electronic Acknowledgement Receipt

EFS ID:	44539118
Application Number:	11722018
International Application Number:	
Confirmation Number:	5532
Title of Invention:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS
First Named Inventor/Applicant Name:	Giampiero De Luca
Customer Number:	151167
Filer:	Eric J.I. Myers/Malika Ash Shakur
Filer Authorized By:	Eric J.I. Myers
Attorney Docket Number:	000758US
Receipt Date:	17-DEC-2021
Filing Date:	18-JUN-2007
Time Stamp:	08:12:29
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$3160
RAM confirmation Number	E2021BG912401820
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		2021-12-17-Request-for-Reconsideration-as-filed.pdf	2821751 9450149c82e6be8b2858cd531a0e5cae7236d726	yes	78

Multipart Description/PDF files in .zip description

Document Description	Start	End
Transmittal Letter	1	1
Extension of Time	2	2
37 CFR 1.750 Request for Reconsideration	3	7
Transmittal Letter	8	8
Affidavit-not covered under specific rule	9	40
Affidavit-not covered under specific rule	41	62
Affidavit-not covered under specific rule	63	70
Affidavit-not covered under specific rule	71	74
Affidavit-not covered under specific rule	75	78

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	38411 015422b04f8be3fd65af39fce2289a86d5bad91b	no	2

Warnings:

Information:

Total Files Size (in bytes):	2860162

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

FEE TRANSMITTAL		
	Application Number	11/722,018
	Filing Date	June 18, 2007
	First Named Inventor	Giampiero De Luca
☐No fee required	Art Unit	1649
	Examiner Name	BALLARD, KIMBERLY
☒Total payment $ 3160	Attorney Docket No.	000758US
	Title	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

☐Applicant asserts small entity status, 37 CFR 1.27

☐Applicant asserts micro entity status, 37 CFR 1.29 *(Form PTO/SB/15 or equivalent enclosed or already submitted)*

☐Track 1 Prioritized Examination

Claims Fees:

Total:	(- 20) ×	$100	$
Independent:	(- 3) ×	$480	$
☐Multiple dependency		$860	$
☐Late filing declaration		$160	$
☐Non-electronic filing fee		$400	$
☐Non-English translation		$140	$

Extension Fees under 37 CFR 1.136(a) and 1.17(a), see petition filed herewith, if applicable:

☐Within first month	$ 220	$
☐Within second month	$ 640	$
☐Within third month	$1480	$
☐Within fourth month	$2320	$
☒Within fifth month	$3160	$3160

☐Terminal Disclaimer	$ 170	$
☐RCE – 1st Request	$1360	$
☐RCE – 2nd or Subseq.	$2000	$
☐Notice of Appeal	$ 840	$
☐Appl'n Size (pp.-100)/50 ×	$ 420	$

Other:

☐	$
☐	$
☐	$
☐	$

Payment in the amount of $ 3160 paid by:

☒Credit Card (online if electronically filed, or attached if paper filed)

☐Deposit Account No. **601920**.

☒ Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. **601920** under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. **601920**.

☒ If these papers are not considered timely, then Applicants hereby petition under 37 CFR 1.136 for any necessary extension of time, further authorizing any necessary extension of time fees to be charged to Deposit Account No. **601920**.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Dr. Kirsten Grueneberg
Registration No. 47,297

Eric Myers
Registration No. 68,546

Customer Number
151167
Phone: (571) 458-7790
Fax: (571) 458-7789

PETITION FOR EXTENSION OF TIME Under 37 CFR 1.136(a)		
	Application Number	11/722,018
	Filing Date	June 18, 2007
	First Named Inventor	Giampiero De Luca
	Art Unit	1649
	Examiner Name	BALLARD, KIMBERLY
	Attorney Docket No.	000758US
	Title	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

Applicants respectfully request that the Office grant an extension of time under 37 CFR 1.136(a) in the above-identified application, for

☐ one month ☐ four months
☐ two months ☒ five months
☐ three months

to December 20, 2021, for filing:

☒ a response to the Office Action (NOTICE OF DETERMINATION OF INELIGIBILITY), mailed May 20, 2021 .
☐ a response to the Notice of Allowability, mailed _____.
☐ a response to the Notice of File Missing Parts, mailed _____.
☐ a Notice of Appeal.
☐ an Appeal Brief, following the Notice of Appeal filed on _____.

Applicants accompany this petition with a Fee Transmittal form to pay the required extension of time fees in accordance with 37 CFR 1.17(a) by credit card (online if electronically filed, or attached if paper filed) or from Deposit Account No. **601920**.

Please charge additional fee(s) or underpayment of fee(s) to Deposit Account No. **601920** under 37 CFR 1.16 and 1.17, and please credit any overpayment of fee(s) to Deposit Account No. **601920**.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Dr. Kirsten Grueneberg
Registration No. 47,297

Eric Myers
Registration No. 68,546

Customer Number
151167
Phone: (571) 458-7790
Fax: (571) 458-7789

Docket No. 000758US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT:	U.S. PAT. NO. 7,713,947
ISSUED:	MAY 11, 2010
APPLICATION:	11/722,018
FILED:	JUNE 18, 2007
INVENTORS:	DE LUCA ET AL.
EXPIRATION:	OCTOBER 16, 2026
TITLE:	CLADRIBINE REGIMEN FOR TREATING MULTIPLE SCLEROSIS

REQUEST FOR RECONSIDERATION
OF FINAL DETERMINATION OF INELIGIBILITY
ON APPLICATION FOR EXTENSION OF TERM UNDER 35 USC §156

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

Merck Serono SA Switzerland ("Applicant") files the present Request for Reconsideration of the Notice of Determination of Ineligibility ("Notice") dated May 20, 2021 and regarding U.S. Patent No. 7,713,947 ("the '947 patent"). The Notice was in response to an application for Patent Term Extension ("PTE"), which Applicant initially filed for the '947 patent on May 24, 2019.

The Notice provides a two-month period for filing a request for reconsideration, extendable pursuant to 37 C.F.R. 1.136. Applicant hereby petitions for a three-month extension of time under 37 C.F.R. 1.136 and authorizes the United States Patent and Trademark Office ("USPTO") to charge the applicable extension fee, and any additional required fees, to Deposit Account No. 601920.

Applicant respectfully requests reconsideration from the Food and Drug Administration ("FDA") and the USPTO as to whether approval of New Drug Application (NDA) number 22561 qualifies as the first permitted marketing or use of the Approved Product, Mavenclad. Mavenclad contains, among other components, cladribine and hydroxypropyl betadex. (Exhibit H, submitted with the original application for Patent Term Extension for the'947 patent and resubmitted herewith, at pages 19-20). Hydroxypropyl betadex may form complexes. (*Id.* at 23).

As the USPTO has noted, the term of a patent which claims a product shall be extended if, *inter alia*, the permission for the commercial marketing or use of the product is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred. (35 U.S.C. §156(a)(5)(A)). The term "product" in the present context extends to "any salt or ester" thereof. (35 U.S.C. §156(f)(1)-(2)). However, the Federal Circuit has found that this broadened definition of the term "product" is limited, and does not extend, for example, to metabolites or de-esterified forms. (*Biogen International GmbH v. Banner Life Sciences*, 956 F. 3d 1351, 1357 (Fed. Cir. 2020)). In addition, for purposes of Patent Term Extension, the relevant product is that which is present in the drug at the time of administration. (*PhotoCure Asa v. Kappos*, 603 F. 3d 1372, 1376 (Fed. Cir. 2010)).

The Notice provides a conclusory statement equating Mavenclad with "cladribine alone," citing the October 13, 2020 letter from the FDA to the USPTO ("FDA Letter"). (Notice at pages 1-2). In turn, the FDA Letter also equates Mavenclad with cladribine, but does not provide supporting analysis or citation for this conclusion. (FDA Letter at page 1). Thus, both the FDA and the USPTO appear to have equated cladribine and Mavenclad without analysis or explanation evidencing a full consideration of the content of Mavenclad.

However, as noted above, the relevant product is that which is present in the drug at the time of administration. As also noted above, Mavenclad contains cladribine and hydroxypropyl betadex. Applicant respectfully submits that the FDA and the USPTO do not appear to have considered the full composition of Mavenclad, as it exists at the time of administration, in stating that the relevant product is "cladribine alone." Reconsideration is respectfully requested.

Moreover, both the Notice and in the FDA letter have concluded that Mavenclad does not represent the first permitted commercial marketing or use of the product based, for example, on a list of four approved formulations that include cladribine. (Notice at page 2; FDA letter at page 1) However, these formulations do not further include hydroxypropyl betadex. First, the Notice and the FDA letter cite the approval of NDA 20229 for Leustatin (cladribine), but the components of this formulation are cladribine, sodium chloride, and optionally phosphoric acid and/or dibasic sodium phosphate. (Exhibit L, submitted with the original application for Patent Term Extension for the'947 patent and resubmitted herewith, at page 1 of the label). Second, the Notice and the FDA letter cite the approval of ANDA 75405, but the components of this formulation are also cladribine, sodium chloride, and optionally phosphoric acid and/or dibasic sodium phosphate. (Exhibit T, "CLADRIBINE INJECTION" (ANDA 75405) label, newly submitted herewith, at page 1). Third and fourth, the Notice and the FDA letter cite the approval of ANDA 76571 and ANDA 200510, but these are both equivalents of ANDA 75405. (Exhibit U, FDA website for ANDA 76571, newly submitted herewith, at page 2; Exhibit V, FDA website for ANDA 200510, newly submitted herewith, at page 2). The FDA and the USPTO further do not appear to have considered whether these products or any other approved products are the same as, or constitute any salt or ester of, the relevant product of Mavenclad, or whether instead the relationship is not one of identity, salt, or ester, but of another type, analogous to metabolites

or de-esterified forms, which would not have constituted the same product for purposes of PTE eligibility.

Thus, the FDA and the USPTO have not provided evidence of any earlier approval of a product containing cladribine with hydroxypropyl betadex.

The question regarding Mavenclad as a first permitted marketing or use under 35 U.S.C. §156(a)(5)(A) appears to have been the sole basis for the dismissal of the PTE application for the'947 patent. (Notice at pages 1-3). Applicant maintains that this and all other requirements under 35 U.S.C. §156 have been satisfied for the grant of PTE as set forth in Applicant's initial PTE application filed May 24, 2019.

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought.

Correspondence relating to the application for patent term extension should be addressed to:

Dr. Kirsten Grüneberg
Grüneberg and Myers, PLLC
1775 Tysons Blvd
5th Floor
Tysons, VA 22102

Telephone: 571-458-7783
Email: patent@gandmpatent.com
Fax: 571-458-7789

* * *

In accordance with the above statements and the exhibits provided herewith, Applicant respectfully requests reconsideration of the Notice and extension of the term of the '947 patent under 35 U.S.C. §156 due to regulatory delay for a period of **1826 days**, as set forth in the original PTE application.

Respectfully Submitted,
GRÜNEBERG AND MYERS PLLC

/Kirsten Grueneberg/

Customer Number
151167
Phone: (571) 458-7790
Fax: (571) 458-7789

Dr. Kirsten Grueneberg
Attorney of Record
Registration No. 47,297

Eric Myers
Registration No. 68,546

LIST OF EXHIBITS

Exhibit	Contents
H	Mavenclad Label (submitted previously and resubmitted herewith)
L	Leustatin (cladribine) NDA 020229: listing and label (submitted previously and resubmitted herewith)
T	"CLADRIBINE INJECTION" (ANDA 75405) label
U	FDA website for ANDA 76571
V	FDA website for ANDA 200510

AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court for the District of Delaware on the following

☐ Trademarks or ☑ Patents (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/25/2022	for the District of Delaware

PLAINTIFF	DEFENDANT
MERCK KGaA and MERCK SERONO SA	ACCORD HEALTHCARE, INC. and INTAS PHARMACEUTICALS LTD.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	7,713,947 B2	5/10/2010	Merck Serono SA
2	8,377,903 B2	2/19/2013	Merck Serono SA
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**