UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD,

Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY

IN THE CITY OF NEW YORK,

Patent Owner.

Case No. IPR2024-00313

U.S. Patent No. RE47,045

Declaration of Shauna L. Wiest

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I. Introduction

1. I have prepared this Declaration in connection with the above referenced *Inter Partes* Review regarding U.S. Patent No. RE47,045. The Exhibits referenced in this Declaration are attached as Exhibits to this Declaration.

2. I am a senior research analyst with the Research & Information Services team at Finnegan, Henderson, Farabow, Garrett & Dunner, LLP located at 3300 Hillview Avenue, Palo Alto, CA 94304 ("Finnegan").

3. I am over eighteen years of age, and I am competent to make this Declaration. I make this Declaration based on my own personal knowledge, and my professional knowledge of library science practices.

4. I earned a Master of Science in Library Science degree from the University of North Carolina at Chapel Hill in 1999, and a Bachelor of Arts in Political Science degree from the University of California at San Diego in 1989. I have worked as a law librarian for over eighteen years. I have been employed in the Research & Information Services Department at Finnegan since 2021. Before that, from 2000-2015, I was employed as a Law Librarian at Stoel Rives LLP, and from 2015-2016, I was employed as a Competitive Intelligence Specialist for Nossaman LLP. Additionally, as a graduate student at the University of North Carolina at Chapel Hill, I served as an intern at the Environmental Protection Agency at Research Triangle Park ("EPA-RTP") where one of my rotations included original

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cataloging for EPA technical documents, state agency reports and documents, international organization documents, dissertations, and, on occasion, monographs.

II. Standard Library Practices for Receiving, Searching, and Making Materials Publicly Available

5. I have knowledge of and experience with standard library practices regarding the receipt, cataloging, searching, accessing, and making print and electronic materials available to the public. I also have knowledge of and experience with searching, identifying, borrowing, and downloading materials from Open Access resources and the Internet Archive and Wayback Machine.

III. Open Access Resources

6. Open Access (OA) refers to all electronic resources that are available online without any licensing or copyright restrictions. A publication is considered 'open access' when there are no financial, legal, or technical barriers to accessing it. This means anyone can read, download, copy, distribute, print, search for, and search within the information or use it for education or any other legal purpose. Examples of Open Access resources include articles, journals, books, conference proceedings, theses, videos, music, and more. Open Access has become increasingly popular in scholarly research and communication as academic resource prices have significantly increased over the past decade, and academic libraries' budgets have not kept pace with these new expenses.

IV. The Internet Archive

7. The Internet Archive, a 501(c)(3) non-profit and founded in 1996, is a publicly available digital library of Internet sites and other cultural artifacts that can be searched and accessed in digital form. Its mission is to provide Universal Access to All Knowledge including books, films, magazines, websites, videos, software programs, audio recordings, and television. Like a physical library, it provides free access to everyone. The Internet Archive is available here: https://archive.org/.

8. The Internet Archive created a resource known as the "Wayback Machine" (https://web.archive.org/). The Wayback Machine is named in reference to the famous Mr. Peabody's WABAC (pronounced way-back) machine from the Rocky and Bullwinkle cartoon show. The Wayback Machine makes it possible to search and browse more than 450 billion publicly available web pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search the Archive by keyword or a website URL. If archived records for a URL or the key words are available, the visitor will be presented with a display of available dates. The visitor may select one of those dates and be taken to the collection of web captures associated with the specific web crawl and point in time the capture came from.

9. This archived data made viewable by the Wayback Machine is obtained using web archiving software that automatically stores copies of files

available via the Internet, each file preserved as it existed at a particular point in time.

10. The Internet Archive assigns a URL to all archived files within the Wayback Machine in the following format: http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code inhh:mm:ss]/[Archived URL]. This is known as an "extended URL" format.

11. For example, the Internet Archive extended URL http://web.archive.org/web/19970126045828/http://www.archive.org/ denotes the URL for the record of the Internet Archive home page archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28).

V. Soriatane

12. **Exhibit 2123** is a true and correct copy of a Wayback Machine webpage for RxList, *Soriatane Drug Description* (2008), which was retrieved from the publicly available Internet Archive website at the following extended URL: https://web.archive.org/web/20080616120730/http://www.rxlist.com/cgi/generic/acitretin.htm.

13. I confirmed this on September 20, 2024. On September 20, 2024, I used Google Chrome to navigate to the publicly available website, https://www.rxlist.com/acitretin/generic-drug.htm. This reference is appended to my Declaration as Exhibit A.1. I next navigated to the Internet Archive website at

https://archive.org/, which is appended to my Declaration as Exhibit A.2. I next navigated to The Wayback Machine (which is prominently displayed on the homepage of the Internet Archive website) and clicked on its URL: https://web.archive.org/. In the search box, I entered the URL for RxList, Soriatane Drug Description (2008), which is http://www.rxlist.com/cgi/generic/acitretin.htm. This search took me to a page displaying the Wayback Machine's 20 saved captures of the webpage http://www.rxlist.com/cgi/generic/acitretin.htm between April 5, 2007 and July 8, 2012 at the extended URL https://web.archive.org/web/20240000000000*/http://www.rxlist.com/cgi/generic/acitretin.htm, which is appended to my Declaration as Exhibit A.3.

14. I then navigated to the year 2008 on Exhibit A.3 and clicked on the link for year 2008, which brought me to the following page and extended URL, https://web.archive.org/web/20080101000000*/http://www.rxlist.com/cgi/generic/acitretin.htm, which is appended to my Declaration as Exhibit A.4.

15. I then navigated to June 16, 2008 on Exhibit A.4 and clicked on the link, which brought me to the following page and extended URL https://web.archive.org/web/20080616120730/http://www.rxlist.com/cgi/generic/acitretin.htm, which is appended to my Declaration as Exhibit A.5.

16. This resulted in a document identical to the document downloaded and saved as Exhibit 2123, except for a different date and time in the header.

VI. Targretin

17. **Exhibit 2124** is a true and correct copy of a Wayback Machine web archive of RxList, *Targretin Drug Description* (2008), which was retrieved from the publicly available Internet Archive website at the following extended URL https://web.archive.org/web/20080615214054/http://www.rxlist.com/cgi/generic/bexarotene.htm.

18. I confirmed this on September 20, 2024. On September 20, 2024, I used Google Chrome to navigate to the publicly available website, http://www.rxlist.com/cgi/generic/bexarotene.htm. This reference is appended to my Declaration as Exhibit A.6. I next navigated to the Internet Archive website at https://archive.org/, which is appended to my Declaration as Exhibit A.2. I next navigated to The Wayback Machine (which is prominently displayed on the homepage of the Internet Archive website) and clicked on its URL: https://web.archive.org/. In the search box, I entered the URL for RxList, *Targretin Drug Description* (2008), which is http://www.rxlist.com/cgi/generic/bexarotene.htm. This search took me to a page displaying the Wayback Machine's 22 saved captures of the webpage http://www.rxlist.com/cgi/generic/bexarotene.htm between April 5, 2007 and September 4, 2015 at the extended URL

https://web.archive.org/web/20240000000000*/http://www.rxlist.com/cgi/generic/bexarotene.htm, which is appended to my Declaration as Exhibit A.7.

19. I then navigated to the year 2008 on Exhibit A.7 and clicked on the link for year 2008, which brought me to the following page and extended URL, https://web.archive.org/web/20080101000000*/http://www.rxlist.com/cgi/generic/bexarotene.htm, which is appended to my Declaration as Exhibit A.8.

20. I then navigated to June 15, 2008 on Exhibit A.8 and clicked on the link, which brought me to the following page and extended URL https://web.archive.org/web/20080615214054/http://www.rxlist.com/cgi/generic/bexarotene.htm, which is appended to my Declaration as Exhibit A.9.

21. This resulted in a document identical to the document downloaded and saved as **Exhibit 2124**, except for a different date and time in the header.

VII. Accutane

22. **Exhibit 2125** is a true and correct copy of a Wayback Machine web archive of RxList, *Accutane Drug Description* (2008), which was retrieved from the publicly available Internet Archive website at the following extended URL: https://web.archive.org/web/20080902152402/http://www.rxlist.com/cgi/generic/isotret.htm.

23. I confirmed this on September 20, 2024. On September 20, 2024, I used Google Chrome to navigate to the publicly available website

http://www.rxlist.com/cgi/generic/isotret.htm, which as of September 20, 2024 is displayed as https://www.rxlist.com/accutane-drug.htm. The Accutane reference at https://www.rxlist.com/accutane-drug.htm is appended to my Declaration as Exhibit A.10.

24. I next navigated to the Internet Archive website at https://archive.org/, which is appended to my Declaration as Exhibit A.2. I next navigated to The Wayback Machine (which is prominently displayed on the homepage of the Internet Archive website) and clicked on its URL: https://web.archive.org/.

25. In the search box, I entered the URL for RxList, Accutane Drug Description (2008), which is http://www.rxlist.com/cgi/generic/isotret.htm. This search took me to a page displaying the Wayback Machine's 231 saved captures of the webpage http://www.rxlist.com/cgi/generic/isotret.htm between November 14, 1996 and April 30, 2024 at the extended URL https://web.archive.org/web/20240000000000*/http://www.rxlist.com/cgi/generic/isotret.htm, which is appended to my Declaration as Exhibit A.11.

26. I then navigated to the year 2008 on Exhibit A.11 and clicked on the link for year 2008, which brought me to the following page and extended URL, https://web.archive.org/web/20080101000000*/http://www.rxlist.com/cgi/generic/isotret.htm, which is appended to my Declaration as Exhibit A.12.

27. I then navigated to September 2, 2008 on Exhibit A.12 and clicked on the link, which brought me to the following page and extended URL https://web.archive.org/web/20080902152402/http://www.rxlist.com/cgi/generic/isotret.htm, which is appended to my Declaration as Exhibit A.13.

28. This resulted in a document identical to the document downloaded and saved as **Exhibit 2125**, except for a different date and time in the header of Exhibit A.13.

VIII. Isotretinoin

29. **Exhibit 2131** is a true and correct copy of a Wayback Machine web archive of Chemo Care, *Isotretinoin* (2008), which was retrieved from the publicly available Internet Archive website at the following extended URL: https://web.archive.org/web/20080603203929/http://www.chemocare.com/bio/isotretinoin.asp#expand.

30. I confirmed this on September 20, 2024. On September 20, 2024, I used Google Chrome to navigate to the publicly available website http://www.chemocare.com/bio/isotretinoin.asp#expand, which on September 20, 2024 is displayed as https://chemocare.com/#expand. This reference at https://chemocare.com/#expand is appended to my Declaration as Exhibit A.14.

31. On September 22, 2024, I navigated to the Internet Archive website at https://archive.org/, which is appended to my Declaration as Exhibit A.2. I next

navigated to The Wayback Machine (which is prominently displayed on the homepage of the Internet Archive website) and clicked on its URL: https://web.archive.org/.

32. In the Wayback Machine search box, I entered the term "chemocare," which brought me to the publicly available Internet Archive page at https://web.archive.org/web/20240000000000*/chemocare, which is appended to my Declaration as Exhibit A.15.

33. I selected the first reference listed on Exhibit A.15, http://chemocare.com, and clicked on the link detailing "94,703 captures from 2002 to 2016," which brought me to the page https://web.archive.org/web/20240000000000*/http://chemocare.com/, which is appended to my Declaration as Exhibit A.16.

34. I next navigated to the year 2008 on Exhibit A.16 and clicked on the link for year 2008, which brought me to the page and extended URL https://web.archive.org/web/20080101000000*/http://chemocare.com/ which is appended to my Declaration as Exhibit A.17.

35. From Exhibit A.17 I clicked on "Chemotherapy Drugs," which took me to the page and extended URL https://web.archive.org/web/20080925172601/http://www.chemocare.com/bio/, which is appended to my Declaration as Exhibit A.18.

36. From Exhibit A.18, I selected the link for Isotretinoin, which brought me to the page and extended URL https://web.archive.org/web/20081210045453/http://www.chemocare.com/bio/isotretinoin.asp, which is appended to my Declaration as Exhibit A.19

37. This resulted in a document identical to the document downloaded and saved as **Exhibit 2131**, except for a different date and time in the header.

IX. EX2095 (Alkeus Press Release 2021.09.17)

38. This attestation relates to the public accessibility of Alkeus Pharmaceuticals, "*Alkeus Pharmaceuticals Announces Results from the SAGA Study of Oral Gildeuretinol in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration"* (2021) (*Alkeus Press Release 2021.09.17*). I understand that the *Alkeus Press Release 2021.09.17* has been submitted as **Exhibit 2095** in the proceeding.

39. **Exhibit 2095** is a true and correct copy of Alkeus Pharmaceuticals, *Alkeus Pharmaceuticals Announces Results from the SAGA Study of Oral Gildeuretinol in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration* (2021), which was retrieved free of charge from the publicly available website https://alkeuspharma.com/wp-content/uploads/2024/09/Alkeus-SAGA-topline-press-release_09172024_FINAL.pdf and attached here as **Exhibit 2095.** I confirmed this on September 22, 2024. On September 22, 2024, I used

Google to Chrome to navigate to and access the publicly available website, https://alkeuspharma.com, which is attached here as **Exhibit A.21**. From here I clicked on "News," and from the resulting pull-down menu, I clicked "Press Releases," which resulted in the webpage, https://alkeuspharma.com/category/press-releases/, which is attached here as **Exhibit A.22**. From here, I scrolled down the webpage until I located the press release titled, "Alkeus Pharmaceuticals Announces Results from the SAGA Study of Oral Gildeuretinol in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration," dated September 17, 2024. I clicked "Learn More" under the link for "Alkeus Pharmaceuticals Announces Results from the SAGA Study of Oral Gildeuretinol in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration," which resulted in the webpage, https://alkeuspharma.com/alkeus-pharmaceuticals-announces-results-from-the-saga-study-of-oral-gildeuretinol-in-patients-with-geographic-atrophy-secondary-to-age-related-macular-degeneration/, which is appended to my Attestation as **Exhibit A.23**. From this page I clicked "Download Press Release," resulting in webpage, https://alkeuspharma.com/wp-content/uploads/2024/09/Alkeus-SAGA-topline-press-release_09172024_FINAL.pdf, and downloaded the press release in PDF format. This resulted in the document downloaded and saved as **Exhibit 2095**.

X. EX2093 (Alkeus Press Release 2024.01.10)

40. This attestation relates to the public accessibility of Alkeus Pharmaceuticals, *Alkeus Pharmaceuticals Presents Positive Interim Data Showing Gildeuretinol Halted Stargardt Disease Progression* (2024) (*Alkeus Press Release 2024.01.10*). I understand that *Alkeus Press Release 2024.01.10* has been submitted as **Exhibit 2093** in the proceeding.

41. **Exhibit 2093** is a true and correct copy of Alkeus Pharmaceuticals, *Alkeus Pharmaceuticals Presents Positive Interim Data Showing Gildeuretinol Halted Stargardt Disease Progression* (2024), which was retrieved from the publicly available website https://alkeuspharma.com/wp-content/uploads/2024/01/alkeus-pharmaceuticals-presents-positive-interim-data-TEASE-3.pdf. I confirmed this on September 23, 2024. On September 23, 2024, I used Google Chrome to navigate to and access the publicly available website, https://alkeuspharma.com, which is attached to my Attestation as Exhibit A.21. From here I clicked "News," and from the resulting pull-down menu, I clicked "Press Releases," which resulted in the webpage, https://alkeuspharma.com/category/press-releases/, which is attached to my Attestation as Exhibit A.22.

42. From here, I scrolled through the pages linked on the bottom until I located and clicked on "Alkeus Pharmaceuticals Presents Positive Interim Data

Showing Gildeuretinol Halted Stargardt Disease Progression," dated January 10, 2024. I clicked on "Learn More" under the link for "Alkeus Pharmaceuticals Presents Positive Interim Data Showing Gildeuretinol Halted Stargardt Disease Progression," dated January 10, 2024, which resulted in the webpage, https://alkeuspharma.com/positive-interim-data-tease-3/, which is attached to my Attestation as Exhibit A.27. From this page I clicked on "Download Press Release," resulting in the webpage, https://alkeuspharma.com/wp-content/uploads/2024/01/alkeus-pharmaceuticals-presents-positive-interim-data-TEASE-3.pdf, and downloaded the press release in PDF format This resulted in the document downloaded and saved as **Exhibit 2093.**

XI. EX2092 (Alkeus Press Release 2024.07.18)

43. This attestation relates to the public accessibility of Alkeus Pharmaceuticals, *Alkeus Pharmaceuticals Announces Presentation of a TEASE-3 Study Update Showing Progression Stalled in Early-Stage Stargardt Disease Patients Treated with Gildeuretinol* (2024) (*Alkeus Press Release 2024.07.18*). I understand that *Alkeus Press Release 2024.07.18* has been submitted as **Exhibit 2092** in the proceeding.

44. **Exhibit 2092** is a true and correct copy of Alkeus Pharmaceuticals, *Alkeus Pharmaceuticals Announces Presentation of a TEASE-3 Study Update Showing Progression Stalled in Early-Stage Stargardt Disease Patients Treated*

with Gildeuretinol (2024), which was retrieved from the publicly available website https://alkeuspharma.com/wp-content/uploads/2024/07/Alkeus-ASRS-TEASE-3-update-press-release_07182024_final.pdf.

45. I confirmed this on September 23, 2024. On September 23, 2024, I used Google Chrome to navigate to and access the publicly available website, https://alkeuspharma.com, which is attached to my Attestation as Exhibit A.21. From here I clicked "News," and from the resulting pull-down menu, I clicked on "Press Releases," which resulted in the webpage, https://alkeuspharma.com/category/press-releases/, which is attached to my Attestation as Exhibit A.22. From here I scrolled down the webpage until I located "Alkeus Pharmaceuticals Announces Presentation of a TEASE-3 Study Update Showing Progression Stalled in Early-Stage Stargardt Disease Patients Treated with Gildeuretinol," dated July 18, 2024. I clicked on "Learn More" under the link for "Alkeus Pharmaceuticals Announces Presentation of a TEASE-3 Study Update Showing Progression Stalled in Early-Stage Stargardt Disease Patients Treated with Gildeuretinol," dated July 18, 2024 which resulted in the webpage, https://alkeuspharma.com/alkeus-pharmaceuticals-announces-presentation-of-a-tease-3-study-update-showing-progression-stalled-in-early-stage-stargardt-disease-patients-treated-with-gildeuretinol/, which is saved to my Attestation as Exhibit A.33. From this page I clicked "Download Press Release," resulting in the

webpage, https://alkeuspharma.com/wp-content/uploads/2024/07/Alkeus-ASRS-TEASE-3-update-press-release_07182024_final.pdf, and downloaded the press release in PDF format. This resulted in the document downloaded and saved as **Exhibit 2092.**

XII. EX2182 (Charters 2024)

46. This attestation relates to the public accessibility of Lynda Charters, *TEASE-3 study: Positive interim data reported for Stargardt drug*, Modern Retina (2009) (*Charters 2024*). I understand that *Charters 2024* has been submitted as **Exhibit 2182** in the proceeding.

47. **Exhibit 2182** is a true and correct copy of Lynda Charters, *TEASE-3 study: Positive interim data reported for Stargardt drug*, Modern Retina (2009), which was retrieved from the publicly available website https://www.modernretina.com/view/tease-3-study-positive-interim-data-reported-for-stargardt-drug.

48. I confirmed this on September 23, 2024. On September 23, 2024, I used Google Chrome to navigate to and access the publicly available website, https://www.modernretina.com/, which is saved to my Attestation as Exhibit A.43. From here I clicked on "News," and from the resulting pull-down menu, I clicked on "All News," which resulted in the webpage, https://www.modernretina.com/news, which is attached to my Attestation as

Exhibit A.44. From here I scrolled through the pages linked on the bottom until I found "TEASE-3 study: Positive interim data reported for Stargardt drug, dated March 17, 2024, on page 13 at https://www.modernretina.com/news?page=13, which is saved to my Attestation as Exhibit A.45. From here, I clicked "TEASE-3 study: Positive interim data reported for Stargardt drug," dated March 17, 2024, resulting in the webpage, https://www.modernretina.com/view/tease-3-study-positive-interim-data-reported-for-stargardt-drug, which I downloaded and saved as Exhibit 2182.

XIII. EX2183 (FDA Patient Listening Sessions 2024)

49. This attestation relates to the public accessibility of FDA, *FDA Patient Listening Sessions* (2024) (*FDA Patient Listening Sessions 2024*). I understand that *FDA Patient Listening Sessions 2024* has been submitted as **Exhibit 2183** in the proceeding.

50. **Exhibit 2183** is a true and correct copy of FDA, *FDA Patient Listening Sessions* (2024), which was retrieved from the publicly available website https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions. I confirmed this on September 23, 2024. On September 23, 2024, I used Google Chrome to navigate to and access the publicly available website, https://www.fda.gov/, which is attached to my Attestation as Exhibit A.47. From here I clicked on "Menu" in the upper corner and from the resulting pull-

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down menu, I clicked on "Patients" under "Information For," which resulted in the webpage, https://www.fda.gov/patients, which is saved to my Attestation as Exhibit A.48. From here I scrolled down the page and clicked on "Patient Listening Sessions," under "Patient Perspectives," which resulted in the webpage https://www.fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions, and downloaded a PDF form of the webpage. This resulted in the document downloaded and saved as **Exhibit 2183.**

XIV. EX2172

51. **Exhibit 2172** is a true and correct copy of Orphanet Encyclopedia, *Stargardt disease* (2003), which was retrieved from the publicly available website https://www.orpha.net/pdfs/data/patho/GB/uk-Stargardt.pdf. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://www.orpha.net/pdfs/data/patho/GB/uk-Stargardt.pdf , and downloaded the website in PDF form. This resulted in the document downloaded and saved as **Exhibit 2172**.

XV. EX2164

52. **Exhibit 2164** is a true and correct copy of Irena Tsui, Brian J. Song, Chyuan-Sheng Lin, & Stephen H. Tsang, *A Practical Approach to Retinal Dystrophies*, Retinal Physician (2007), which was retrieved from the publicly available website https://retinalphysician.com/issues/2007/april/a-practical-

approach-to-retinal-dystrophies/. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://retinalphysician.com/issues/2007/april/a-practical-approach-to-retinal-dystrophies/, and downloaded the website in PDF form. This resulted in a document identical to the document downloaded and saved as **Exhibit 2164**, except for a different date and time in the header.

XVI. EX2135

53. **Exhibit 2135** is a true and correct copy of UCSF Health, *Stargardt Disease* (2024), which was retrieved from the publicly available website https://www.ucsfhealth.org/conditions/stargardt-disease#. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://www.ucsfhealth.org/conditions/stargardt-disease#, and downloaded the website in PDF form. This resulted in a document identical to the document downloaded and saved as **Exhibit 2135**, except for a different date and time in the header.

XVII. EX2149

54. **Exhibit 2149** is a true and correct copy of *Stargardt Disease (STGD1), FDA Patient-led Listening Session, Minutes of the June 30, 2022, Meeting* (2022), which was retrieved from the publicly available website https://www.fda.gov/patients/learn-about-fda-patient-engagement/patient-listening-

session-summaries. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://www.fda.gov/patients/learn-about-fda-patient-engagement/patient-listening-session-summaries, and downloaded the website in PDF form. This resulted in a document identical to pages 1-5 of the document downloaded and saved as **Exhibit 2149**, except for a different date and time in the header. On that website, I clicked the link "Stargardt Disease," which led to the publicly available website, https://www.fda.gov/media/165186/download?attachment, and downloaded the website in PDF form. This resulted in a document identical to identical to pages 6-25 of the document downloaded and saved as **Exhibit 2149**.

XVIII. EX2159

55. **Exhibit 2159** is a true and correct copy of Foundation Fighting Blindness, *New Report: Vitamin A Supplementation Provides No Vision Benefit to RP Patients* (2023), which was retrieved from the publicly available website https://www.fightingblindness.org/news/new-report-vitamin-a-supplementation-provides-no-vision-benefit-to-rp-patients-867. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://www.fightingblindness.org/news/new-report-vitamin-a-supplementation-provides-no-vision-benefit-to-rp-patients-867, and downloaded the website in PDF

form. This resulted in a document identical to the document downloaded and saved as **Exhibit 2159**, except for a different date and time in the header.

XIX. EX2118

56. **Exhibit 2118** is a true and correct copy of C. Owsley & G. R. Jackson, *Aging and scotopic dysfunction* (2000), which was retrieved from the publicly available website https://research.vu.nl/ws/portalfiles/portal/1722559/Theeuwes+Perception+29+2000+u.pdf. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://research.vu.nl/ws/portalfiles/portal/1722559/Theeuwes+Perception+29+2000+u.pdf, and downloaded and saved page 80 of that website. This resulted in the document downloaded and saved as **Exhibit 2118**.

XX. EX2157

57. **Exhibit 2157** is a true and correct copy of Christopher Hodge & Christopher Taylor, *Vitamin A Deficiency* (2024), which was retrieved from the publicly available website https://www.ncbi.nlm.nih.gov/books/NBK567744/?report=printable. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://www.ncbi.nlm.nih.gov/books/NBK567744/?report=printable, and

downloaded the website in PDF form. This resulted in a document identical to the document downloaded and saved as **Exhibit 2157**, except for a different date and time in the header.

XXI. EX2134

58. **Exhibit 2134** is a true and correct copy of National Eye Institute, *Stargardt Disease* (2021), which was retrieved from the publicly available website https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/stargardt-disease. I confirmed this on September 23, 2024. On September 23, 2024, I accessed the publicly available website, https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/stargardt-disease, and downloaded the website in PDF form. This resulted in a document identical to the document downloaded and saved as **Exhibit 2134**, except for a different date and time in the header.

XXII. Conclusion

59. In signing this Declaration, I understand it will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I understand I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

60. I declare that all statements made herein of my knowledge are true, that all statements made on information and belief are believed to be true, and 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.

Executed on September 23, 2024 in Palo Alto, California

Shauna L. Wiest

Shauna Wiest

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ACITRETIN

Brand Name: Soriatane

Drug Class: Retinoid-like Agents, Topical, Antipsoriatics, Systemic

Pharmacy Author: Divya Jacob, Pharm. D.

Medical Reviewer: Sarfaroj Khan, BHMS, PGD Health Operations

Reviewed on 5/2/2023

Related Drugs Related Supplements

Uses | Side Effects | Dosages | Drug Interactions | Warnings & Precautions

What Is Acitretin and How Does It Work?

Acitretin is a prescription medication used to treat the symptoms of psoriasis.

- Acitretin is available under the following different brand names: Soriatane

What Are Side Effects Associated with Using Acitretin?

Common side effects of Acitretin include:

- chapped lips,
- dry mouth,
- itchy or scaly skin,
- weak nails,
- fragile skin,
- peeling skin on the hands and feet,

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- hair loss,
- dry eyes,
- discomfort while wearing contact lenses,
- dry or runny nose,
- nosebleeds,
- joint pain, and
- tight muscles

Serious side effects of Acitretin include:

- hives,
- difficulty breathing,
- swelling of the face, lips, tongue, or throat,
- mood changes,
- depression,
- aggression,
- unusual thoughts or behavior,
- thoughts of self-harm,
- chest pain,
- dizziness,
- nausea,
- shortness of breath,
- sudden numbness or weakness (especially on one side of the body),
- sudden severe headache,
- problems with speech or balance,
- swelling or warmth in one or both legs,
- increased thirst,
- increased urination,

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- dry mouth,
- fruity breath odor,
- headache,
- blurred vision,
- ringing in the ears,
- dizziness,
- pain behind the eyes,
- vomiting,
- loss of appetite,
- dark urine,
- yellowing of the skin or eyes (jaundice)
- loss of feeling in the hands or feet,
- trouble moving,
- pain in the back, joints, muscles, or bones,
- itching,
- redness,
- pain,
- swelling or peeling of the skin,
- sudden swelling,
- rapid weight gain,
- fever,
- muscle pain, and
- light-headedness

Rare side effects of Acitretin include:

- none

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This is not a complete list of side effects and other serious side effects or health problems that may occur as a result of the use of this drug. Call your doctor for medical advice about serious side effects or adverse reactions. You may report side effects or health problems to FDA at 1-800-FDA-1088.

What Are Dosages of Acitretin?

Adult dosage

Capsule

- 10mg
- 25mg

Psoriasis

- Adult dosage
- 25-50 mg orally once a day

Dosage Considerations – Should be Given as Follows:

See “Dosages”

What Other Drugs Interact with Acitretin?

If your medical doctor is using this medicine to treat your pain, your doctor or pharmacist may already be aware of any possible drug interactions and may be monitoring you for them. Do not start, stop, or change the dosage of any medicine before checking with your doctor, health care provider, or pharmacist first

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- Acitretin has severe interactions with the following drugs:
    - demeclocycline
    - doxycycline
    - ethanol
    - methotrexate
    - minocycline
    - omadacycline
    - sarecycline
    - tetracycline
- Acitretin has serious interactions with the following drugs:
    - aminolevulinic acid oral
    - aminolevulinic acid topical
    - medroxyprogesterone
    - methyl aminolevulinate
    - norethindrone
    - norethindrone acetate
- Acitretin has moderate interactions with the following drugs:
    - nitazoxanide
    - ospemifene
- Acitretin has minor interactions with the following drug:
    - vitamin A

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This information does not contain all possible interactions or adverse effects. Visit the RxList Drug Interaction Checker for any drug interactions. Therefore, before using this product, tell your doctor or pharmacist about all your products. Keep a list of all your medications with you and share this information with your doctor and pharmacist. Check with your health care professional or doctor for additional medical advice, or if you have health questions or concerns.

What Are Warnings and Precautions for Acitretin?

Contraindications

- Hypersensitivity to retinoids (.g, angioedema, urticaria), parabens
- Coadministration with methotrexate (increased risk for hepatitis)
- Coadministration with tetracyclines (increases ICP, pseudotumor cerebri)
- Alcohol (see Black Box Warnings)
- Severely impairment of liver or kidney function and in patients with chronic abnormally elevated blood lipid values (see Black Box Warnings)
- Pregnancy: teratogenic (see Black Box Warnings)

Effects of drug abuse

- None

Short-Term Effects

- See “What Are Side Effects Associated with Using Acitretin?”

Long-Term Effects

- See “What Are Side Effects Associated with Using Acitretin?”

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Cautions

- Check LFTs 1 day before starting, pregnancy test 2 weeks before starting therapy
- Hyperostosis reported with long-term treatment
- New or progression of preexisting vertebral/skeletal abnormalities (.g, degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, ligament calcification, and narrowing and destruction of cervical disc space)
- Exfoliative dermatitis and erythroderma reported
- Depression and/or other psychiatric symptoms such as aggressive feelings or thoughts of self-harm are reported in patients taking retinoids; since other factors may contribute to these events, it is not known if they are related to therapy; counsel patients to stop taking this drug and to notify their prescriber immediately if they experience psychiatric symptoms
- Minimize exposing treated areas to the sun or other UV light; significantly lower doses of phototherapy are required when this drug is used; effects on the stratum corneum induced by this drug can increase the risk of erythema (burning)

Ophthalmic effects

- Ophthalmic conditions include dry eyes, irritation of the eyes, and brow and lash loss; Bell's palsy, blepharitis and/or crusting of lids, blurred vision, conjunctivitis, corneal epithelial abnormality, cortical cataract, decreased night vision, diplopia, itchy eyes or eyelids, nuclear cataract, pannus, papilledema, photophobia, posterior subcapsular cataract, recurrent sties, and subepithelial corneal lesions, reported; patients treated experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation

Pseudomotor cerebri

- Retinoids administered orally have been associated with cases of pseudotumor cerebri (benign intracranial hypertension); some events involved concomitant use of isotretinoin and tetracyclines; however, an event seen in a single patient was not associated with tetracycline use
- Early signs and symptoms include papilledema, headache, nausea and vomiting, and visual disturbances; patients with these signs and symptoms should be examined for papilledema and, if present, therapy should be discontinued immediately and be referred for neurological evaluation and care
- Since both acitretin and tetracyclines can cause increased intracranial pressure, their combined use is contraindicated

Capillary leak syndrome

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- Capillary leak syndrome, a potential manifestation of the retinoic acid syndrome, has been reported in patients receiving this drug; features of this syndrome may include localized or generalized edema with secondary weight gain, fever, and hypotension
- Rhabdomyolysis and myalgias have been reported in association with capillary leak syndrome, and laboratory tests may reveal neutrophilia, hypoalbuminemia, and an elevated hematocrit; discontinue therapy if capillary leak syndrome develops during therapy

Skeletal abnormalities

- In adults receiving long-term treatment, appropriate examinations should be periodically performed given possible ossification abnormalities; as the frequency and severity of iatrogenic bony abnormality in adults is low, periodic radiography is only warranted in presence of symptoms or long-term use
- If such disorders arise, a continuation of therapy should be discussed with the patient on basis of careful risk/benefit analysis; in clinical trials abnormalities of the spine that showed new changes or progression of pre-existing findings were reported
- Changes included degenerative spurs, anterior bridging of spinal vertebrae, diffuse idiopathic skeletal hyperostosis, ligament calcification, and narrowing and destruction of cervical disc space; De novo changes (formation of small spurs) were also reported

Lipids and possible cardiovascular effects

- Blood lipid determinations should be performed before the drug is administered and again at intervals of 1 to 2 weeks until the lipid response to the drug is established, usually within 4 to 8 weeks; elevation in triglycerides and cholesterol reported in clinical trials, respectively; decreased high-density lipoproteins (HDL) also reported in 40% of subjects; these effects of were generally reversible upon cessation of therapy
- Increased tendency to develop hypertriglyceridemia associated with disturbances of lipid metabolism, diabetes mellitus, obesity, increased alcohol intake, or familial history of these conditions; because of the risk of hypertriglyceridemia, serum lipids must be more closely monitored in high-risk patients and during long-term treatment
- Hypertriglyceridemia and lowered HDL may increase a patient's cardiovascular risk status; although no causal relationship established, there have been post-marketing reports of acute myocardial infarction or thromboembolic events in patients on therapy
- In addition, the elevation of serum triglycerides to greater than 800 mg per dL has been associated with fatal fulminant pancreatitis; dietary modifications, reduction in dose, or drug therapy should be employed to control significant elevations of triglycerides; despite these measures, hypertriglyceridemia and low HDL levels persist, the discontinuation of therapy should be considered

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- Triglyceride increases sufficient to be associated with pancreatitis not common; however, fatal fulminant pancreatitis; there have been rare reports of pancreatitis during therapy in the absence of hypertriglyceridemia

Pregnancy & Lactation

- May cause severe birth defects; female patients must not be pregnant when therapy is initiated; they must not become pregnant while taking this drug and for at least 3 years after stopping therapy, so that the drug can be eliminated to below a blood concentration that would be associated with an increased incidence of birth defects; because this threshold has not been established for this drug in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely.
- Major human fetal abnormalities have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of bones (hip, ankle, forearm, skull, cerebral vertebrae), low-set ears, high palate, decreased cranial volume, and cardiovascular malformations

Lactation

- Studies on lactating rats have shown that retinoids are excreted in the milk; there is one prospective case report where acitretin is reported to be excreted in human milk; nursing mothers should not receive the drug before or during nursing because of the potential for serious adverse reactions in nursing infants

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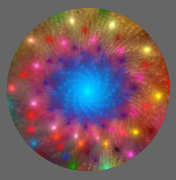
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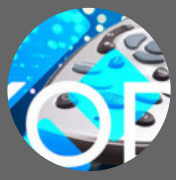
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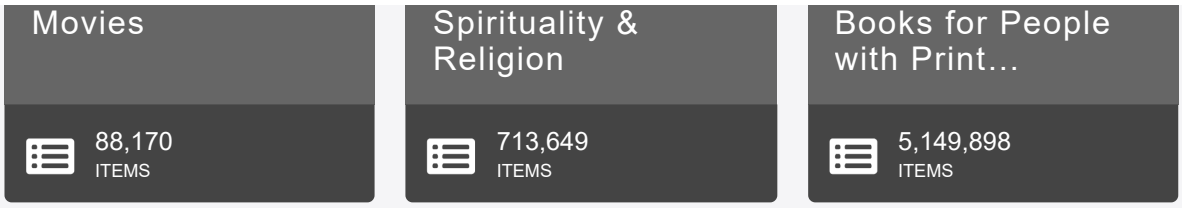






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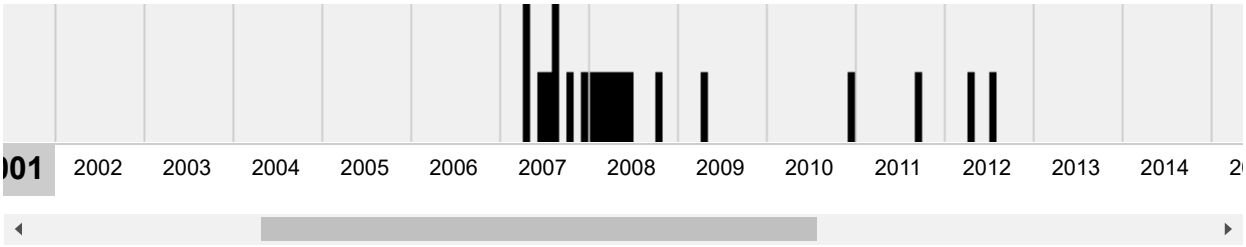
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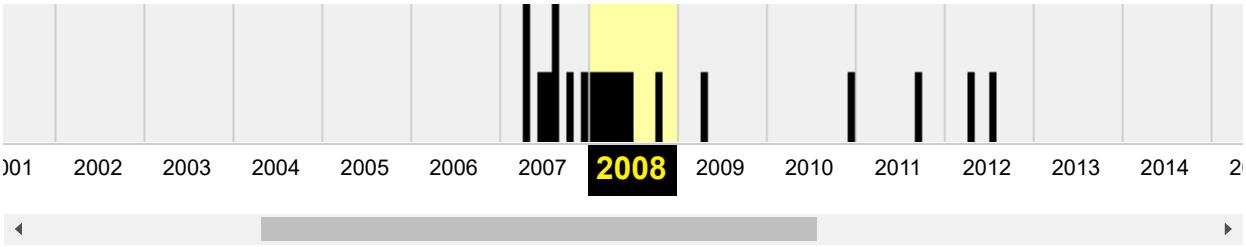
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Soriatane

Drug Description

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SORIATANE®
(acitretin) Capsules

CAUSES BIRTH DEFECTS
DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS: Soriatane must not be used by females who are pregnant, or who intend to become pregnant during therapy or at any time for at least 3 years following discontinuation of therapy. Soriatane also must not be used by females who may not use reliable contraception while undergoing treatment and for at least 3 years following discontinuation of treatment. Acitretin is a metabolite of etretinate (Tegison®), and major human fetal abnormalities have been reported with the administration of acitretin and etretinate. Potentially, any fetus exposed can be affected.

Clinical evidence has shown that concurrent ingestion of acitretin and ethanol has been associated with the formation of etretinate, which has a significantly longer elimination half-life than acitretin. Because the longer elimination half-life of etretinate would increase the duration of teratogenic potential for female patients, ethanol must not be ingested by female patients either during treatment with Soriatane or for 2 months after cessation of therapy. This allows for elimination of acitretin, thus removing the substrate for transesterification to etretinate. The mechanism of the metabolic process for conversion of acitretin to etretinate has not been fully defined. It is not known whether substances other than ethanol are associated with transesterification.

Acitretin has been shown to be embryotoxic and/or teratogenic in rabbits, mice, and rats at oral doses of 0.6, 3 and 15 mg/kg, respectively. These doses are approximately 0.2, 0.3 and 3 times the maximum recommended therapeutic dose, respectively, based on a mg/m² comparison.

Major human fetal abnormalities associated with acitretin and/or etretinate administration have been reported including meningomyelocele, meningoencephalocele, multiple synostoses, facial dysmorphia, syndactyly, absence of terminal phalanges, malformations of hip, ankle and forearm, low-set ears, high palate, decreased cranial volume, cardiovascular malformation and alterations of the skull and cervical vertebrae.

Soriatane should be prescribed only by those who have special competence in the diagnosis and treatment of severe psoriasis, are experienced in the use of systemic retinoids, and understand the risk of teratogenicity.

Because of Soriatane's teratogenicity, a program called the *Do Your P.A.R.T* program, Pregnancy Prevention Actively Required During and After Treatment, has been developed to educate women of childbearing potential and their healthcare providers about the serious risks associated with acitretin and to help prevent pregnancies from occurring with the use of this drug and for 3 years after its discontinuation. The *Do Your P.A.R.T.* program requirements are described below (see also PRECAUTIONS section).

Important Information for Women of Childbearing Potential:

Soriatane should be considered only for women with severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments.

Females of reproductive potential must not be given a prescription for Soriatane until pregnancy is excluded. Soriatane is contraindicated in females of reproductive potential unless the patient meets ALL of the following conditions:

- **Must have had 2 negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Soriatane prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue Soriatane therapy. The second pregnancy test (a confirmation test) should be done during the first 5 days of the menstrual period immediately preceding the beginning of Soriatane therapy. For patients with amenorrhea, the second test should be done at least 11 days after the last act of unprotected sexual intercourse (without using 2 effective forms of contraception [birth control] simultaneously).**

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- **Must have a pregnancy test repeated every month during Soriatane treatment. The patient must have a negative result from a urine or serum pregnancy test before receiving a Soriatane prescription. To encourage compliance with this recommendation, a limited supply of the drug should be prescribed. For at least 3 years after discontinuing Soriatane therapy, a pregnancy test must be repeated every 3 months.**
- **Must have selected and have committed to use 2 effective forms of contraception (birth control) simultaneously, at least 1 of which must be a primary form, unless absolute abstinence is the chosen method, or the patient has undergone a hysterectomy or is clearly postmenopausal.**
- **Patients must use 2 effective forms of contraception (birth control) simultaneously for at least 1 month prior to initiation of Soriatane therapy, during Soriatane therapy, and for at least 3 years after discontinuing Soriatane therapy. A Soriatane Patient Referral Form is available so that patients can receive an initial free contraceptive counseling session and pregnancy testing. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis by the prescriber during Soriatane therapy and every 3 months for at least 3 years following discontinuation of Soriatane therapy.**

Effective forms of contraception include both primary and secondary forms of contraception. Primary forms of contraception include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, and injectable/implantable/insertable/topical hormonal birth control products. Secondary forms of contraception include latex condoms (with or without spermicide), diaphragms and cervical caps (which must be used with a spermicide).

Any birth control method can fail. Therefore, it is critically important that women of childbearing potential use 2 effective forms of contraception (birth control) simultaneously. It has not been established if there is a pharmacokinetic interaction between acitretin and combined oral contraceptives. However, it has been established that acitretin interferes with the contraceptive effect of microdosed progestin preparations.[1] Microdosed "minipill" progestin preparations are not recommended for use with Soriatane. *It is not known whether other progestational contraceptives, such as implants and injectables, are adequate methods of contraception during acitretin therapy.*

Prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products. Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort (see PRECAUTIONS).

- **Must have signed a Patient Agreement/Informed Consent for Female Patients that contains warnings about the risk of potential birth defects if the fetus is exposed to Soriatane, about contraceptive failure, about the fact that they must not ingest beverages or products containing ethanol while taking Soriatane and for 2 months after Soriatane treatment has been discontinued, and about preventing pregnancy while taking Soriatane and for at least 3 years after discontinuing Soriatane therapy.**

If pregnancy does occur during Soriatane therapy or at any time for at least 3 years following discontinuation of Soriatane therapy, the prescriber and patient should discuss the possible effects on the pregnancy. The available information is as follows:

Acitretin, the active metabolite of etretinate, is teratogenic and is contraindicated during pregnancy. The risk of severe fetal malformations is well established when systemic retinoids are taken during pregnancy. Pregnancy must also be prevented after stopping acitretin therapy, while the drug is being eliminated to below a threshold blood concentration that would be associated with an increased incidence of birth defects. Because this threshold has not been established for acitretin in humans and because elimination rates vary among patients, the duration of posttherapy contraception to achieve adequate elimination cannot be calculated precisely. It is strongly recommended that contraception be continued for at least 3 years after stopping treatment with acitretin, based on the following considerations:

- **In the absence of transesterification to form etretinate, greater than 98% of the acitretin would be eliminated within 2 months, assuming a mean elimination half-life of 49 hours.**
- **In cases where etretinate is formed, as has been demonstrated with concomitant administration of acitretin and ethanol,**
  - **greater than 98% of the etretinate formed would be eliminated in 2 years, assuming a mean elimination half-life of 120 days.**
  - **greater than 98% of the etretinate formed would be eliminated in 3 years, based on the longest demonstrated elimination half-life of 168 days.**

However, etretinate was found in plasma and subcutaneous fat in one patient reported to have had sporadic alcohol intake, 52 months after she stopped acitretin

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therapy.[2]

- Severe birth defects have been reported where conception occurred during the time interval when the patient was being treated with acitretin and/or etretinate. In addition, severe birth defects have also been reported when conception occurred after the mother completed therapy. These cases have been reported both prospectively (before the outcome was known) and retrospectively (after the outcome was known). The events below are listed without distinction as to whether the reported birth defects are consistent with retinoid-induced embryopathy or not.
  - There have been 318 prospectively reported cases involving pregnancies and the use of etretinate, acitretin or both. In 238 of these cases, the conception occurred after the last dose of etretinate (103 cases), acitretin (126) or both (9). Fetal outcome remained unknown in approximately one-half of these cases, of which 62 were terminated and 14 were spontaneous abortions. Fetal outcome is known for the other 118 cases and 15 of the outcomes were abnormal (including cases of absent hand/wrist, clubfoot, GI malformation, hypocalcemia, hypotonia, limb malformation, neonatal apnea/anemia, neonatal ichthyosis, placental disorder/death, undescended testicle and 5 cases of premature birth). In the 126 prospectively reported cases where conception occurred after the last dose of acitretin only, 43 cases involved conception at least 1 year but less than 2 years after the last dose. There were 3 reports of abnormal outcomes out of these 43 cases (involving limb malformation, GI tract malformations and premature birth). There were only 4 cases where conception occurred at least 2 years after the last dose but there were no reports of birth defects in these cases.
  - There is also a total of 35 retrospectively reported cases where conception occurred at least one year after the last dose of etretinate, acitretin or both. From these cases there are 3 reports of birth defects when the conception occurred at least 1 year but less than 2 years after the last dose of acitretin (including heart malformations, Turner's Syndrome, and unspecified congenital malformations) and 4 reports of birth defects when conception occurred 2 or more years after the last dose of acitretin (including foot malformation, cardiac malformations [2 cases] and unspecified neonatal and infancy disorder). There were 3 additional abnormal outcomes in cases where conception occurred 2 or more years after the last dose of etretinate (including chromosome disorder, forearm aplasia, and stillbirth).
  - Females who have taken Tegison (etretinate) must continue to follow the contraceptive recommendations for Tegison. Tegison is no longer marketed in the US; for information, call Stiefel at 1-888-500-DERM (3376).
  - Patients should not donate blood during and for at least 3 years following the completion of Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.

Important Information For Males Taking Soriatane:

- Patients should not donate blood during and for at least 3 years following Soriatane therapy because women of childbearing potential must not receive blood from patients being treated with Soriatane.
- Samples of seminal fluid from 3 male patients treated with acitretin and 6 male patients treated with etretinate have been assayed for the presence of acitretin. The maximum concentration of acitretin observed in the seminal fluid of these men was 12.5 ng/mL. Assuming an ejaculate volume of 10 mL, the amount of drug transferred in semen would be 125 ng, which is y00,000 of a single 25 mg capsule. Thus, although it appears that residual acitretin in seminal fluid poses little, if any, risk to a fetus while a male patient is taking the drug or after it is discontinued, the no-effect limit for teratogenicity is unknown and there is no registry for birth defects associated with acitretin. The available data are as follows:

There have been 25 cases of reported conception when the male partner was taking acitretin. The pregnancy outcome is known in 13 of these 25 cases. Of these, 9 reports were retrospective and 4 were prospective (meaning the pregnancy was reported prior to knowledge of the outcome)[3].

Timing of Paternal Acitretin Treatment Relative to Conception	Delivery of Healthy Neonate	Spontaneous Abortion	Induced Abortion	Total
At time of conception	5*	5	1	11
Discontinued ~4 weeks prior	0	0	1**	1
Discontinued ~6 to 8 months prior	0	1	0	1

*Four of 5 cases were prospective.

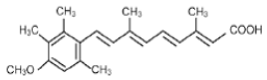
**With malformation pattern not typical of retinoid embryopathy (bilateral cystic hygromas of neck, hypoplasia of lungs bilateral, pulmonary atresia, VSD with overriding truncus arteriosus).

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For All Patients: **A SORIATANE MEDICATION GUIDE MUST BE GIVEN TO THE PATIENT EACH TIME SORIATANE IS DISPENSED, AS REQUIRED BY LAW.**

DRUG DESCRIPTION

Soriatane (acitretin), a retinoid, is available in 10 mg and 25 mg gelatin capsules for oral administration. Chemically, acitretin is all-trans-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid. It is a metabolite of etretinate and is related to both retinoic acid and retinol (vitamin A). It is a yellow to greenish-yellow powder with a molecular weight of 326.44. The structural formula is:



Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink and maltodextrin (a mixture of polysaccharides).

Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.

REFERENCES

1. Berbis Ph, et al.: *Arch Dermatol Res* (1988) 280:388-389.

2. Maier H, Honigsmann H: Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 348:1107, 1996.

3. Geiger JM, Walker M: Is there a reproductive safety risk in male patients treated with acitretin (Neotigason®/Soriatane®)? *Dermatology* 205:105-107, 2002.

Brand Name: Soriatane
Generic Name: Acitretin

Next: Soriatane - Indications & Dosage »

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BEXAROTENE

Brand Name: Targretin, Targretin Gel

Drug Class: Antineoplastics, Other, Retinoid-like Agents, Topical

Medical Author: Dr. Vinod Katiboina, Pharm. D.

Medical Reviewer: Divya Jacob, Pharm. D.

Reviewed on 9/13/2023

Related Drugs Related Supplements

Uses | Side Effects | Dosages | Drug Interactions | Warnings and Precautions

What Is Bexarotene and How Does It Work?

Bexarotene is a prescription medication indicated for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma in patients who are refractory to at least one prior systemic therapy.

- Bexarotene is available under the following different brand names: Targretin

What Are Side Effects Associated with Using Bexarotene?

Common side effects of Bexarotene include:

- headache
- tiredness
- fatigue
- nausea
- vomiting

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- dry skin
- diarrhea
- trouble sleeping
- an increase in fat levels in the blood (blood lipids) such as cholesterol or triglycerides (blood tests will detect this)
- an underactive thyroid (blood tests will detect this)
- blood problems
- weakness or loss of strength
- swelling
- rash
- infections

Serious side effects of Bexarotene include:

- hives
- difficulty breathing
- swelling of the face, lips, tongue, or throat
- blurred vision, eye pain, or seeing halos around lights
- low blood cell counts--fever, chills, tiredness, mouth sores, skin sores, sore throat, cough, pale skin, cold hands and feet, and feeling light-headed or short of breath
- pancreatitis--severe pain in your upper stomach spreading to your back, nausea, and vomiting; or
- signs of underactive thyroid--extreme tiredness, dry skin, constipation, feeling more sensitive to cold temperatures, weight gain

Rare side effects of Bexarotene include:

- none

Seek medical care or call 911 at once if you have the following serious side effects:

- Severe headache, confusion, slurred speech, arm or leg weakness, trouble walking, coordination loss, unsteady, very stiff muscles, high fever, profuse sweating, or tremors.

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- Serious eye symptoms such as sudden vision loss, blurred vision, tunnel vision, eye pain or swelling, or seeing halos around lights.
- Serious heart symptoms include fast, irregular, or pounding heartbeats; fluttering in the chest; shortness of breath; sudden dizziness, lightheadedness, or passing out.

This is not a complete list of side effects and other serious side effects or health problems that may occur because of the use of this drug. Call your doctor for medical advice about serious side effects or adverse reactions. You may report side effects or health problems to FDA at 1-800-FDA-1088.

Ad removed. Details

What Are the Dosages of Bexarotene?

Adult dosage

Capsule

- 75 mg

Gel

- 1%

Cutaneous T-cell lymphoma

Adult dosage

- 300 mg/m² orally once a day with food; titrate based on response or toxicity; may increase the dose to 400 mg/m²/day if no response after 8 weeks of therapy
- Topical: Apply to lesions every other day for 1 week initially, then increase every week up to every 6 hours
- Monitor: WBC, LFTs, lipids, thyroid function

Dosage Considerations – Should be Given as Follows:

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- See “Dosages”

What Other Drugs Interact with Bexarotene?

If your medical doctor is using this medicine to treat your pain, your doctor or pharmacist may already be aware of any possible drug interactions and may be monitoring you for them. Do not start, stop, or change the dosage of any medicine before checking with your doctor, healthcare provider, or pharmacist first.

- Bexarotene has severe interactions with the following drugs:
    - doravirine
    - lonafarnib
    - mavacamten
- Bexarotene has serious interactions with at least 38 other drugs.
- Bexarotene has moderate interactions with at least 89 other drugs.
- Bexarotene has minor interactions with the following drugs:
    - artemether/lumefantrine
    - darunavir
    - fosphenytoin
    - hydrocortisone
    - insulin aspart
    - insulin detemir
    - insulin glargine
    - insulin glulisine
    - insulin lispro
    - insulin NPH

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This information does not contain all possible interactions or adverse effects. Visit the RxList Drug Interaction Checker for any drug interactions. Therefore, before using this product, tell your doctor or pharmacist about all the products you use. Keep a list of all your medications with you and share this information with your doctor and pharmacist. Check with your healthcare professional or doctor for additional medical advice, health questions, or concerns.

What Are Warnings and Precautions for Bexarotene?

Contraindications

- Hypersensitivity to retinoids
- Pregnancy (use 2 forms of contraception)

Effects of drug abuse

- None

Short-Term Effects

- See “What Are Side Effects Associated with Using Bexarotene?”

Long-Term Effects

- See “What Are Side Effects Associated with Using Bexarotene?”

Cautions

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- Oral
    - Suppresses TSH levels; may cause hypothyroidism; may require supplementation
    - Neutropenia and leukopenia may occur
    - May induce significant lipid abnormalities in a majority of patients
    - ALT, AST, and bilirubin elevation reported
    - Pancreatitis secondary to hypertriglyceridemia reported
    - Photosensitivity and phototoxicity may occur
    - Evaluate visual abnormalities experienced by the patient
    - Use caution in patients with diabetes mellitus and hepatic impairment

- Topical
    - Do not use occlusive dressings with gel
    - May induce significant lipid abnormalities; use caution in patients with hypertriglyceridemia
    - May cause photosensitization
    - Neutropenia and leukopenia may occur

Pregnancy and Lactation

- Do not use during pregnancy
- **Lactation**
    - It is not known whether bexarotene is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from bexarotene, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the importance of the drug to the mother

References

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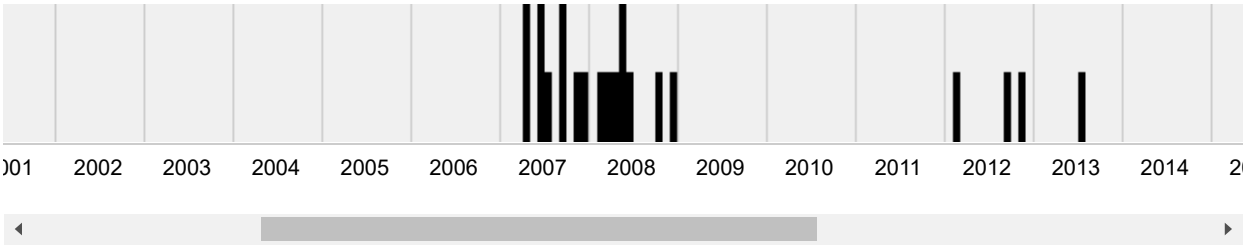
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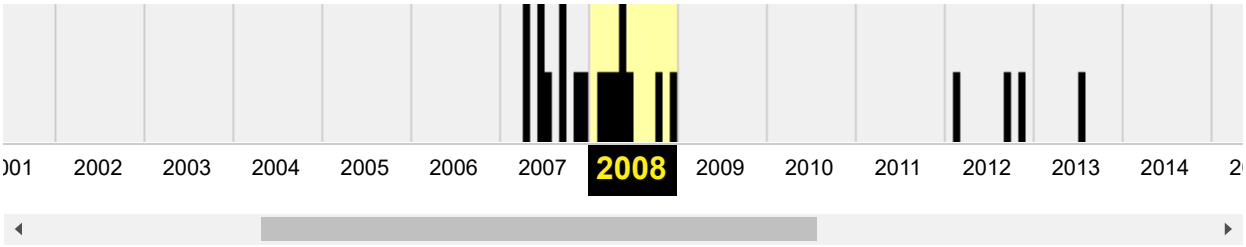
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Targretin

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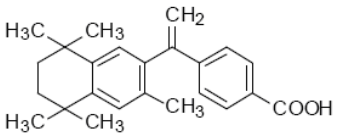
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DRUG DESCRIPTION

Targretin ® capsules are a member of the retinoid class of drugs that is associated with birth defects in humans. Targretin ® capsules also caused birth defects when administered orally to pregnant rats. Targretin ® capsules must not be administered to a pregnant woman. See CONTRAINDICATIONS.

Targretin ® (bexarotene) is a member of a subclass of retinoids that selectively activate retinoid X receptors (RXRs). These retinoid receptors have biologic activity distinct from that of retinoic acid receptors (RARs). Each soft gelatin capsule for oral administration contains 75 mg of bexarotene.

The chemical name is 4-[1-(5,6,7,8 -tetrahydro- 3,5,5,8,8-pentamethyl -2-naphthalenyl) ethenyl] benzoic acid, and the structual formula is as follows:



Bexarotene is an off-white to white powder with a molecular weight of 348.48 and a molecular formula of $C_{24}H_{28}O_2$. It is insoluble in water and slightly soluble in vegetable oils and ethanol, USP.

Each Targretin ® (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF, polysorbate 20, NF, povidone, USP, and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF, sorbitol special-glycerin blend, and titanium dioxide, USP.

Brand Name: Targretin
Generic Name: Bexarotene

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ACCUTANE

Generic Name: isotretinoin

Brand Name: Accutane

Drug Class: Acne Agents, Topical

Medical Editor: John P. Cunha, DO, FACOEP Last updated on RxList: 8/15/2022

Related Drugs Related Supplements

Drug Summary

What Is Accutane?

Accutane (isotretinoin) is a retinoid used for the treatment and prevention of severe acne. The brand name Accutane is discontinued in the U.S., but generic formulations are available.

What Are Side Effects of Accutane?

The most common side effects of Accutane are:

- dry skin,
- itching,
- rash,
- dry nose,
- nosebleeds,
- cracks in the corners of the mouth,
- dry mouth,
- dry lips,
- cracking or peeling skin,
- inflammation of the whites of the eyes,
- dry eyes,

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- joint pain,
- back pain,
- dizziness,
- drowsiness,
- nervousness, or
- changes in your fingernails or toenails.

Accutane may cause serious side effects including:

- hives,
- difficulty breathing,
- swelling of your face, lips, tongue, or throat,
- dizziness,
- fever,
- sore throat,
- burning eyes,
- skin pain,
- red or purple skin rash with blistering and peeling,
- problems with your vision or hearing,
- muscle or joint pain,
- bone pain,
- back pain,
- increased thirst,
- increased urination,
- hallucinations,
- unusual mood changes,
- crying spells,
- feelings of low self-worth,
- loss of interest in things you once enjoyed,

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- new sleep problems,
- thoughts of self-harm,
- loss of appetite,
- upper stomach pain (that may spread to your back),
- nausea,
- vomiting,
- fast heart rate,
- dark urine,
- yellowing of the skin or eyes (jaundice),
- severe stomach or chest pain,
- pain when swallowing,
- heartburn,
- diarrhea,
- rectal bleeding,
- bloody or tarry stools,
- severe headaches,
- ringing in your ears,
- vision problems, and
- pain behind your eyes

Get medical help right away, if you have any of the symptoms listed above.

Seek medical care or call 911 at once if you have the following serious side effects:

- Serious eye symptoms such as sudden vision loss, blurred vision, tunnel vision, eye pain or swelling, or seeing halos around lights;
- Serious heart symptoms such as fast, irregular, or pounding heartbeats; fluttering in your chest; shortness of breath; and sudden dizziness, lightheartedness, or passing out;
- Severe headache, confusion, slurred speech, arm or leg weakness, trouble walking, loss of coordination, feeling unsteady, very stiff muscles, high fever, profuse sweating, or tremors.

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This document does not contain all possible side effects and others may occur. Check with your physician for additional information about side effects.

Dosage for Accutane

The recommended dose of Accutane is 0.5 to 2 mg per kg of body weight daily.

What Drugs, Substances, or Supplements Interact with Accutane?

Accutane may interact with:

- steroids,
- seizure medications, or
- tetracycline antibiotics

Tell your doctor all medications and supplements you use.

Combining vitamin A with Accutane may increase side effects.

Accutane During Pregnancy and Breastfeeding

Accutane is harmful to the fetus and therefore should not be used during pregnancy. Accutane is harmful to the fetus and therefore should not be used during pregnancy. It is unknown if Accutane passes into breast milk. Consult your doctor before breastfeeding.

Additional Information

Our Accutane Side Effects Drug Center provides a comprehensive view of available drug information on the potential side effects when taking this medication.



CONTRAINDICATIONS AND WARNINGS

Accutane must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Accutane in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

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Birth defects which have been documented following Accutane exposure include

- abnormalities of the face,
- eyes,
- ears,
- skull,
- central nervous system,
- cardiovascular system, and
- thymus and parathyroid glands.

Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities include:

- skull abnormality;
- ear abnormalities (including anotia, micropinna, small or absent external auditory canals);
- eye abnormalities (including microphthalmia);
- facial dysmorphia;
- cleft palate.

Documented internal abnormalities include:

- CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit);
- cardiovascular abnormalities;
- thymus gland abnormality;
- parathyroid hormone deficiency.

In some cases death has occurred with certain of the abnormalities previously noted.

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If pregnancy does occur during treatment of a female patient who is taking Accutane, Accutane must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Special Prescribing Requirements

Because of Accutane's teratogenicity and to minimize fetal exposure, Accutane is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE™. Accutane must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Accutane must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see **PRECAUTIONS**).

Table 1 : Monthly Required iPLEDGE Interactions

	Female Patients of Childbearing Potential	Male Patients, And Female Patients Not of Childbearing Potential
PRESCRIBER		
Confirms patient counseling	X	X
Enters the 2 contraception methods chosen by the patient	X	
Enters pregnancy test results	X	
PATIENT		
Answers educational questions before every prescription	X	
Enters 2 forms of contraception	X	
PHARMACIST		
Contacts system to get an authorization	X	X

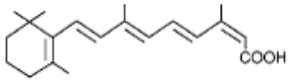
Description for Accutane

Isotretinoin, a retinoid, is available as Accutane in 10-mg, 20-mg and 40-mg soft gelatin capsules for oral administration. Each capsule contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems:

- 10 mg — iron oxide (red) and titanium dioxide;
- 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide;
- 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

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Chemically, isotretinoin is 13-*cis*-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



Uses for Accutane

Severe Recalcitrant Nodular Acne

Accutane (isotretinoin) is indicated for the treatment of severe recalcitrant nodular acne. Nodules are inflammatory lesions with a diameter of 5 mm or greater. The nodules may become suppurative or hemorrhagic. “Severe,” by definition,[2] means “many” as opposed to “few or several” nodules. Because of significant adverse effects associated with its use, Accutane (isotretinoin) should be reserved for patients with severe nodular acne who are unresponsive to conventional therapy, including systemic antibiotics. In addition, Accutane (isotretinoin) is indicated only for those female patients who are not pregnant, because Accutane (isotretinoin) can cause severe birth defects (see **Boxed CONTRAINDICATIONS AND WARNINGS**).

A single course of therapy for 15 to 20 weeks has been shown to result in complete and prolonged remission of disease in many patients.[1,3,4] If a second course of therapy is needed, it should not be initiated until at least 8 weeks after completion of the first course, because experience has shown that patients may continue to improve while off Accutane (isotretinoin) . The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth (see **WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis, and Premature Epiphyseal Closure**).

Dosage for Accutane

Accutane (isotretinoin) should be administered with a meal (see **PATIENT INFORMATION**).

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The recommended dosage range for Accutane (isotretinoin) is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. In studies comparing 0.1, 0.5, and 1.0 mg/kg/day,[8] it was found that all dosages provided initial clearing of disease, but there was a greater need for retreatment with the lower dosages. During treatment, the dose may be adjusted according to response of the disease and/or the appearance of clinical side effects — some of which may be dose related. Adult patients whose disease is very severe with scarring or is primarily manifested on the trunk may require dose adjustments up to 2.0 mg/kg/day, as tolerated. Failure to take Accutane (isotretinoin) with food will significantly decrease absorption. Before upward dose adjustments are made, the patients should be questioned about their compliance with food instructions.

The safety of once daily dosing with Accutane (isotretinoin) has not been established. Once daily dosing is not recommended.

If the total nodule count has been reduced by more than 70% prior to completing 15 to 20 weeks of treatment, the drug may be discontinued. After a period of 2 months or more off therapy, and if warranted by persistent or recurring severe nodular acne, a second course of therapy may be initiated. The optimal interval before retreatment has not been defined for patients who have not completed skeletal growth. Long-term use of Accutane (isotretinoin) , even in low doses, has not been studied, and is not recommended. It is important that Accutane (isotretinoin) be given at the recommended doses for no longer than the recommended duration. The effect of long-term use of Accutane on bone loss is unknown (see **WARNINGS: Skeletal: Bone Mineral Density, Hyperostosis, and Premature Epiphyseal Closure**).

Contraceptive measures must be followed for any subsequent course of therapy (see **PRECAUTIONS**).

Table 4 : Accutane (isotretinoin) Dosing by Body Weight (Based on Administration With Food)

Body Weight		Total mg/day		
kilograms	pounds	0.5 mg/kg	1 mg/kg	2 mg/kg*
40	88	20	40	80
50	110	25	50	100
60	132	30	60	120
70	154	35	70	140
80	176	40	80	160
90	198	45	90	180
100	220	50	100	200

*See **DOSAGE AND ADMINISTRATION**: the recommended dosage range is 0.5 to 1.0 mg/kg/day.

INFORMATION FOR PHARMACISTS

Access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866495-0654) to obtain an authorization and the “do not dispense to patient after” date. Accutane (isotretinoin) must only be dispensed in no more than a 30-day supply.

REFILLS REQUIRE A NEW PRESCRIPTION AND A NEW AUTHORIZATION FROM THE iPLEDGE SYSTEM.

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An Accutane (isotretinoin) Medication Guide must be given to the patient each time Accutane (isotretinoin) is dispensed, as required by law. This Accutane (isotretinoin) Medication Guide is an important part of the risk management program for the patient.

HOW SUPPLIED

Soft gelatin capsules, 10 mg (light pink), imprinted ACCUTANE (isotretinoin) 10 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (**NDC** 0004-0155-49).

Soft gelatin capsules, 20 mg (maroon), imprinted ACCUTANE (isotretinoin) 20 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (**NDC** 0004-0169-49).

Soft gelatin capsules, 40 mg (yellow), imprinted ACCUTANE (isotretinoin) 40 ROCHE. Boxes of 100 containing 10 Prescription Paks of 10 capsules (**NDC** 0004-0156-49).

Storage

Store at controlled room temperature (59° to 86°F, 15° to 30°C). Protect from light.

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4. Jones H, Blanc D, Cunliffe WJ. 13-cisretinoic acid and acne. Lancet 2:1048-1049, 1980.

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Distributed by: Roche Laboratories Inc., 340 Kingsland Street, Nutley, New Jersey 07110-1199. PI Revised: January 2010.

Side Effects for Accutane

Clinical Trials and Postmarketing Surveillance

The adverse reactions listed below reflect the experience from investigational studies of Accutane (isotretinoin) , and the postmarketing experience. The relationship of some of these events to Accutane (isotretinoin) therapy is unknown. Many of the side effects and adverse

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reactions seen in patients receiving Accutane (isotretinoin) are similar to those described in patients taking very high doses of vitamin A (dryness of the skin and mucous membranes, eg, of the lips, nasal passage, and eyes).

Dose Relationship

Cheilitis and hypertriglyceridemia are usually dose related. Most adverse reactions reported in clinical trials were reversible when therapy was discontinued; however, some persisted after cessation of therapy (see **WARNINGS and ADVERSE REACTIONS**).

Body as a Whole

allergic reactions, including vasculitis, systemic hypersensitivity (see **PRECAUTIONS: Hypersensitivity**), edema, fatigue, lymphadenopathy, weight loss

Cardiovascular

palpitation, tachycardia, vascular thrombotic disease, stroke

Endocrine/Metabolic

hypertriglyceridemia (see **WARNINGS: Lipids**), alterations in blood sugar levels (see **PRECAUTIONS: Laboratory Tests**)

Gastrointestinal

inflammatory bowel disease (see **WARNINGS: Inflammatory Bowel Disease**), hepatitis (see **WARNINGS: Hepatotoxicity**), pancreatitis (see **WARNINGS: Lipids**), bleeding and inflammation of the gums, colitis, esophagitis/esophageal ulceration, ileitis, nausea, other nonspecific gastrointestinal symptoms

Hematologic

allergic reactions (see **PRECAUTIONS: Hypersensitivity**), anemia, thrombocytopenia, neutropenia, rare reports of agranulocytosis (see **PATIENT INFORMATION**). See **PRECAUTIONS: Laboratory Tests** for other hematological parameters.

Musculoskeletal

skeletal hyperostosis, calcification of tendons and ligaments, premature epiphyseal closure, decreases in bone mineral density (see **WARNINGS: Skeletal**), musculoskeletal symptoms (sometimes severe) including back pain, myalgia, and arthralgia (see **PATIENT INFORMATION**), transient pain in the chest (see **PATIENT INFORMATION**), arthritis, tendonitis, other types of bone abnormalities, elevations of CPK/rare reports of rhabdomyolysis (see **PRECAUTIONS: Laboratory Tests**).

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Neurological

pseudotumor cerebri (see **WARNINGS: Pseudotumor Cerebri**), dizziness, drowsiness, headache, insomnia, lethargy, malaise, nervousness, paresthesias, seizures, stroke, syncope, weakness

Psychiatric

suicidal ideation, suicide attempts, suicide, depression, psychosis, aggression, violent behaviors (see **WARNINGS: Psychiatric Disorders**), emotional instability

Of the patients reporting depression, some reported that the depression subsided with discontinuation of therapy and recurred with reinstitution of therapy.

Reproductive System

abnormal menses

Respiratory

bronchospasms (with or without a history of asthma), respiratory infection, voice alteration

Skin and Appendages

acne fulminans, alopecia (which in some cases persists), bruising, cheilitis (dry lips), dry mouth, dry nose, dry skin, epistaxis, eruptive xanthomas,[7] erythema multiforme, flushing, fragility of skin, hair abnormalities, hirsutism, hyperpigmentation and hypopigmentation, infections (including disseminated herpes simplex), nail dystrophy, paronychia, peeling of palms and soles, photoallergic/photosensitizing reactions, pruritus, pyogenic granuloma, rash (including facial erythema, seborrhea, and eczema), Stevens-Johnson syndrome, sunburn susceptibility increased, sweating, toxic epidermal necrolysis, urticaria, vasculitis (including Wegener's granulomatosis; see **PRECAUTIONS: Hypersensitivity**), abnormal wound healing (delayed healing or exuberant granulation tissue with crusting; see **PATIENT INFORMATION**)

Special Senses

Hearing - hearing impairment (see **WARNINGS: Hearing Impairment**), tinnitus.

Vision- corneal opacities (see **WARNINGS: Corneal Opacities**), decreased night vision which may persist (see **WARNINGS: Decreased Night Vision**), cataracts, color vision disorder, conjunctivitis, dry eyes, eyelid inflammation, keratitis, optic neuritis, photophobia, visual disturbances

Urinary System

glomerulonephritis (see **PRECAUTIONS: Hypersensitivity**), nonspecific urogenital findings (see **PRECAUTIONS: Laboratory Tests** for other urological parameters)

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Laboratory

Elevation of plasma triglycerides (see **WARNINGS: Lipids**), decrease in serum high-density lipoprotein (HDL) levels, elevations of serum cholesterol during treatment

Increased alkaline phosphatase, SGOT (AST), SGPT (ALT), GGTP or LDH (see **WARNINGS: Hepatotoxicity**)

Elevation of fasting blood sugar, elevations of CPK (see **PRECAUTIONS: Laboratory Tests**), hyperuricemia

Decreases in red blood cell parameters, decreases in white blood cell counts (including severe neutropenia and rare reports of agranulocytosis; see **PATIENT INFORMATION**), elevated sedimentation rates, elevated platelet counts, thrombocytopenia

White cells in the urine, proteinuria, microscopic or gross hematuria

Drug Interactions for Accutane

- ***Vitamin A***: Because of the relationship of Accutane (isotretinoin) to vitamin A, patients should be advised against taking vitamin supplements containing vitamin A to avoid additive toxic effects.
- ***Tetracyclines***: Concomitant treatment with Accutane (isotretinoin) and tetracyclines should be avoided because Accutane (isotretinoin) use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines.
- ***Micro-dosed Progesterone Preparations***: Micro-dosed progesterone preparations ("minipills" that do not contain an estrogen) may be an inadequate method of contraception during Accutane (isotretinoin) therapy. Although other hormonal contraceptives are highly effective, there have been reports of pregnancy from female patients who have used combined oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products. These reports are more frequent for female patients who use only a single method of contraception. It is not known if hormonal contraceptives differ in their effectiveness when used with Accutane (isotretinoin) . Therefore, it is critically important for female patients of childbearing potential to select and commit to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form (see **PRECAUTIONS**).

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- ***Norethindrone/ethinyl estradiol***: In a study of 31 premenopausal female patients with severe recalcitrant nodular acne receiving OrthoNovum® 7/7/7 Tablets as an oral contraceptive agent, Accutane (isotretinoin) at the recommended dose of 1 mg/kg/day, did not induce clinically relevant changes in the pharmacokinetics of ethinyl estradiol and norethindrone and in the serum levels of progesterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Prescribers are advised to consult the package insert of medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

- ***St. John's Wort***: **Accutane (isotretinoin) use is associated with depression in some patients (see WARNINGS: Psychiatric Disorders and ADVERSE REACTIONS: Psychiatric).** Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

- ***Phenytoin***: Accutane (isotretinoin) has not been shown to alter the pharmacokinetics of phenytoin in a study in seven healthy volunteers. These results are consistent with the *in vitro* finding that neither isotretinoin nor its metabolites induce or inhibit the activity of the CYP 2C9 human hepatic P450 enzyme. Phenytoin is known to cause osteomalacia. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between phenytoin and Accutane (isotretinoin) . Therefore, caution should be exercised when using these drugs together.

- ***Systemic Corticosteroids***: Systemic corticosteroids are known to cause osteoporosis. No formal clinical studies have been conducted to assess if there is an interactive effect on bone loss between systemic corticosteroids and Accutane (isotretinoin) . Therefore, caution should be exercised when using these drugs together.

Laboratory Tests

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- ***Pregnancy Test***

    - Female patients of childbearing potential must have had two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial Accutane (isotretinoin) prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for Accutane (isotretinoin) . The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the two tests must be at least 19 days.
    - For patients with regular menstrual cycles, the second pregnancy test must be done during the first 5 days of the menstrual period immediately preceding the beginning of Accutane (isotretinoin) therapy and after the patient has used 2 forms of contraception for 1 month.
    - For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of Accutane (isotretinoin) therapy and after the patient has used 2 forms of contraception for 1 month.
    - Each month of therapy, patients must have a negative result from a urine or serum pregnancy test. A pregnancy test must be repeated each month, in a CLIA-certified laboratory, prior to the female patient receiving each prescription.

- ***Lipids:*** Pretreatment and follow-up blood lipids should be obtained under fasting conditions. After consumption of alcohol, at least 36 hours should elapse before these determinations are made. It is recommended that these tests be performed at weekly or biweekly intervals until the lipid response to Accutane (isotretinoin) is established. The incidence of hypertriglyceridemia is 1 patient in 4 on Accutane therapy (see **WARNINGS: Lipids**).
- ***Liver Function Tests:*** Since elevations of liver enzymes have been observed during clinical trials, and hepatitis has been reported, pretreatment and follow-up liver function tests should be performed at weekly or biweekly intervals until the response to Accutane has been established (see **WARNINGS: Hepatotoxicity**).
- ***Glucose:*** Some patients receiving Accutane (isotretinoin) have experienced problems in the control of their blood sugar. In addition, new cases of diabetes have been diagnosed during Accutane (isotretinoin) therapy, although no causal relationship has been established.
- ***CPK:*** Some patients undergoing vigorous physical activity while on Accutane (isotretinoin) therapy have experienced elevated CPK levels; however, the clinical significance is unknown. There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity. In a clinical trial of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, transient elevations in CPK were observed in 12% of patients, including those undergoing strenuous physical activity in association with reported musculoskeletal adverse events such as back pain, arthralgia, limb injury, or muscle sprain. In these patients, approximately half of the CPK elevations returned to normal within 2 weeks and half returned to normal within 4 weeks. No cases of rhabdomyolysis were reported in this trial.

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Warnings for Accutane

Psychiatric Disorders

Accutane (isotretinoin) may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts, suicide, and aggressive and/or violent behaviors. No mechanism of action has been established for these events (see ADVERSE REACTIONS: Psychiatric). Prescribers should read the brochure, *Recognizing Psychiatric Disorders in Adolescents and Young Adults: A Guide for Prescribers of Isotretinoin*. Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Accutane (isotretinoin) therapy, patients and family members should be asked about any history of psychiatric disorder, and at each visit during therapy patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. Signs and symptoms of depression, as described in the brochure ("Recognizing Psychiatric Disorders in Adolescents and Young Adults"), include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment. Patients should stop Accutane (isotretinoin) and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Accutane (isotretinoin) therapy may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether Accutane (isotretinoin) therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of Accutane (isotretinoin) therapy.

Pseudotumor Cerebri

Accutane (isotretinoin) use has been associated with a number of cases of pseudotumor cerebri (benign intracranial hypertension), some of which involved concomitant use of tetracyclines. Concomitant treatment with tetracyclines should therefore be avoided. Early

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signs and symptoms of pseudotumor cerebri include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, they should be told to discontinue Accutane (isotretinoin) immediately and be referred to a neurologist for further diagnosis and care (see ADVERSE REACTIONS: Neurological).

Serious Skin Reactions

There have been post-marketing reports of erythema multiforme and severe skin reactions [eg, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)] associated with isotretinoin use. These events may be serious and result in death, life-threatening events, hospitalization, or disability. Patients should be monitored closely for severe skin reactions, and discontinuation of Accutane (isotretinoin) should be considered if warranted.

Pancreatitis

Acute pancreatitis has been reported in patients with either elevated or normal serum triglyceride levels. **In rare instances, fatal hemorrhagic pancreatitis has been reported.** Accutane (isotretinoin) should be stopped if hypertriglyceridemia cannot be controlled at an acceptable level or if symptoms of pancreatitis occur.

Lipids

Elevations of serum triglycerides in excess of 800 mg/dL have been reported in patients treated with Accutane (isotretinoin) . Marked elevations of serum triglycerides were reported in approximately 25% of patients receiving Accutane (isotretinoin) in clinical trials. In addition, approximately 15% developed a decrease in high-density lipoproteins and about 7% showed an increase in cholesterol levels. In clinical trials, the effects on triglycerides, HDL, and cholesterol were reversible upon cessation of Accutane (isotretinoin) therapy. Some patients have been able to reverse triglyceride elevation by reduction in weight, restriction of dietary fat and alcohol, and reduction in dose while continuing Accutane (isotretinoin) .[5]

Blood lipid determinations should be performed before Accutane (isotretinoin) is given and then at intervals until the lipid response to Accutane (isotretinoin) is established, which usually occurs within 4 weeks. Especially careful consideration must be given to risk/benefit for patients who may be at high risk during Accutane (isotretinoin) therapy (patients with diabetes, obesity, increased alcohol intake, lipid metabolism disorder or familial history of lipid metabolism disorder). If Accutane (isotretinoin) therapy is instituted, more frequent checks of serum values for lipids and/or blood sugar are recommended (see **PRECAUTIONS: Laboratory Tests**).

The cardiovascular consequences of hypertriglyceridemia associated with Accutane (isotretinoin) are unknown. *Animal Studies*: In rats given 8 or 32 mg/kg/day of isotretinoin (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area) for 18 months or longer, the incidences of focal calcification, fibrosis and inflammation of the myocardium, calcification of coronary, pulmonary and mesenteric arteries, and metastatic calcification of the gastric mucosa were greater than in control rats of similar age. Focal endocardial and myocardial calcifications associated with calcification of the coronary arteries

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were observed in two dogs after approximately 6 to 7 months of treatment with isotretinoin at a dosage of 60 to 120 mg/kg/day (30 to 60 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area).

Hearing Impairment

Impaired hearing has been reported in patients taking Accutane (isotretinoin) ; in some cases, the hearing impairment has been reported to persist after therapy has been discontinued. Mechanism(s) and causality for this event have not been established. Patients who experience tinnitus or hearing impairment should discontinue Accutane (isotretinoin) treatment and be referred for specialized care for further evaluation (see **ADVERSE REACTIONS: Special Senses**).

Hepatotoxicity

Clinical hepatitis considered to be possibly or probably related to Accutane (isotretinoin) therapy has been reported. Additionally, mild to moderate elevations of liver enzymes have been observed in approximately 15% of individuals treated during clinical trials, some of which normalized with dosage reduction or continued administration of the drug. If normalization does not readily occur or if hepatitis is suspected during treatment with Accutane (isotretinoin) , the drug should be discontinued and the etiology further investigated.

Inflammatory Bowel Disease

Accutane (isotretinoin) has been associated with inflammatory bowel disease (including regional ileitis) in patients without a prior history of intestinal disorders. In some instances, symptoms have been reported to persist after Accutane (isotretinoin) treatment has been stopped. Patients experiencing abdominal pain, rectal bleeding or severe diarrhea should discontinue Accutane immediately (see **ADVERSE REACTIONS: Gastrointestinal**).

Skeletal

Bone Mineral Density

Effects of multiple courses of Accutane (isotretinoin) on the developing musculoskeletal system are unknown. There is some evidence that long-term, high-dose, or multiple courses of therapy with isotretinoin have more of an effect than a single course of therapy on the musculoskeletal system. In an open-label clinical trial (N=217) of a single course of therapy with Accutane (isotretinoin) for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change > -4% and total hip change > -5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density > 4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density > 4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density > 5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density > 5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months

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thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range –1.6% to –7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13-18 years, who started a second course of Accutane (isotretinoin) 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see **PRECAUTIONS: Pediatric Use**).

Spontaneous reports of osteoporosis, osteopenia, bone fractures, and delayed healing of bone fractures have been seen in the Accutane (isotretinoin) population. While causality to Accutane (isotretinoin) has not been established, an effect cannot be ruled out. Longer term effects have not been studied. It is important that Accutane (isotretinoin) be given at the recommended doses for no longer than the recommended duration.

Hyperostosis

A high prevalence of skeletal hyperostosis was noted in clinical trials for disorders of keratinization with a mean dose of 2.24 mg/kg/day. Additionally, skeletal hyperostosis was noted in 6 of 8 patients in a prospective study of disorders of keratinization.[6] Minimal skeletal hyperostosis and calcification of ligaments and tendons have also been observed by x-ray in prospective studies of nodular acne patients treated with a single course of therapy at recommended doses. The skeletal effects of multiple Accutane (isotretinoin) treatment courses for acne are unknown.

In a clinical study of 217 pediatric patients (12 to 17 years) with severe recalcitrant nodular acne, hyperostosis was not observed after 16 to 20 weeks of treatment with approximately 1 mg/kg/day of Accutane (isotretinoin) given in two divided doses. Hyperostosis may require a longer time frame to appear. The clinical course and significance remain unknown.

Premature Epiphyseal Closure

There are spontaneous reports of premature epiphyseal closure in acne patients receiving recommended doses of Accutane (isotretinoin) . The effect of multiple courses of Accutane (isotretinoin) on epiphyseal closure is unknown.

Vision Impairment

Visual problems should be carefully monitored. All Accutane (isotretinoin) patients experiencing visual difficulties should discontinue Accutane (isotretinoin) treatment and have an ophthalmological examination (see **ADVERSE REACTIONS: Special Senses**).

Corneal Opacities

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Corneal opacities have occurred in patients receiving Accutane (isotretinoin) for acne and more frequently when higher drug dosages were used in patients with disorders of keratinization. The corneal opacities that have been observed in clinical trial patients treated with Accutane (isotretinoin) have either completely resolved or were resolving at follow-up 6 to 7 weeks after discontinuation of the drug (see **ADVERSE REACTIONS: Special Senses**).

Decreased Night Vision

Decreased night vision has been reported during Accutane (isotretinoin) therapy and in some instances the event has persisted after therapy was discontinued. Because the onset in some patients was sudden, patients should be advised of this potential problem and warned to be cautious when driving or operating any vehicle at night.

Precautions for Accutane

Accutane (isotretinoin) must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Accutane (isotretinoin) must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE. Registered and activated pharmacies must receive Accutane (isotretinoin) only from wholesalers registered with iPLEDGE.

iPLEDGE program requirements for wholesalers, prescribers, and pharmacists are described below:

Wholesalers

For the purpose of the iPLEDGE program, the term wholesaler refers to wholesaler, distributor, and/or chain pharmacy distributor. To distribute Accutane (isotretinoin) , wholesalers must be registered with iPLEDGE, and agree to meet all iPLEDGE requirements for wholesale distribution of isotretinoin products. Wholesalers must register with iPLEDGE by signing and returning the iPLEDGE wholesaler agreement that affirms they will comply with all iPLEDGE requirements for distribution of isotretinoin. These include:

- Registering prior to distributing isotretinoin and re-registering annually thereafter
- Distributing only FDA approved isotretinoin product

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- Only shipping isotretinoin to
    - wholesalers registered in the iPLEDGE program with prior written consent from the manufacturer or
    - pharmacies licensed in the US and registered and activated in the iPLEDGE program
- Notifying the isotretinoin manufacturer (or delegate) of any non-registered and/or nonactivated pharmacy or unregistered wholesaler that attempts to order isotretinoin
- Complying with inspection of wholesaler records for verification of compliance with the iPLEDGE program by the isotretinoin manufacturer (or delegate)
- Returning to the manufacturer (or delegate) any undistributed product if registration is revoked by the manufacturer or if the wholesaler chooses to not re-register annually

Prescribers

To prescribe isotretinoin, the prescriber must be registered and activated with the pregnancy risk management program iPLEDGE. Prescribers can register by signing and returning the completed registration form. Prescribers can only activate their registration by affirming that they meet requirements and will comply with all iPLEDGE requirements by attesting to the following points:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I know the risk factors for unplanned pregnancy and the effective measures for avoidance of unplanned pregnancy.
- I have the expertise to provide the patient with detailed pregnancy prevention counseling or I will refer her to an expert for such counseling, reimbursed by the manufacturer.
- I will comply with the iPLEDGE program requirements described in the booklets entitled *The Guide to Best Practices for the iPLEDGE Program and The iPLEDGE Program Prescriber Contraception Counseling Guide.*
- Before beginning treatment of female patients of childbearing potential with isotretinoin and on a monthly basis, the patient will be counseled to avoid pregnancy by using two forms of contraception simultaneously and continuously one month before, during, and one month after isotretinoin therapy, unless the patient commits to continuous abstinence.
- I will not prescribe isotretinoin to any female patient of childbearing potential until verifying she has a negative screening pregnancy test and monthly negative CLIA-certified (Clinical Laboratory Improvement Amendment) pregnancy tests. Patients should have a pregnancy test at the completion of the entire course of isotretinoin and another pregnancy test 1 month later.

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- I will report any pregnancy case that I become aware of while the female patient is on isotretinoin or 1 month after the last dose to the pregnancy registry.

To prescribe isotretinoin, the prescriber must access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) to:

1. Register each patient in the iPLEDGE program.
2. Confirm monthly that each patient has received counseling and education.
3. For *female patients of childbearing potential:*
    - Enter patient's two chosen forms of contraception each month.
    - Enter monthly result from CLIA-certified laboratory conducted pregnancy test.

Isotretinoin must only be prescribed to female patients who are known not to be pregnant as confirmed by a negative CLIA-certified laboratory conducted pregnancy test.

Isotretinoin must only be dispensed by a pharmacy registered and activated with the pregnancy risk management program iPLEDGE and only when the registered patient meets all the requirements of the iPLEDGE program. Meeting the requirements for a female patient of childbearing potential signifies that she:

- **Has** been counseled and has signed a Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin. The patient must sign the informed consent form before starting treatment and patient counseling must also be done at that time and on a monthly basis thereafter.

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- **Has had** two negative urine or serum pregnancy tests with a sensitivity of at least 25 mIU/mL before receiving the initial isotretinoin prescription. The first test (a screening test) is obtained by the prescriber when the decision is made to pursue qualification of the patient for isotretinoin. The second pregnancy test (a confirmation test) must be done in a CLIA-certified laboratory. The interval between the 2 tests should be at least 19 days.

    - For patients with regular menstrual cycles, the second pregnancy test should be done during the first 5 days of the menstrual period immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.
    - For patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding, the second pregnancy test must be done immediately preceding the beginning of isotretinoin therapy and after the patient has used 2 forms of contraception for 1 month.

- **Has had** a negative result from a urine or serum pregnancy test in a CLIA-certified laboratory before receiving each subsequent course of isotretinoin. A pregnancy test must be repeated every month, in a CLIA-certified laboratory, prior to the female patient receiving each prescription.
- **Has** selected and has committed to use 2 forms of effective contraception simultaneously, at least 1 of which must be a primary form, unless the patient commits to continuous abstinence from heterosexual contact, or the patient has undergone a hysterectomy or bilateral oophorectomy, or has been medically confirmed to be post-menopausal. Patients must use 2 forms of effective contraception for at least 1 month prior to initiation of isotretinoin therapy, during isotretinoin therapy, and for 1 month after discontinuing isotretinoin therapy. Counseling about contraception and behaviors associated with an increased risk of pregnancy must be repeated on a monthly basis.
  If the patient has unprotected heterosexual intercourse at any time 1 month before, during, or 1 month after therapy, she must:
    1. Stop taking Accutane (isotretinoin) immediately, if on therapy
    2. Have a pregnancy test at least 19 days after the last act of unprotected heterosexual intercourse
    3. Start using 2 forms of effective contraception simultaneously again for 1 month before resuming Accutane (isotretinoin) therapy
    4. Have a second pregnancy test after using 2 forms of effective contraception for 1 month as described above depending on whether she has regular menses or not.

Effective forms of contraception include both primary and secondary forms of contraception:

Primary forms	Secondary forms

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Barrier:

- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide

Other:

- vaginal sponge (contains spermicide)

- tubal sterilization
- partner's vasectomy
- intrauterine device
- hormonal (combination oral contraceptives, transdermal patch, injectables, implantables, or vaginal ring)

Any birth control method can fail. There have been reports of pregnancy from female patients who have used oral contraceptives, as well as transdermal patch/injectable/implantable/vaginal ring hormonal birth control products; these pregnancies occurred while these patients were taking Accutane (isotretinoin) . These reports are more frequent for female patients who use only a single method of contraception. Therefore, it is critically important that female patients of childbearing potential use 2 effective forms of contraception simultaneously. Patients must receive written warnings about the rates of possible contraception failure (included in patient education kits).

Using two forms of contraception simultaneously substantially reduces the chances that a female will become pregnant over the risk of pregnancy with either form alone. A drug interaction that decreases effectiveness of hormonal contraceptives has not been entirely ruled out for Accutane (see **PRECAUTIONS: DRUG INTERACTIONS**). Although hormonal contraceptives are highly effective, prescribers are advised to consult the package insert of any medication administered concomitantly with hormonal contraceptives, since some medications may decrease the effectiveness of these birth control products.

Patients should be prospectively cautioned not to self-medicate with the herbal supplement St. John's Wort because a possible interaction has been suggested with hormonal contraceptives based on reports of breakthrough bleeding on oral contraceptives shortly after starting St. John's Wort. Pregnancies have been reported by users of combined hormonal contraceptives who also used some form of St. John's Wort.

If a pregnancy does occur during isotretinoin treatment, isotretinoin must be discontinued immediately. The patient should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure during

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or 1 month after isotretinoin therapy must be reported immediately to the FDA via the MedWatch number 1-800-FDA-1088 and also to the iPLEDGE pregnancy registry at 1-866-495-0654 or via the internet (www.ipledgeprogram.com).

All Patients

Isotretinoin is contraindicated in female patients who are pregnant. To receive isotretinoin all patients must meet all of the following conditions:

- **Must** be registered with the iPLEDGE program by the prescriber
- **Must** understand that severe birth defects can occur with the use of isotretinoin by female patients
- **Must** be reliable in understanding and carrying out instructions
- **Must** sign a Patient Information/Informed Consent (for all patients) form that contains warnings about the potential risks associated with isotretinoin
- **Must** fill and pick up the prescription within 7 days of the date of specimen collection for the pregnancy test for female patients of childbearing potential
- **Must** fill and pick up the prescription within 30 days of the office visit for male patients and female patients not of childbearing potential
- **Must** not donate blood while on isotretinoin and for 1 month after treatment has ended
- **Must** not share isotretinoin with anyone, even someone who has similar symptoms

Female Patients of Childbearing Potential

Isotretinoin is contraindicated in female patients who are pregnant. In addition to the requirements for all patients described above, female patients of childbearing potential must meet the following conditions:

- **Must** NOT be pregnant or breast-feeding
- **Must** comply with the required pregnancy testing at a CLIA-certified laboratory
- **Must** fill and pick up the prescription within 7 days of the date of specimen collection for the pregnancy test
- **Must** be capable of complying with the mandatory contraceptive measures required for isotretinoin therapy, or commit to continuous abstinence from heterosexual intercourse, and understand behaviors associated with an increased risk of pregnancy

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- **Must** understand that it is her responsibility to avoid pregnancy one month before, during and one month after isotretinoin therapy
- **Must** have signed an additional Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form, before starting isotretinoin, that contains warnings about the risk of potential birth defects if the fetus is exposed to isotretinoin
- **Must** access the iPLEDGE system via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654), before starting isotretinoin, on a monthly basis during therapy, and 1 month after the last dose to answer questions on the program requirements and to enter the patient's two chosen forms of contraception
- **Must** have been informed of the purpose and importance of providing information to the iPLEDGE program should she become pregnant while taking isotretinoin or within 1 month of the last dose

Pharmacists

To dispense isotretinoin, pharmacies must be registered and activated with the pregnancy risk management program iPLEDGE.

The Responsible Site Pharmacist must register the pharmacy by signing and returning the completed registration form. After registration, the Responsible Site Pharmacist can only activate the pharmacy registration by affirming that they meet requirements and will comply with all iPLEDGE requirements by attesting to the following points:

- I know the risk and severity of fetal injury/birth defects from isotretinoin.
- I will train all pharmacists, who participate in the filling and dispensing of isotretinoin prescriptions, on the iPLEDGE program requirements.
- I will comply and seek to ensure all pharmacists who participate in the filling and dispensing of isotretinoin prescriptions comply with the iPLEDGE program requirements described in the booklet entitled *Pharmacist Guide for the iPLEDGE Program*.
- I will obtain Accutane (isotretinoin) product only from iPLEDGE registered wholesalers.
- I will not sell, buy, borrow, loan or otherwise transfer isotretinoin in any manner to or from another pharmacy.
- I will return to the manufacturer (or delegate) any unused product if registration is revoked by the manufacturer or if the pharmacy chooses to not reactivate annually.
- I will not fill isotretinoin for any party other than a qualified patient.

To dispense isotretinoin, the pharmacist must:

1. be trained by the Responsible Site Pharmacist concerning the iPLEDGE program requirements.

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2. obtain authorization from the iPLEDGE program via the internet (www.ipledgeprogram.com) or telephone (1-866-495-0654) for every isotretinoin prescription. Authorization signifies that the patient has met all program requirements and is qualified to receive isotretinoin.
3. write the Risk Management Authorization (RMA) number on the prescription.

Accutane (isotretinoin) must only be dispensed:

- in no more than a 30-day supply
- with an Accutane **Medication Guide**
- after authorization from the iPLEDGE program
- prior to the "do not dispense to patient after" date provided by the iPLEDGE system (within 30 days of the office visit for male patients and female patients not of childbearing potential and within 7 days of the date of specimen collection for female patients of childbearing potential)
- with a new prescription for refills and another authorization from the iPLEDGE program (No automatic refills are allowed)

An Accutane **Medication Guide** must be given to the patient each time Accutane (isotretinoin) is dispensed, as required by law. This Accutane **Medication Guide** is an important part of the risk management program for the patients.

Accutane (isotretinoin) must not be prescribed, dispensed or otherwise obtained through the internet or any other means outside of the iPLEDGE program. Only FDA-approved Accutane (isotretinoin) products must be distributed, prescribed, dispensed, and used. Patients must fill Accutane (isotretinoin) prescriptions only at US licensed pharmacies.

A description of the iPLEDGE program educational materials available with iPLEDGE is provided below. The main goal of these educational materials is to explain the iPLEDGE program requirements and to reinforce the educational messages.

1. *The Guide to Best Practices for the iPLEDGE Program* includes: isotretinoin teratogenic potential, information on pregnancy testing, and the method to complete a qualified isotretinoin prescription.
2. *The iPLEDGE Program Prescriber Contraception Counseling Guide* includes: specific information about effective contraception, the limitations of contraceptive methods, behaviors associated with an increased risk of contraceptive failure and pregnancy and the methods to evaluate pregnancy risk.
3. *The Pharmacist Guide for the iPLEDGE Program* includes: isotretinoin teratogenic potential and the method to obtain authorization to dispense an isotretinoin prescription.

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4. The iPLEDGE program is a systematic approach to comprehensive patient education about their responsibilities and includes education for contraception compliance and reinforcement of educational messages. The iPLEDGE program includes information on the risks and benefits of isotretinoin which is linked to the Medication Guide dispensed by pharmacists with each isotretinoin prescription.

5. Female patients not of childbearing potential and male patients, and female patients of childbearing potential are provided with separate booklets. Each booklet contains information on isotretinoin therapy including precautions and warnings, a Patient Information/Informed Consent (for all patients) form, and a toll-free line which provides isotretinoin information in 2 languages.

6. The booklet for female patients not of childbearing potential and male patients, *The iPLEDGE Program Guide to Isotretinoin for Male Patients and Female Patients Who Cannot Get Pregnant,* also includes information about male reproduction and a warning not to share isotretinoin with others or to donate blood during isotretinoin therapy and for 1 month following discontinuation of isotretinoin.

7. The booklet for female patients of childbearing potential, *The iPLEDGE Program Guide to Isotretinoin for Female Patients Who Can Get Pregnant,* includes a referral program that offers female patients free contraception counseling, reimbursed by the manufacturer, by a reproductive specialist; and a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form concerning birth defects.

8. The booklet, *The iPLEDGE Program Birth Control Workbook* includes information on the types of contraceptive methods, the selection and use of appropriate, effective contraception, the rates of possible contraceptive failure and a toll-free contraception counseling line.

9. In addition, there is a patient educational DVD with the following videos — "Be Prepared, Be Protected" and "Be Aware: The Risk of Pregnancy While on Isotretinoin" (see **PATIENT INFORMATION**).

General

Although an effect of Accutane (isotretinoin) on bone loss is not established, physicians should use caution when prescribing Accutane (isotretinoin) to patients with a genetic predisposition for age-related osteoporosis, a history of childhood osteoporosis conditions, osteomalacia, or other disorders of bone metabolism. This would include patients diagnosed with anorexia nervosa and those who are on chronic drug therapy that causes drug-induced osteoporosis/osteomalacia and/or affects vitamin D metabolism, such as systemic corticosteroids and any anticonvulsant.

Patients may be at increased risk when participating in sports with repetitive impact where the risks of spondylolisthesis with and without pars fractures and hip growth plate injuries in early and late adolescence are known. There are spontaneous reports of fractures and/or delayed healing in patients while on therapy with Accutane (isotretinoin) or following cessation of therapy with Accutane (isotretinoin) while involved in these activities. While causality to Accutane (isotretinoin) has not been established, an effect must not be ruled out.

Information for Patients

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See **PRECAUTIONS and Boxed CONTRAINDICATIONS AND WARNINGS**.

- Patients must be instructed to read the **Medication Guide** supplied as required by law when Accutane (isotretinoin) is dispensed. The complete text of the **Medication Guide** is reprinted at the end of this document. For additional information, patients must also be instructed to read the iPLEDGE program patient educational materials. All patients must sign the **Patient Information/Informed Consent** (for all patients) form.
- Female patients of childbearing potential must be instructed that they must not be pregnant when Accutane (isotretinoin) therapy is initiated, and that they should use 2 forms of effective contraception simultaneously for 1 month before starting Accutane (isotretinoin) , while taking Accutane (isotretinoin) , and for 1 month after Accutane (isotretinoin) has been stopped, unless they commit to continuous abstinence from heterosexual intercourse. They should also sign a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) form prior to beginning Accutane (isotretinoin) therapy. They should be given an opportunity to view the patient DVD provided by the manufacturer to the prescriber. The DVD includes information about contraception, the most common reasons that contraception fails, and the importance of using 2 forms of effective contraception when taking teratogenic drugs and comprehensive information about types of potential birth defects which could occur if a female patient who is pregnant takes Accutane (isotretinoin) at any time during pregnancy. Female patients should be seen by their prescribers monthly and have a urine or serum pregnancy test, in a CLIA-certified laboratory, performed each month during treatment to confirm negative pregnancy status before another Accutane prescription is written (see **Boxed CONTRAINDICATIONS AND WARNINGS and PRECAUTIONS**).
- Accutane (isotretinoin) is found in the semen of male patients taking Accutane (isotretinoin) , but the amount delivered to a female partner would be about 1 million times lower than an oral dose of 40 mg. While the no-effect limit for isotretinoin induced embryopathy is unknown, 20 years of postmarketing reports include 4 with isolated defects compatible with features of retinoid exposed fetuses; however 2 of these reports were incomplete, and 2 had other possible explanations for the defects observed.

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- Prescribers should be alert to the warning signs of psychiatric disorders to guide patients to receive the help they need. Therefore, prior to initiation of Accutane (isotretinoin) treatment, patients and family members should be asked about any history of psychiatric disorder, and at each visit during treatment patients should be assessed for symptoms of depression, mood disturbance, psychosis, or aggression to determine if further evaluation may be necessary. **Signs and symptoms of depression include sad mood, hopelessness, feelings of guilt, worthlessness or helplessness, loss of pleasure or interest in activities, fatigue, difficulty concentrating, change in sleep pattern, change in weight or appetite, suicidal thoughts or attempts, restlessness, irritability, acting on dangerous impulses, and persistent physical symptoms unresponsive to treatment.** Patients should stop Accutane (isotretinoin) and the patient or a family member should promptly contact their prescriber if the patient develops depression, mood disturbance, psychosis, or aggression, without waiting until the next visit. Discontinuation of Accutane (isotretinoin) treatment may be insufficient; further evaluation may be necessary. While such monitoring may be helpful, it may not detect all patients at risk. Patients may report mental health problems or family history of psychiatric disorders. These reports should be discussed with the patient and/or the patient's family. A referral to a mental health professional may be necessary. The physician should consider whether Accutane (isotretinoin) therapy is appropriate in this setting; for some patients the risks may outweigh the benefits of Accutane (isotretinoin) therapy.

- Patients must be informed that some patients, while taking Accutane (isotretinoin) or soon after stopping Accutane (isotretinoin) , have become depressed or developed other serious mental problems. Symptoms of depression include sad, “anxious” or empty mood, irritability, acting on dangerous impulses, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking Accutane (isotretinoin) have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on Accutane (isotretinoin) becoming aggressive or violent. No one knows if Accutane (isotretinoin) caused these behaviors or if they would have happened even if the person did not take Accutane (isotretinoin) . Some people have had other signs of depression while taking Accutane (isotretinoin) .

- Patients must be informed that they must not share Accutane (isotretinoin) with anyone else because of the risk of birth defects and other serious adverse events.

- Patients must be informed not to donate blood during therapy and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to Accutane (isotretinoin) .

- Patients should be reminded to take Accutane with a meal (see **DOSAGE AND ADMINISTRATION**). To decrease the risk of esophageal irritation, patients should swallow the capsules with a full glass of liquid.

- Patients should be informed that transient exacerbation (flare) of acne has been seen, generally during the initial period of therapy.

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- Wax epilation and skin resurfacing procedures (such as dermabrasion, laser) should be avoided during Accutane (isotretinoin) therapy and for at least 6 months thereafter due to the possibility of scarring (see **ADVERSE REACTIONS: Skin and Appendages**).
- Patients should be advised to avoid prolonged exposure to UV rays or sunlight.
- Patients should be informed that they may experience decreased tolerance to contact lenses during and after therapy.
- Patients should be informed that approximately 16% of patients treated with Accutane (isotretinoin) in a clinical trial developed musculoskeletal symptoms (including arthralgia) during treatment. In general, these symptoms were mild to moderate, but occasionally required discontinuation of the drug. Transient pain in the chest has been reported less frequently. In the clinical trial, these symptoms generally cleared rapidly after discontinuation of Accutane (isotretinoin) , but in some cases persisted (see **ADVERSE REACTIONS: Musculoskeletal**). There have been rare postmarketing reports of rhabdomyolysis, some associated with strenuous physical activity (see **Laboratory Tests: CPK**).
- Pediatric patients and their caregivers should be informed that approximately 29% (104/358) of pediatric patients treated with Accutane (isotretinoin) developed back pain. Back pain was severe in 13.5% (14/104) of the cases and occurred at a higher frequency in female patients than male patients. Arthralgias were experienced in 22% (79/358) of pediatric patients. Arthralgias were severe in 7.6% (6/79) of patients. Appropriate evaluation of the musculoskeletal system should be done in patients who present with these symptoms during or after a course of Accutane (isotretinoin) . Consideration should be given to discontinuation of Accutane (isotretinoin) if any significant abnormality is found.
- Neutropenia and rare cases of agranulocytosis have been reported. Accutane (isotretinoin) should be discontinued if clinically significant decreases in white cell counts occur.
- Patients should be advised that severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) have been reported in post-marketing data. Accutane (isotretinoin) should be discontinued if clinically significant skin reactions occur.

Hypersensitivity

Anaphylactic reactions and other allergic reactions have been reported. Cutaneous allergic reactions and serious cases of allergic vasculitis, often with purpura (bruises and red patches) of the extremities and extracutaneous involvement (including renal) have been reported. Severe allergic reaction necessitates discontinuation of therapy and appropriate medical management.

Carcinogenesis, Mutagenesis and Impairment of Fertility

In male and female Fischer 344 rats given oral isotretinoin at dosages of 8 or 32 mg/kg/day (1.3 to 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area) for greater than 18 months, there was a dose-related increased incidence of pheochromocytoma relative to controls. The incidence of adrenal medullary hyperplasia was also increased at the higher dosage in both sexes. The relatively high level of

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spontaneous pheochromocytomas occurring in the male Fischer 344 rat makes it an equivocal model for study of this tumor; therefore, the relevance of this tumor to the human population is uncertain.

The Ames test was conducted with isotretinoin in two laboratories. The results of the tests in one laboratory were negative while in the second laboratory a weakly positive response (less than 1.6 x background) was noted in *S. typhimurium* TA100 when the assay was conducted with metabolic activation. No dose-response effect was seen and all other strains were negative. Additionally, other tests designed to assess genotoxicity (Chinese hamster cell assay, mouse micronucleus test, *S. cerevisiae* D_7 assay, *in vitro* clastogenesis assay with human-derived lymphocytes, and unscheduled DNA synthesis assay) were all negative.

In rats, no adverse effects on gonadal function, fertility, conception rate, gestation or parturition were observed at oral dosages of isotretinoin of 2, 8, or 32 mg/kg/day (0.3, 1.3, or 5.3 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area).

In dogs, testicular atrophy was noted after treatment with oral isotretinoin for approximately 30 weeks at dosages of 20 or 60 mg/kg/day (10 or 30 times the recommended clinical dose of 1.0 mg/kg/day, respectively, after normalization for total body surface area). In general, there was microscopic evidence for appreciable depression of spermatogenesis but some sperm were observed in all testes examined and in no instance were completely atrophic tubules seen. In studies of 66 men, 30 of whom were patients with nodular acne under treatment with oral isotretinoin, no significant changes were noted in the count or motility of spermatozoa in the ejaculate. In a study of 50 men (ages 17 to 32 years) receiving Accutane (isotretinoin) therapy for nodular acne, no significant effects were seen on ejaculate volume, sperm count, total sperm motility, morphology or seminal plasma fructose.

Pregnancy

Category X. See **Boxed CONTRAINDICATIONS AND WARNINGS**.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because of the potential for adverse effects, nursing mothers should not receive Accutane (isotretinoin) .

Pediatric Use

The use of Accutane (isotretinoin) in pediatric patients less than 12 years of age has not been studied. The use of Accutane (isotretinoin) for the treatment of severe recalcitrant nodular acne in pediatric patients ages 12 to 17 years should be given careful consideration, especially for those patients where a known metabolic or structural bone disease exists (see **PRECAUTIONS: General**). Use of Accutane (isotretinoin) in this age group for severe recalcitrant nodular acne is supported by evidence from a clinical study comparing 103 pediatric patients (13 to 17 years) to 197 adult patients (≥ 18 years). Results from this study demonstrated that Accutane (isotretinoin) , at a dose of 1 mg/kg/day given in two divided doses, was equally effective in treating severe recalcitrant nodular acne in both pediatric and adult patients.

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In studies with Accutane (isotretinoin) , adverse reactions reported in pediatric patients were similar to those described in adults except for the increased incidence of back pain and arthralgia (both of which were sometimes severe) and myalgia in pediatric patients (see **ADVERSE REACTIONS**).

In an open-label clinical trial (N=217) of a single course of therapy with Accutane (isotretinoin) for severe recalcitrant nodular acne, bone density measurements at several skeletal sites were not significantly decreased (lumbar spine change > -4% and total hip change > -5%) or were increased in the majority of patients. One patient had a decrease in lumbar spine bone mineral density > 4% based on unadjusted data. Sixteen (7.9%) patients had decreases in lumbar spine bone mineral density > 4%, and all the other patients (92%) did not have significant decreases or had increases (adjusted for body mass index). Nine patients (4.5%) had a decrease in total hip bone mineral density > 5% based on unadjusted data. Twenty-one (10.6%) patients had decreases in total hip bone mineral density > 5%, and all the other patients (89%) did not have significant decreases or had increases (adjusted for body mass index). Follow-up studies performed in 8 of the patients with decreased bone mineral density for up to 11 months thereafter demonstrated increasing bone density in 5 patients at the lumbar spine, while the other 3 patients had lumbar spine bone density measurements below baseline values. Total hip bone mineral densities remained below baseline (range -1.6% to -7.6%) in 5 of 8 patients (62.5%).

In a separate open-label extension study of 10 patients, ages 13 to 18 years, who started a second course of Accutane (isotretinoin) 4 months after the first course, two patients showed a decrease in mean lumbar spine bone mineral density up to 3.25% (see **WARNINGS: Skeletal: Bone Mineral Density**).

Geriatric Use

Clinical studies of isotretinoin did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Although reported clinical experience has not identified differences in responses between elderly and younger patients, effects of aging might be expected to increase some risks associated with isotretinoin therapy (see **WARNINGS and PRECAUTIONS**).

REFERENCES

5. Katz RA, Jorgensen H, Nigra TP. Elevation of serum triglyceride levels from oral isotretinoin in disorders of keratinization. Arch Dermatol 116:1369-1372, 1980.

6. Ellis CN, Madison KC, Pennes DR, Martel W, Voorhees JJ. Isotretinoin therapy is associated with early skeletal radiographic changes. J Am Acad Dermatol 10:1024-1029, 1984.

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Overdose Information for Accutane

The oral LD_{50} of isotretinoin is greater than 4000 mg/kg in rats and mice (> 600 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the rat dose for total body surface area and > 300 times the recommended clinical dose of 1.0 mg/kg/day after normalization of the mouse dose for total body surface area) and is approximately 1960 mg/kg in rabbits (653 times the recommended clinical dose of 1.0 mg/kg/day after normalization for total body surface area). In humans, overdosage has been associated with vomiting, facial flushing, cheilosis, abdominal pain, headache, dizziness, and ataxia. These symptoms quickly resolve without apparent residual effects.

Accutane (isotretinoin) causes serious birth defects at any dosage (see **Boxed CONTRAINDICATIONS AND WARNINGS**). Female patients of childbearing potential who present with isotretinoin overdose must be evaluated for pregnancy. Patients who are pregnant should receive counseling about the risks to the fetus, as described in the **Boxed CONTRAINDICATIONS AND WARNINGS**. Non-pregnant patients must be warned to avoid pregnancy for at least one month and receive contraceptive counseling as described in **PRECAUTIONS**. Educational materials for such patients can be obtained by calling the manufacturer. Because an overdose would be expected to result in higher levels of isotretinoin in semen than found during a normal treatment course, male patients should use a condom, or avoid reproductive sexual activity with a female patient who is or might become pregnant, for 1 month after the overdose. All patients with isotretinoin overdose should not donate blood for at least 1 month.

Contraindications for Accutane

Pregnancy

Category X. See **Boxed CONTRAINDICATIONS AND WARNINGS**.

Allergic Reactions

Accutane (isotretinoin) is contraindicated in patients who are hypersensitive to this medication or to any of its components. Accutane (isotretinoin) should not be given to patients who are sensitive to parabens, which are used as preservatives in the gelatin capsule (see **PRECAUTIONS: Hypersensitivity**).

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Clinical Pharmacology for Accutane

Isotretinoin is a retinoid, which when administered in pharmacologic dosages of 0.5 to 1.0 mg/kg/day (see **DOSAGE AND ADMINISTRATION**), inhibits sebaceous gland function and keratinization. The exact mechanism of action of isotretinoin is unknown.

Nodular Acne

Clinical improvement in nodular acne patients occurs in association with a reduction in sebum secretion. The decrease in sebum secretion is temporary and is related to the dose and duration of treatment with Accutane (isotretinoin) , and reflects a reduction in sebaceous gland size and an inhibition of sebaceous gland differentiation.[1]

Pharmacokinetics

Absorption

Due to its high lipophilicity, oral absorption of isotretinoin is enhanced when given with a high-fat meal. In a crossover study, 74 healthy adult subjects received a single 80 mg oral dose (2 x 40 mg capsules) of Accutane (isotretinoin) under fasted and fed conditions. Both peak plasma concentration (Cmax) and the total exposure (AUC) of isotretinoin were more than doubled following a standardized high-fat meal when compared with Accutane (isotretinoin) given under fasted conditions (see Table 2). The observed elimination half-life was unchanged. This lack of change in half-life suggests that food increases the bioavailability of isotretinoin without altering its disposition. The time to peak concentration (Tmax) was also increased with food and may be related to a longer absorption phase. Therefore, Accutane (isotretinoin) capsules should always be taken with food (see **DOSAGE AND ADMINISTRATION**). Clinical studies have shown that there is no difference in the pharmacokinetics of isotretinoin between patients with nodular acne and healthy subjects with normal skin.

Table 2 : Pharmacokinetic Parameters of Isotretinoin Mean (%CV), N=74

Accutane 2 x 40 mg Capsules	AUC0-∞ (ng×hr/mL)	Cmax (ng/mL)	Tmax (hr)	t½ (hr)
Fed*	10,004 (22%)	862 (22%)	5.3 (77%)	21 (39%)
Fasted	3,703 (46%)	301 (63%)	3.2 (56%)	21 (30%)

*Eating a standardized high-fat meal

Distribution

Isotretinoin is more than 99.9% bound to plasma proteins, primarily albumin.

Metabolism

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Following oral administration of isotretinoin, at least three metabolites have been identified in human plasma: 4-oxo-isotretinoin, retinoic acid (tretinoin), and 4-*oxo*-retinoic acid (4-oxotretinoin). Retinoic acid and 13-*cis*-retinoic acid are geometric isomers and show reversible interconversion. The administration of one isomer will give rise to the other. Isotretinoin is also irreversibly oxidized to 4-oxo-isotretinoin, which forms its geometric isomer 4-oxo-tretinoin.

After a single 80 mg oral dose of Accutane (isotretinoin) to 74 healthy adult subjects, concurrent administration of food increased the extent of formation of all metabolites in plasma when compared to the extent of formation under fasted conditions.

All of these metabolites possess retinoid activity that is in some *in vitro* models more than that of the parent isotretinoin. However, the clinical significance of these models is unknown. After multiple oral dose administration of isotretinoin to adult cystic acne patients (≥ 18 years), the exposure of patients to 4-oxo-isotretinoin at steady-state under fasted and fed conditions was approximately 3.4 times higher than that of isotretinoin.

In vitro studies indicate that the primary P450 isoforms involved in isotretinoin metabolism are 2C8, 2C9, 3A4, and 2B6. Isotretinoin and its metabolites are further metabolized into conjugates, which are then excreted in urine and feces.

Elimination

Following oral administration of an 80 mg dose of 14C-isotretinoin as a liquid suspension, 14Cactivity in blood declined with a half-life of 90 hours. The metabolites of isotretinoin and any conjugates are ultimately excreted in the feces and urine in relatively equal amounts (total of 65% to 83%). After a single 80 mg oral dose of Accutane (isotretinoin) to 74 healthy adult subjects under fed conditions, the mean ± SD elimination half-lives (t½) of isotretinoin and 4-oxo-isotretinoin were 21.0 ± 8.2 hours and 24.0 ± 5.3 hours, respectively. After both single and multiple doses, the observed accumulation ratios of isotretinoin ranged from 0.90 to 5.43 in patients with cystic acne.

Special Patient Populations

Pediatric Patients

The pharmacokinetics of isotretinoin were evaluated after single and multiple doses in 38 pediatric patients (12 to 15 years) and 19 adult patients (≥ 18 years) who received Accutane (isotretinoin) for the treatment of severe recalcitrant nodular acne. In both age groups, 4-oxo-isotretinoin was the major metabolite; tretinoin and 4-oxo-tretinoin were also observed. The dose-normalized pharmacokinetic parameters for isotretinoin following single and multiple doses are summarized in Table 3 for pediatric patients. There were no statistically significant differences in the pharmacokinetics of isotretinoin between pediatric and adult patients.

Table 3 : Pharmacokinetic Parameters of Isotretinoin Following Single and Multiple Dose Administration in Pediatric Patients, 12 to 15 Years of Age Mean (± SD), N=38*

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Parameter	Isotretinoin (Single Dose)	Isotretinoin (Steady-State)
Cmax (ng/mL)	573.25 (278.79)	731.98 (361.86)
AUC(0-12) (nghr/mL) ×	3033.37 (1394.17)	5082.00 (2184.23)
AUC(0-24) (ng x hr/mL)	6003.81 (2885.67)	–
Tmax (hr)†	6.00 (1.00-24.60)	4.00 (0-12.00)
Cssmin (ng/mL)	–	352.32 (184.44)
T½ (hr)	–	15.69 (5.12)
CL/F (L/hr)	–	17.96 (6.27)

*The single and multiple dose data in this table were obtained following a non-standardized meal that is not comparable to the high-fat meal that was used in the study in Table 2.
†Median (range)

In pediatric patients (12 to 15 years), the mean ± SD elimination half-lives (t½) of isotretinoin and 4-oxo-isotretinoin were 15.7 ± 5.1 hours and 23.1 ± 5.7 hours, respectively. The accumulation ratios of isotretinoin ranged from 0.46 to 3.65 for pediatric patients.

REFERENCES

1. Peck GL, Olsen TG, Yoder FW, et al. Prolonged remissions of cystic and conglobate acne with 13-cis-retinoic acid. N Engl J Med 300:329-333, 1979.

Patient Information for Accutane

Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)

To be completed by the patient (and her parent or guardian* if patient is under age 18) and signed by her doctor.

Read each item below and initial in the space provided to show that you understand each item and agree to follow your doctor's instructions. **Do not sign this consent and do not take isotretinoin if there is anything that you do not understand.**

*A parent or guardian of a minor patient (under age 18) must also read and initial each item before signing the consent.

_____

(Patient's Name)

1. I understand that there is a very high chance that my unborn baby could have severe birth defects if I am pregnant or become pregnant while taking isotretinoin. This can happen with any amount and even if taken for short periods of time. This is why I must not be pregnant while

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taking isotretinoin.

Initial: _____

2. I understand that I must not get pregnant 1 month before, during the entire time of my treatment, and for 1 month after the end of my treatment with isotretinoin.

Initial: _____

3. I understand that I must avoid sexual intercourse completely, o r I must use 2 separate, effective forms of birth control (contraception) at the same time. The only exceptions are if I have had surgery to remove the uterus (a hysterectomy) or both of my ovaries (bilateral oophorectomy), or my doctor has medically confirmed that I am post-menopausal.

Initial: _____

4. I understand that hormonal birth control products are among the most effective forms of birth control. Combination birth control pills and other hormonal products include skin patches, shots, under-the-skin implants, vaginal rings, and intrauterine devices (IUDs). Any form of birth control can fail. That is why I must use 2 different birth control methods at the same time, starting 1 month before, during, and for 1 month after stopping therapy every time I have sexual intercourse, even if 1 of the methods I choose is hormonal birth control.

Initial: _____

5. I understand that the following are effective forms of birth control:

Primary forms

- tying my tubes (tubal sterilization)
- partner's vasectomy
- intrauterine device
- hormonal (combination birth control pills, skin patches, shots, under-the-skin implants, or vaginal ring)

Secondary forms

Barrier:

- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide

Other:

- vaginal sponge (contains spermicide)

A diaphragm and cervical cap must each be used with spermicide, a special cream that kills sperm

I understand that at least 1 of my 2 forms of birth control must be a primary method.

Initial: _____

6. I will talk with my doctor about any medicines including herbal products I plan to take during my isotretinoin treatment because hormonal birth control methods may not work if I am taking certain medicines or herbal products.

Initial: _____

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7. I may receive a free birth control counseling session from a doctor or other family planning expert. My isotretinoin doctor can give me an isotretinoin Patient Referral Form for this free consultation.

Initial: _____

8. I must begin using the birth control methods I have chosen as described above at least 1 month before I start taking isotretinoin.

Initial: _____

9. I cannot get my first prescription for isotretinoin unless my doctor has told me that I have 2 negative pregnancy test results. The first pregnancy test should be done when my doctor decides to prescribe isotretinoin. The second pregnancy test must be done in a lab during the first 5 days of my menstrual period right before starting isotretinoin therapy treatment, or as instructed by my doctor. I will then have 1 pregnancy test; in a lab.

- every month during treatment
- at the end of treatment
- and 1 month after stopping treatment

I must not start taking isotretinoin until I am sure that I am not pregnant, have negative results from 2 pregnancy tests, and the second test has been done in a lab.

Initial: _____

10. I have read and understand the materials my doctor has given to me, including *The iPLEDGE Program Guide for Isotretinoin for Female Patients Who Can Get Pregnant, The iPLEDGE Birth Control Workbook and The Ipledge Program Patient Introductory Brochure.*

My doctor gave me and asked me to watch the DVD containing a video about birth control and a video about birth defects and isotretinoin.

I was told about a private counseling line that I may call for more information about birth control. I have received information on emergency birth control.

Initial: _____

11. I must stop taking isotretinoin right away and call my doctor if I get pregnant, miss my expected menstrual period, stop using birth control, or have sexual intercourse without using my 2 birth control methods at any time.

Initial: _____

12. My doctor gave me information about the purpose and importance of providing information to the iPLEDGE program should I become pregnant while taking isotretinoin or within 1 month of the last dose. If I become pregnant, I agree to be contacted by the iPLEDGE program and be

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asked questions about my pregnancy. I also understand that if I become pregnant, information about my pregnancy, my health, and my baby's health may be given to the maker of isotretinoin and government health regulatory authorities.

Initial: _____

13. I understand that being qualified to receive isotretinoin in the iPLEDGE program means that I:

- have had 2 negative urine or blood pregnancy tests before receiving the first isotretinoin prescription. The second test must be done in a lab. I must have a negative result from a urine or blood pregnancy test done in a lab repeated each month before I receive another isotretinoin prescription.
- have chosen and agreed to use 2 forms of effective birth control at the same time. At least 1 method must be a primary form of birth control, **unless I have chosen never to have sexual contact with a male (abstinence),** or I have undergone a hysterectomy. I must use 2 forms of birth control for at least 1 month before I start isotretinoin therapy, during
- therapy, and for 1 month after stopping therapy. I must receive counseling, repeated on a monthly basis, about birth control and behaviors associated with an increased risk of pregnancy.
- have signed a Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant) that contains warnings about the chance of possible birth defects if I am pregnant or become pregnant and my unborn baby is exposed to isotretinoin.
- have been informed of and understand the purpose and importance of providing information to the iPLEDGE program should I become pregnant while taking isotretinoin or within 1 month of the last dose. I agree to be contacted by the iPLEDGE program and be asked questions about my pregnancy.
- have interacted with the iPLEDGE program before starting isotretinoin and on a monthly basis to answer questions on the program requirements and to enter my two chosen forms of birth control.

Initial: _____

My doctor has answered all my questions about isotretinoin and I understand that it is my responsibility not to get pregnant 1 month before, during isotretinoin treatment, or for 1 month after I stop taking isotretinoin.

Initial: _____

I now authorize my doctor _____ to begin my treatment with isotretinoin.

Patient Signature:_____ Date: _____

Parent/Guardian Signature (if under age 18):_____ Date:_____

Please print: Patient Name and Address_____

_____ Telephone _____ have fully explained to the patient, _____, the nature and purpose of the treatment described above and the

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risks to female patients of childbearing potential. I have asked the patient if she has any questions regarding her treatment with isotretinoin and have answered those questions to the best of my ability.

Doctor Signature: _____ Date: _____

PLACE THE ORIGINAL SIGNED DOCUMENTS IN THE PATIENT'S MEDICAL RECORD. PLEASE PROVIDE A COPY TO THE PATIENT.

Patient Information/Informed Consent (for all patients):

To be completed by patient (and parent or guardian if patient is under age 18) and signed by the doctor.

Read each item below and initial in the space provided if you understand each item and agree to follow your doctor's instructions. A parent or guardian of a patient under age 18 must also read and understand each item before signing the agreement.

Do not sign this agreement and do not take isotretinoin if there is anything that you do not understand about all the information you have received about using isotretinoin.

1. I, _____,

(Patient's Name)

understand that isotretinoin is a medicine used to treat severe nodular acne that cannot be cleared up by any other acne treatments, including antibiotics. In severe nodular acne, many red, swollen, tender lumps form in the skin. If untreated, severe nodular acne can lead to permanent scars.

Initials: _____

2. My doctor has told me about my choices for treating my acne.

Initials: _____

3. I understand that there are serious side effects that may happen while I am taking isotretinoin. These have been explained to me. These side effects include serious birth defects in babies of pregnant patients. [Note: There is a second Patient Information/Informed Consent About Birth Defects (for female patients who can get pregnant)].

Initials: _____

4. I understand that some patients, while taking isotretinoin or soon after stopping isotretinoin, have become depressed or developed other serious mental problems. Symptoms of depression include sad, “anxious” or empty mood, irritability, acting on dangerous impulses, anger, loss of pleasure or interest in social or sports activities, sleeping too much or too little, changes in weight or appetite, school or work performance going down, or trouble concentrating. Some patients taking isotretinoin have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives. There were reports that some of these people did not appear depressed. There have been reports of patients on isotretinoin becoming aggressive or violent.

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No one knows if isotretinoin caused these behaviors or if they would have happened even if the person did not take isotretinoin. Some people have had other signs of depression while taking isotretinoin (see #7 below).

Initials: _____

5. Before I start taking isotretinoin, I agree to tell my doctor if I have ever had symptoms of depression (see #7 below), been psychotic, attempted suicide, had any other mental problems, or take medicine for any of these problems. Being psychotic means having a loss of contact with reality, such as hearing voices or seeing things that are not there.

Initials: _____

6. Before I start taking isotretinoin, I agree to tell my doctor if, to the best of my knowledge, anyone in my family has ever had symptoms of depression, been psychotic, attempted suicide, or had any other serious mental problems.

Initials: _____

7. Once I start taking isotretinoin, I agree to stop using isotretinoin and tell my doctor right away if any of the following signs and symptoms of depression or psychosis happen. I:

- Start to feel sad or have crying spells
- Lose interest in activities I once enjoyed
- Sleep too much or have trouble sleeping
- Become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- Have a change in my appetite or body weight
- Have trouble concentrating
- Withdraw from my friends or family
- Feel like I have no energy
- Have feelings of worthlessness or guilt
- Start having thoughts about hurting myself or taking my own life (suicidal thoughts)
- Start acting on dangerous impulses
- Start seeing or hearing things that are not real

Initials: _____

8. **I agree to return to see my doctor every month I take isotretinoin to get a new prescription for isotretinoin, to check my progress, and to check for signs of side effects.**

Initials: _____

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9. Isotretinoin will be prescribed just for me — I will not share isotretinoin with other people because it may cause serious side effects, including birth defects.

Initials: _____

10. I will not give blood while taking isotretinoin or for 1 month after I stop taking isotretinoin. I understand that if someone who is pregnant gets my donated blood, her baby may be exposed to isotretinoin and may be born with serious birth defects.

Initials: _____

11. I have read *The iPLEDGE Program Patient Introductory Brochure,* and other materials my provider gave me containing important safety information about isotretinoin. I understand all the information I received.

Initials: _____

12. My doctor and I have decided I should take isotretinoin. I understand that I must be qualified in the iPLEDGE program to have my prescription filled each month. I understand that I can stop taking isotretinoin at any time. I agree to tell my doctor if I stop taking isotretinoin.

Initials: _____

I now allow my doctor _____ to begin my treatment with isotretinoin.

Patient Signature: _____ Date: _____
Parent/Guardian Signature (if under age 18): _____ Date: _____
Patient Name (print) _____ Patient Address
_____ Telephone (___.___.___) _____

I have:

- fully explained to the patient, _____, the nature and purpose of isotretinoin treatment, including its benefits and risks
- given the patient the appropriate educational materials, *The iPLEDGE Program Patient Introductory Brochure* and asked the patient if he/she has any questions regarding his/her treatment with isotretinoin
- answered those questions to the best of my ability

Doctor Signature: _____ Date: _____

PLACE THE ORIGINAL SIGNED DOCUMENTS IN THE PATIENT'S MEDICAL RECORD. PLEASE PROVIDE A COPY TO THE PATIENT.

MEDICATION GUIDE

ACCUTANE (ACK-U-TANE)
(isotretinoin capsules)

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Read the Medication Guide that comes with Accutane (isotretinoin) before you start taking it and each time you get a prescription. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about Accutane (isotretinoin) ?

- Accutane (isotretinoin) is used to treat a type of severe acne (nodular acne) that has not been helped by other treatments, including antibiotics.
- Because Accutane (isotretinoin) can cause birth defects, Accutane (isotretinoin) is only for patients who can understand and agree to carry out all of the instructions in the iPLEDGE program.
- Accutane (isotretinoin) may cause serious mental health problems.

1. **Birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births.** Female patients who are pregnant or who plan to become pregnant must not take Accutane (isotretinoin) . **Female patients must not get pregnant:**

- for 1 month before starting Accutane (isotretinoin)
- while taking Accutane (isotretinoin)
- for 1 month after stopping Accutane (isotretinoin) .

If you get pregnant while taking Accutane (isotretinoin) , stop taking it right away and call your doctor. Doctors and patients should report all cases of pregnancy to:

- FDA MedWatch at 1-800-FDA-1088, and
- the iPLEDGE pregnancy registry at 1-866-495-0654

2. **Serious mental health problems.** Accutane (isotretinoin) may cause:

- **depression**
- **psychosis** (seeing or hearing things that are not real)
- **suicide**. Some patients taking Accutane (isotretinoin) have had thoughts about hurting themselves or putting an end to their own lives (suicidal thoughts). Some people tried to end their own lives. And some people have ended their own lives.

Stop Accutane (isotretinoin) and call your doctor right away if you or a family member notices that you have any of the following signs and symptoms of depression or psychosis:

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- start to feel sad or have crying spells
- lose interest in activities you once enjoyed
- sleep too much or have trouble sleeping
- become more irritable, angry, or aggressive than usual (for example, temper outbursts, thoughts of violence)
- have a change in your appetite or body weight
- have trouble concentrating
- withdraw from your friends or family
- feel like you have no energy
- have feelings of worthlessness or guilt
- start having thoughts about hurting yourself or taking your own life (suicidal thoughts)
- start acting on dangerous impulses
- start seeing or hearing things that are not real

After stopping Accutane (isotretinoin) , you may also need follow-up mental health care if you had any of these symptoms.

What is Accutane (isotretinoin) ?

Accutane (isotretinoin) is a medicine taken by mouth to treat the most severe form of acne (nodular acne) that cannot be cleared up by any other acne treatments, including antibiotics. Accutane (isotretinoin) can cause serious side effects (see **"What is the most important information I should know about Accutane (isotretinoin) ?"**). Accutane (isotretinoin) can only be:

- prescribed by doctors that are registered in the iPLEDGE program
- dispensed by a pharmacy that is registered with the iPLEDGE program
- given to patients who are registered in the iPLEDGE program and agree to do everything required in the program

What is severe nodular acne?

Severe nodular acne is when many red, swollen, tender lumps form in the skin. These can be the size of pencil erasers or larger. If untreated, nodular acne can lead to permanent scars.

Who should not take Accutane (isotretinoin) ?

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- **Do not take Accutane (isotretinoin) if you are pregnant, plan to become pregnant, or become pregnant during Accutane (isotretinoin) treatment**. Accutane (isotretinoin) causes severe birth defects. See **"What is the most important information I should know about Accutane (isotretinoin) ?"**
- **Do not take Accutane (isotretinoin) if you are allergic to anything in it.** Accutane (isotretinoin) contains parabens as the preservative. See the end of this Medication Guide for a complete list of ingredients in Accutane (isotretinoin) .

What should I tell my doctor before taking Accutane (isotretinoin) ?

Tell your doctor if you or a family member has any of the following health conditions:

- mental problems
- asthma
- liver disease
- diabetes
- heart disease
- bone loss (osteoporosis) or weak bones
- an eating problem called anorexia nervosa (where people eat too little)
- food or medicine allergies

Tell your doctor if you are pregnant or breastfeeding. Accutane (isotretinoin) must not be used by women who are pregnant or breastfeeding.

Tell your doctor about all of the medicines you take including prescription and non-prescription medicines, vitamins and herbal supplements. Accutane (isotretinoin) and certain other medicines can interact with each other, sometimes causing serious side effects. Especially tell your doctor if you take:

- **Vitamin A supplements.** Vitamin A in high doses has many of the same side effects as Accutane (isotretinoin) . Taking both together may increase your chance of getting side effects.
- **Tetracycline antibiotics.** Tetracycline antibiotics taken with Accutane (isotretinoin) can increase the chances of getting increased pressure in the brain.
- **Progestin-only birth control pills (mini-pills).** They may not work while you take Accutane (isotretinoin) . Ask your doctor or pharmacist if you are not sure what type you are using.
- **Dilantin (phenytoin).** This medicine taken with Accutane (isotretinoin) may weaken your bones.

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- **Corticosteroid medicines.** These medicines taken with Accutane (isotretinoin) may weaken your bones.
- **St. John's Wort.** This herbal supplement may make birth control pills work less effectively.

These medicines should not be used with Accutane (isotretinoin) unless your doctor tells you it is okay.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist. Do not take any new medicine without talking with your doctor.

How should I take Accutane (isotretinoin) ?

- You must take Accutane (isotretinoin) exactly as prescribed. You must also follow all the instructions of the iPLEDGE program. Before prescribing Accutane (isotretinoin) , your doctor will:
    - explain the iPLEDGE program to you
    - have you sign the Patient Information/Informed Consent (for all patients). Female patients who can get pregnant must also sign another consent form.
      You will not be prescribed Accutane (isotretinoin) if you cannot agree to or follow all the instructions of the iPLEDGE program.

- You will get no more than a 30-day supply of Accutane (isotretinoin) at a time. This is to make sure you are following the Accutane (isotretinoin) iPLEDGE program. You should talk with your doctor each month about side effects.
- The amount of Accutane (isotretinoin) you take has been specially chosen for you. It is based on your body weight, and may change during treatment.
- Take Accutane (isotretinoin) 2 times a day with a meal, unless your doctor tells you otherwise. **Swallow your Accutane (isotretinoin) capsules whole with a full glass of liquid. Do not chew or suck on the capsule.** Accutane (isotretinoin) can hurt the tube that connects your mouth to your stomach (esophagus) if it is not swallowed whole.
- If you miss a dose, just skip that dose. Do not take 2 doses at the same time.
- If you take too much Accutane (isotretinoin) or overdose, call your doctor or poison control center right away.
- Your acne may get worse when you first start taking Accutane (isotretinoin) . This should last only a short while. Talk with your doctor if this is a problem for you.
- You must return to your doctor as directed to make sure you don't have signs of serious side effects. Your doctor may do blood tests to check for serious side effects from Accutane (isotretinoin) . Female patients who can get pregnant will get a pregnancy test each month.

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- Female patients who can get pregnant must agree to use 2 separate forms of effective birth control at the same time 1 month before, while taking, and for 1 month after taking Accutane (isotretinoin) . **You must access the iPLEDGE system to answer questions about the program requirements and to enter your 2 chosen forms of birth control.** To access the iPLEDGE system, go to www.ipledgeprogram.com or call 1-866-495-0654.
  You must talk about effective birth control methods with your doctor or go for a free visit to talk about birth control with another doctor or family planning expert. Your doctor can arrange this free visit, which will be paid for by the company that makes Accutane (isotretinoin) .
  If you have sex at any time without using 2 forms of effective birth control, get pregnant, or miss your expected period, stop using Accutane (isotretinoin) and call your doctor right away.

What should I avoid while taking Accutane (isotretinoin) ?

- **Do not get pregnant** while taking Accutane (isotretinoin) and for 1 month after stopping Accutane (isotretinoin) . See **"What is the most important information I should know about Accutane (isotretinoin) ?"**
- **Do not breast feed** while taking Accutane (isotretinoin) and for 1 month after stopping Accutane (isotretinoin) . We do not know if Accutane (isotretinoin) can pass through your milk and harm the baby.
- **Do not give blood** while you take Accutane (isotretinoin) and for 1 month after stopping Accutane (isotretinoin) . If someone who is pregnant gets your donated blood, her baby may be exposed to Accutane (isotretinoin) and may be born with birth defects.
- **Do not take other medicines or herbal products** with Accutane (isotretinoin) unless you talk to your doctor. See **"What should I tell my doctor before taking Accutane (isotretinoin) ?"**
- **Do not drive at night until you know if Accutane (isotretinoin) has affected your vision.** Accutane (isotretinoin) may decrease your ability to see in the dark.
- **Do not have cosmetic procedures to smooth your skin, including waxing, dermabrasion, or laser procedures, while you are using Accutane (isotretinoin) and for at least 6 months after you stop.** Accutane (isotretinoin) can increase your chance of scarring from these procedures. Check with your doctor for advice about when you can have cosmetic procedures.
- **Avoid sunlight and ultraviolet lights** as much as possible. Tanning machines use ultraviolet lights. Accutane (isotretinoin) may make your skin more sensitive to light.
- **Do not share Accutane (isotretinoin) with other people.** It can cause birth defects and other serious health problems.

What are the possible side effects of Accutane (isotretinoin) ?

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- **Accutane (isotretinoin) can cause birth defects (deformed babies), loss of a baby before birth (miscarriage), death of the baby, and early (premature) births. See "What is the most important information I should know about Accutane (isotretinoin) ?"**
- **Accutane (isotretinoin) may cause serious mental health problems. See "What is the most important information I should know about Accutane (isotretinoin) ?"**
- **serious brain problems.** Accutane (isotretinoin) can increase t he pressure in your brain. This can lead to permanent loss of eyesight and, in rare cases, death. Stop taking Accutane (isotretinoin) and call your doctor right away if you get any of these signs of increased brain pressure:
    - bad headache
    - blurred vision
    - dizziness
    - nausea or vomiting
    - seizures (convulsions)
    - stroke
- **stomach area (abdomen) problems.** Certain symptoms may mean that your internal organs are being damaged. These organs include the liver, pancreas, bowel (intestines), and esophagus (connection between mouth and stomach). If your organs are damaged, they may not get better even after you stop taking Accutane (isotretinoin) . Stop taking Accutane (isotretinoin) and call your doctor if you get:
    - severe stomach, chest or bowel pain
    - trouble swallowing or painful swallowing
    - new or worsening heartburn
    - diarrhea
    - rectal bleeding
    - yellowing of your skin or eyes
    - dark urine

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- **bone and muscle problems.** Accutane (isotretinoin) may affect bones, muscles, and ligaments and cause pain in your joints or muscles. Tell your doctor if you plan hard physical activity during treatment with Accutane (isotretinoin) . Tell your doctor if you get:
    - back pain
    - joint pain
    - broken bone. Tell all healthcare providers that you take Accutane (isotretinoin) if you break a bone.
      Stop Accutane (isotretinoin) and call your doctor right away if you have muscle weakness. Muscle weakness with or without pain can be a sign of serious muscle damage.
      Accutane (isotretinoin) may stop long bone growth in teenagers who are still growing.

- **hearing problems.** Stop using Accutane (isotretinoin) and call your doctor if your hearing gets worse or if you have ringing in your ears. Your hearing loss may be permanent.
- **vision problems.** Accutane (isotretinoin) may affect your ability to see in the dark. This condition usually clears up after you stop taking Accutane (isotretinoin) , but it may be permanent. Other serious eye effects can occur. Stop taking Accutane (isotretinoin) and call your doctor right away if you have any problems with your vision or dryness of the eyes that is painful or constant. If you wear contact lenses, you may have trouble wearing them while taking Accutane (isotretinoin) and after treatment.
- **lipid (fats and cholesterol in blood) problems.** Accutane (isotretinoin) can raise the level of fats and cholesterol in your blood. This can be a serious problem. Return to your doctor for blood tests to check your lipids and to get any needed treatment. These problems usually go away when Accutane (isotretinoin) treatment is finished.
- **serious allergic reactions.** Stop taking Accutane (isotretinoin) and get emergency care right away if you develop hives, a swollen face or mouth, or have trouble breathing. Stop taking Accutane (isotretinoin) and call your doctor if you get a fever, rash, or red patches or bruises on your legs.
- **blood sugar problems.** Accutane (isotretinoin) may cause blood sugar problems including diabetes. Tell your doctor if you are very thirsty or urinate a lot.
- **decreased red and white blood cells.** Call your doctor if you have trouble breathing, faint, or feel weak.
- **The common, less serious side effects of Accutane (isotretinoin)** are dry skin, chapped lips, dry eyes, and dry nose that may lead to nosebleeds. Call your doctor if you get any side effect that bothers you or that does not go away.

These are not all of the possible side effects with Accutane (isotretinoin) . Your doctor or pharmacist can give you more detailed information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Roche at 1-800-526-6367.

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How should I store Accutane (isotretinoin) ?

- Store Accutane (isotretinoin) at room temperature, between 59° and 86°F. Protect from light.
- **Keep Accutane (isotretinoin) and all medicines out of the reach of children.**

General Information about Accutane (isotretinoin)

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use Accutane (isotretinoin) for a condition for which it was not prescribed. Do not give Accutane (isotretinoin) to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Accutane (isotretinoin) . If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Accutane (isotretinoin) that is written for health care professionals. You can also call iPLEDGE program at 1-866-495-0654 or visit www.ipledgeprogram.com.

What are the ingredients in Accutane?

Active Ingredient: Isotretinoin

Inactive Ingredients: beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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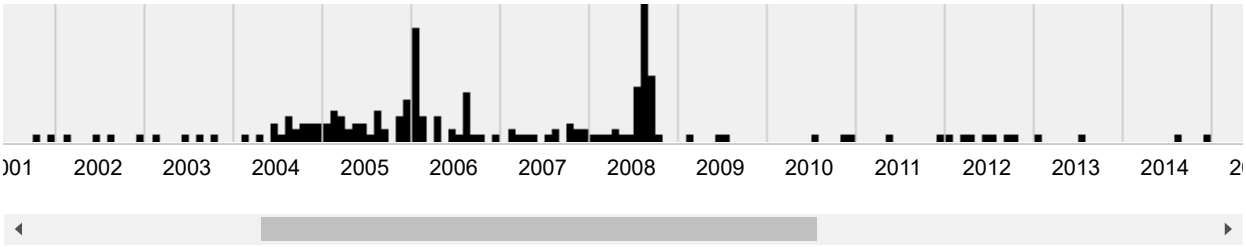
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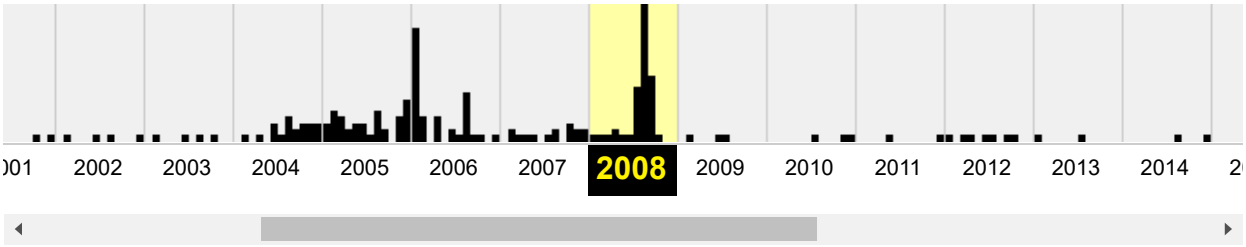
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Accutane

Drug Description

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ACCUTANE®
(isotretinoin) Capsules

CAUSES BIRTH DEFECTS



DO NOT GET PREGNANT

CONTRAINDICATIONS AND WARNINGS

Accutane must not be used by female patients who are or may become pregnant. There is an extremely high risk that severe birth defects will result if pregnancy occurs while taking Accutane in any amount, even for short periods of time. Potentially any fetus exposed during pregnancy can be affected. There are no accurate means of determining whether an exposed fetus has been affected.

Birth defects which have been documented following Accutane exposure include abnormalities of the face, eyes, ears, skull, central nervous system, cardiovascular system, and thymus and parathyroid glands. Cases of IQ scores less than 85 with or without other abnormalities have been reported. There is an increased risk of spontaneous abortion, and premature births have been reported.

Documented external abnormalities include: skull abnormality; ear abnormalities (including anotia, micropinna, small or absent external auditory canals); eye abnormalities (including microphthalmia); facial dysmorphia; cleft palate. Documented internal abnormalities include: CNS abnormalities (including cerebral abnormalities, cerebellar malformation, hydrocephalus, microcephaly, cranial nerve deficit); cardiovascular abnormalities; thymus gland abnormality; parathyroid hormone deficiency. In some cases death has occurred with certain of the abnormalities previously noted.

If pregnancy does occur during treatment of a female patient who is taking Accutane, Accutane must be discontinued immediately and she should be referred to an Obstetrician-Gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Special Prescribing Requirements

Because of Accutane's teratogenicity and to minimize fetal exposure, Accutane is approved for marketing only under a special restricted distribution program approved by the Food and Drug Administration. This program is called iPLEDGE™. Accutane must only be prescribed by prescribers who are registered and activated with the iPLEDGE program. Accutane must only be dispensed by a pharmacy registered and activated with iPLEDGE, and must only be dispensed to patients who are registered and meet all the requirements of iPLEDGE (see **PRECAUTIONS**).

Table 1 Monthly Required iPLEDGE Interactions

	Female Patients of Childbearing Potential	Male Patients, And Female Patients Not of Childbearing Potential
PRESCRIBER		

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Ringworm
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Popular Searches
Adderall
Aricept
Avandia
Botox
Cardura
Chantix
Coumadin
Levaquin
OxyContin
Viagra

Confirms patient counseling	X	X
Enters the 2 contraception methods chosen by the patient	X	
Enters pregnancy test results	X	
PATIENT		
Answers educational questions before every prescription	X	
Enters 2 forms of contraception	X	
PHARMACIST		
Contacts system to get an authorization	X	X

DRUG DESCRIPTION

Isotretinoin, a retinoid, is available as Accutane in 10-mg, 20-mg and 40-mg soft gelatin capsules for oral administration. Each capsule contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg — iron oxide (red) and titanium dioxide; 20 mg — FD&C Red No. 3, FD&C Blue No. 1, and titanium dioxide; 40 mg — FD&C Yellow No. 6, D&C Yellow No. 10, and titanium dioxide.

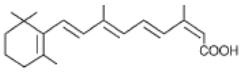
consumer drug excerpt

Accutane (isotretinoin)

Accutane is used to treat severe cystic acne (also known as nodular acne) that has not responded to other treatment (e.g., benzoyl peroxide or clindamycin applied to the skin or tetracycline or minocycline taken by mouth). It belongs to a class of drugs known as retinoids.

» Continue reading about Accutane

Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow to orange crystalline powder with a molecular weight of 300.44. The structural formula is:



Brand Name: Accutane
Generic Name: Isotretinoin

Next: Accutane - Indications & Dosage »

« previous 1 2 3 4 5 6 7 next »

Report Problems to the Food and Drug Administration FDA

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit the FDA MedWatch website or call 1-800-FDA-1088.

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Search ChemoCare.com

Drugs, Side Effects...

SEARCH

Information You Can Trust

Chemocare.com is a comprehensive resource for cancer patients and their caregivers that provides chemotherapy drug and side effect information, cancer wellness information, and links to additional reliable resources and organizations.

All information provided on this website is created and reviewed by a multidisciplinary team at Cleveland Clinic or is referenced from reliable medical and community resources.

About



While undergoing cancer treatment at Cleveland Clinic, Scott Hamilton, an Olympic gold medalist in figure skating, discovered that it was difficult to find a reliable online resource where information about chemotherapy was presented in a clear, easy to understand and easy to locate format. As a result, his idea to create a patient friendly website was born. Chemocare.com went online in December 2002 to provide cancer patients and their caregivers with clear and accurate information about chemotherapy, and to empower them to become active participants in their treatment. Several updates to the site since 2002 include translating the website into Spanish, becoming mobile friendly, educational videos, as well as continuing to add and update all FDA approved drugs for the treatment of cancer.

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Drug Information

Find the latest information about chemotherapy drugs including how they work, their potential side effects, and self care tips while on these therapies.

VIEW ALL SPANISH

Managing Side Effects

Find the latest information about chemotherapy drugs including how they work, their potential side effects, and self care tips while on these therapies.

VIEW ALL SPANISH

Nutrition During Chemotherapy

Practicing healthy eating habits throughout cancer treatment is essential. Staying hydrated and maintaining muscle tissue with enough fluids, calories and nutrients can reduce treatment delays, boost your immune system and help minimize debilitating side effects such as fatigue.

Navigating reliable, useful information can be overwhelming. We want to help you and your caregivers with suggestions for maintaining a healthy diet during chemotherapy.

NUTRITIONAL INFORMATION

★ Quick Access

Eating Well During Chemotherapy
What is Chemotherapy?
Before and After Chemotherapy
Self Help Tool Box
What is Survivorship?
Complementary Medicine
Chemotherapy Resources
Frequently Asked Questions

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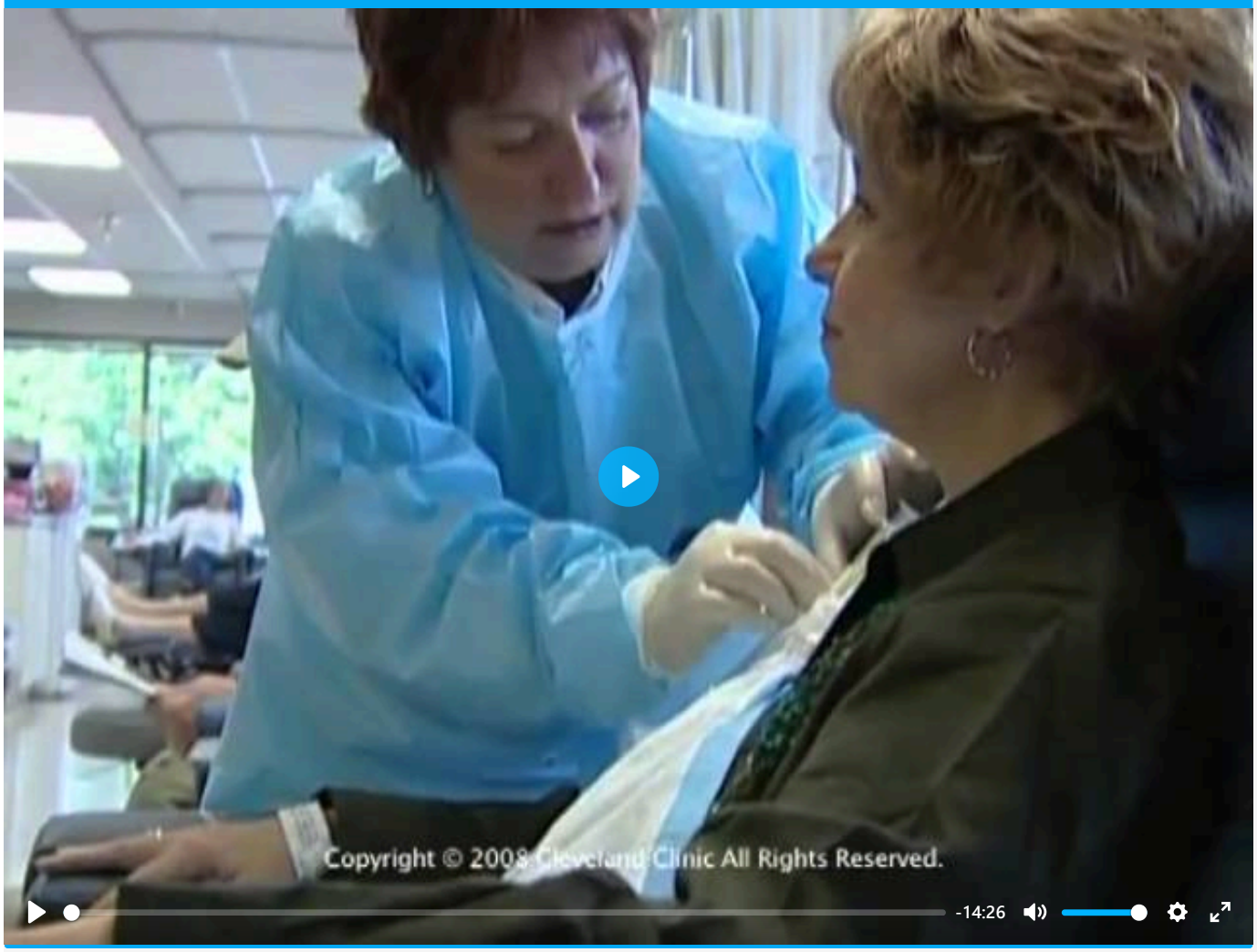
Educational Videos

Peer Mentoring

About Chemocare.com

Spanish Version

Chemotherapy Basics



Patient Friendly Information

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4022



DRUG INFORMATION

391



SIDE EFFECTS

86



ACRONYMS

223



ARTICLES

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6,955 **253** **0** **0**

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http://**chemocare**headwear.com/

chemo care head wear

2,929 **369** **0** **0**

11,197 captures from **2001** to **2016** | Site stats

http://headwearlist.com/

professionals design

2 **0** **0** **0**

13 captures from **2006** to **2007** | Site stats



http://cancerhopenetwork.org/

cancer hope network

260 **259** **0** **2**

4,296 captures from **2000** to **2016** | Site stats

http://procrit.com/

www.procrit.com

1,181 **1,252** **0** **2**

11,939 captures from **1998** to **2016** | Site stats

http://**chemocare**.info/

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***chemocare**.info*

2 0 0 0

4 captures from **2014** to **2015** | Site stats

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http://**chemocare**.org/

***chemocare**.org*

6 0 0 0

19 captures from **2010** to **2016** | Site stats

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http://**chemocare**.co.uk/

clinisis ltd

56 34 0 0

352 captures from **2001** to **2004** | Site stats

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http://windsurfemqw.bodaonxeyh.info/

*hats - **chemocare** headwear, hats ... **chemocare** headwear - bucket*

1 0 0 0

1 capture from **2007** to **2007** | Site stats

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http://yakumofpty.bodaonxeyh.info/

jefferson land trust quimper wildlife corridor -

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1 capture from **2007** to **2007** | Site stats

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http://3336.z0n92f.info/

cached

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1 capture from **2006** to **2006** | Site stats

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http://2727.nvvn.info/

***chemocare**.com*

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1 capture from **2007** to **2007** | Site stats

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http://3395.cqi9hx.info/

similar pages

1 0 0 0

1 capture from **2006** to **2006** | Site stats

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http://3232.rooot.info/

cached

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2 captures from **2007** to **2007** | Site stats

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http://534.ttjdus.info/

similar pages

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3 captures from **2006** to **2007** | Site stats

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http://clinisis.co.uk/

高血压

97 46 0 0

526 captures from **2001** to **2016** | Site stats

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http://3984.79c22bl5.info/

sba express loan

1 0 0 0

1 capture from **2007** to **2007** | Site stats

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http://10529.tm0qw0.info/

similar pages

1 0 0 0

1 capture from **2006** to **2006** | Site stats

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http://cis-healthcare.com/

www.cis-healthcare.com

175 93 0 0

629 captures from **2007** to **2016** | Site stats

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http://7895.sdq8et.info/

cached

1 0 0 0

1 capture from **2006** to **2006** | Site stats

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http://565.tvewx.info/

home health care services for children with special health care ...

1 0 0 0

1 capture from **2007** to **2007** | Site stats

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http://1599.qawrx.be/

similar pages

1 0 0 0

2 captures from **2006** to **2006** | Site stats

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http://3492.6mpa5.info/

relevanz

1 0 0 0

2 captures from **2006** to **2007** | Site stats

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http://1273.2gtfj.info/

shop

1 0 0 0

1 capture from **2007** to **2007** | Site stats

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http://492.urwpf.info/

ford

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1 capture from **2007** to **2007** | Site stats

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http://1815.lvcvz.info/

new homes partner results : energy star

1 0 0 0

2 captures from **2006** to **2006** | Site stats

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http://2296.p3ew21.info/

cached

1 0 0 0

2 captures from **2006** to **2006** | Site stats

http://2027.ogsma.info/

pain

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http://1806.5jsdhsj.info/

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1 capture from **2007** to **2007** | Site stats

http://915.junkymail.olawa.pl/

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http://5070.kz060.info/

similar pages

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2 captures from **2006** to **2006** | Site stats

http://6299.andtsc.info/

similar pages

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1 capture from **2007** to **2007** | Site stats

http://1846.nqy6yl.info/

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1 capture from **2006** to **2006** | Site stats

http://4244.v4tbj5.info/

cached

1 **0** **0** **0**

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http://4022.dvtxfpd.info/

driving school online directory

1 **0** **0** **0**

4 captures from **2006** to **2006** | Site stats

http://163.nightclub.konin.pl/

cached

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3 captures from **2006** to **2006** | Site stats

http://1206.u65n7ab4.info/

relevanz

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http://2614.gmeaya.info/

mad al distributors - wholesaler of candy, trading cards, sports ...

1 **0** **0** **0**

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http://2225.gmeaya.info/

nhlbi-chd cholesterol lowering medicines

1 **0** **0** **0**

2 captures from **2007** to **2007** | Site stats

http://2812.ooct.info/

yes bass tabs @ bass masta.net

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1 capture from **2007** to **2007** | Site stats

http://4721.ogh6so.info/

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5 captures from **2006** to **2006** | Site stats

http://3284.xywtawszl.info/

bone pain encyclopedia of cancer - find articles

1 0 0 0

2 captures from **2007** to **2007** | Site stats

http://611.8s9nqk.info/

similar pages

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http://798.top139.info/

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http://2453.skpfcw.info/

orbitz: cheap car rentals

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http://1058.vdgiicee.info/

dedicated server hosting

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http://1985.b2eekk.info/

similar pages

1 0 0 0

1 capture from **2006** to **2006** | Site stats

http://170.kqjlrb.info/

ice cream franchises

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http://5018.nightclub.zachpomor.pl/

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1 capture from **2006** to **2006** | Site stats

http://4059.get-valium.be/

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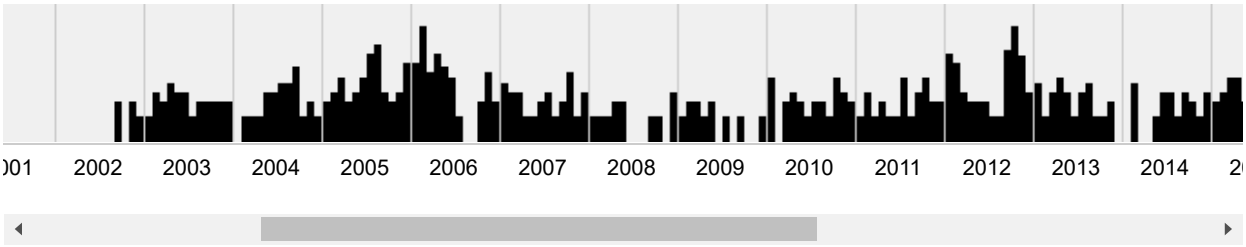
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JAN

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Note

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Green indicates redirects (3xx).

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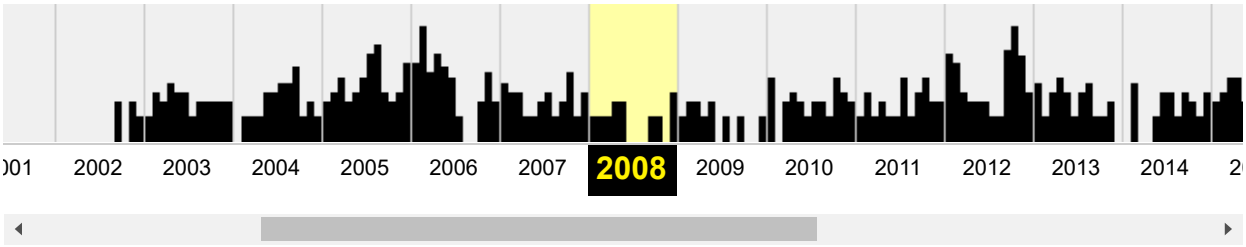
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Chemotherapy Drugs - Drug Names

To find the chemotherapy drug that you are taking, find the chemo drug in the l
and click on the drug name. You may also view our chemotherapy drug list by
(combination of letters, numbers or words that stand for a group of drugs).

- 1
  - 13-cis-Retinoic Acid
- 2
  - 2-CdA
  - 2-Chlorodeoxyadenosine
- 5
  - 5-Azacitidine
  - 5-Fluorouracil
  - 5-FU
- 6
  - 6-Mercaptopurine
  - 6-MP
  - 6-TG
  - 6-Thioguanine
- A
  - Abraxane
  - Accutane ®
  - Actinomycin-D
  - Adriamycin ®
  - Adrucil ®
  - Agrylin ®
  - Ala-Cort ®
  - Aldesleukin
  - Alemtuzumab
  - ALIMTA
  - Alitretinoin
  - Alkaban-AQ ®
  - Alkeran ®
  - All-transretinoic Acid
  - Alpha Interferon
  - Altretamine
  - Amethopterin
  - Amifostine
  - Aminoglutethimide
  - Anagrelide
  - Anandron ®
  - Anastrozole
  - Arabinosylcytosine
  - Ara-C
- K
  - Kidrolase (t)
- L
  - Lanacort ®
  - Lapatinib
  - L-asparaginase
  - LCR
  - Lenalidomide
  - Letrozole
  - Leucovorin
  - Leukeran
  - Leukine ™
  - Leuprolide
  - Leurocristine
  - Leustatin ™
  - Liposomal Ara-C
  - Liquid Pred ®
  - Lomustine
  - L-PAM
  - L-Sarcolysin
  - Lupron ®
  - Lupron Depot ®
- M
  - Matulane ®
  - Maxidex
  - Mechlorethamine
  - Mechlorethamine Hydrochloride
  - Medralone ®
  - Medrol ®
  - Megace ®
  - Megestrol
  - Megestrol Acetate
  - Melphalan
  - Mercaptopurine
  - Mesna
  - Mesnex ™
  - Methotrexate
  - Methotrexate Sodium
  - Methylprednisolone

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- Aranesp ®
- Aredia ®
- Arimidex ®
- Aromasin ®
- Arranon ®
- Arsenic Trioxide
- Asparaginase
- ATRA
- Avastin ®
- Azacitidine

B

- BCG
- BCNU
- Bevacizumab
- Bexarotene
- BEXXAR ®
- Bicalutamide
- BiCNU
- Blenoxane ®
- Bleomycin
- Bortezomib
- Busulfan
- Busulfex ®

C

- C225
- Calcium Leucovorin
- Campath ®
- Camptosar ®
- Camptothecin-11
- Capecitabine
- Carac ™
- Carboplatin
- Carmustine
- Carmustine Wafer
- Casodex ®
- CC-5013
- CCI-779
- CCNU
- CDDP
- CeeNU
- Cerubidine ®
- Cetuximab
- Chlorambucil
- Cisplatin
- Citrovorum Factor
- Cladribine
- Cortisone
- Cosmegen ®
- CPT-11
- Cyclophosphamide
- Cytadren ®
- Meticorten ®
- Mitomycin
- Mitomycin-C
- Mitoxantrone
- M-Prednisol ®
- MTC
- MTX
- Mustargen ®
- Mustine
- Mutamycin ®
- Myleran ®
- Mylocel ™
- Mylotarg ®

N

- Navelbine ®
- Nelarabine
- Neosar ®
- Neulasta ™
- Neumega ®
- Neupogen ®
- Nexavar ®
- Nilandron ®
- Nilutamide
- Nipent ®
- Nitrogen Mustard
- Novaldex ®
- Novantrone ®

O

- Octreotide
- Octreotide acetate
- Oncospar ®
- Oncovin ®
- Ontak ®
- Onxal ™
- Oprevelkin
- Orapred ®
- Orasone ®
- Oxaliplatin

P

- Paclitaxel
- Paclitaxel Protein-bound
- Pamidronate
- Panitumumab
- Panretin ®
- Paraplatin ®
- Pediapred ®
- PEG Interferon
- Pegaspargase
- Pegfilgrastim
- PEG-INTRON ™
- PEG-L-asparaginase

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- Cytarabine
- Cytarabine Liposomal
- Cytosar-U ®
- Cytoxan ®

D

- Dacarbazine
- Dacogen
- Dactinomycin
- Darbepoetin Alfa
- Dasatinib
- Daunomycin
- Daunorubicin
- Daunorubicin Hydrochloride
- Daunorubicin Liposomal
- DaunoXome ®
- Decadron
- Decitabine
- Delta-Cortef ®
- Deltasone ®
- Denileukin Diftitox
- DepoCyt ™
- Dexamethasone
- Dexamethasone Acetate
- Dexamethasone Sodium Phosphate
- Dexasone
- Dexrazoxane
- DHAD
- DIC
- Diodex
- Docetaxel
- Doxil ®
- Doxorubicin
- Doxorubicin Liposomal
- Droxia ™
- DTIC
- DTIC-Dome ®
- Duralone ®

E

- Efudex ®
- Eligard ™
- Ellence ™
- Eloxatin ™
- Elspar ®
- Emcyt ®
- Epirubicin
- Epoetin Alfa
- Erbitux
- Erlotinib
- Erwinia L-asparaginase
- Estramustine
- Ethyol
- PEMETREXED
- Pentostatin
- Phenylalanine Mustard
- Platinol ®
- Platinol-AQ ®
- Prednisolone
- Prednisone
- Prelone ®
- Procarbazine
- PROCRIT ®
- Proleukin ®
- Prolifeprospan 20 with Carmustine Implant
- Purinethol ®

R

- Raloxifene
- Revlimid ®
- Rheumatrex ®
- Rituxan ®
- Rituximab
- Roferon-A ® (Interferon Alfa-2a)
- Rubex ®
- Rubidomycin hydrochloride

S

- Sandostatin ®
- Sandostatin LAR ®
- Sargramostim
- Solu-Cortef ®
- Solu-Medrol ®
- Sorafenib
- SPRYCEL ™
- STI-571
- Streptozocin
- SU11248
- Sunitinib
- Sutent ®

T

- Tamoxifen
- Tarceva ®
- Targretin ®
- Taxol ®
- Taxotere ®
- Temodar ®
- Temozolomide
- Temsirolimus
- Teniposide
- TESPA
- Thalidomide
- Thalomid ®
- TheraCys ®
- Thioguanine

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- Etopophos ®
- Etoposide
- Etoposide Phosphate
- Eulexin ®
- Evista ®
- Exemestane

F

- Fareston ®
- Faslodex ®
- Femara ®
- Filgrastim
- Floxuridine
- Fludara ®
- Fludarabine
- Fluoroplex ®
- Fluorouracil
- Fluorouracil (cream)
- Fluoxymesterone
- Flutamide
- Folinic Acid
- FUDR ®
- Fulvestrant

G

- G-CSF
- Gefitinib
- Gemcitabine
- Gemtuzumab ozogamicin
- Gemzar & Gemzar Side Effects - Chemotherapy Drugs
- Gleevec ™
- Gliadel ® Wafer
- GM-CSF
- Goserelin
- Granulocyte - Colony Stimulating Factor
- Granulocyte Macrophage Colony Stimulating Factor

H

- Halotestin ®
- Herceptin ®
- Hexadrol
- Hexalen ®
- Hexamethylmelamine
- HMM
- Hycamtin ®
- Hydrea ®
- Hydrocort Acetate ®
- Hydrocortisone
- Hydrocortisone Sodium Phosphate
- Hydrocortisone Sodium Succinate
- Hydrocortone Phosphate
- Hydroxyurea
- Thioguanine Tabloid ®
- Thiophosphoamide
- Thioplex ®
- Thiotepa
- TICE ®
- Toposar ®
- Topotecan
- Toremifene
- Torisel ®
- Tositumomab
- Trastuzumab
- Tretinoin
- Trexall ™
- Trisenox ®
- TSPA
- TYKERB ®

V

- VCR
- Vectibix ™
- Velban ®
- Velcade ®
- VePesid ®
- Vesanoid ®
- Viadur ™
- Vidaza ®
- Vinblastine
- Vinblastine Sulfate
- Vincasar Pfs ®
- Vincristine
- Vinorelbine
- Vinorelbine tartrate
- VLB
- VM-26
- Vorinostat
- VP-16
- Vumon ®

X

- Xeloda ®

Z

- Zanosar ®
- Zevalin ™
- Zinecard ®
- Zoladex ®
- Zoledronic acid
- Zolinza
- Zometa ®

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I

- Ibritumomab
- Ibritumomab Tiuxetan
- Idamycin ®
- Idarubicin
- Ifex ®
- IFN-alpha
- Ifosfamide
- IL-11
- IL-2
- Imatinib mesylate
- Imidazole Carboxamide
- Interferon alfa
- Interferon Alfa-2b (PEG Conjugate)
- Interleukin - 2
- Interleukin-11
- Intron A® (interferon alfa-2b)
- Iressa ®
- Irinotecan
- Isotretinoin
- Ixabepilone
- Ixempra ™



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Alkeus Pharmaceuticals Announces Results from the SAGA Study of Oral Gildeuretinol in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

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- Oral gildeuretinol demonstrated a clinically meaningful reduction in the geographic atrophy (GA) lesion growth rate at 24 months, supporting further clinical development.
- Gildeuretinol showed a statistically significant slowing of the rate of decline in low luminance visual acuity (LLVA) at 24 months, a key secondary endpoint. It is the first oral therapy to demonstrate an impact on a functional endpoint in GA.
- A favorable safety and tolerability profile was demonstrated by gildeuretinol, consistent with prior clinical studies in Alkeus' Stargardt disease program.
- SAGA topline data has been accepted as a late breaker at the 128th Annual Meeting of the American Academy of Ophthalmology (AAO) being held October 18-21 in Chicago.

CAMBRIDGE, Mass., September 17, 2024 – Alkeus Pharmaceuticals, Inc. today announced that the SAGA study of oral gildeuretinol acetate (ALK-001) in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) demonstrated a reduction of 0.25 sqmm/year vs. placebo (p=0.07) in the primary endpoint of GA lesion growth rate at 24 months. Gildeuretinol demonstrated a statistically significant reduction in the loss of low luminance visual acuity (LLVA) at 24 months (p=0.03). Gildeuretinol showed a favorable safety profile consistent with other studies of gildeuretinol in Stargardt disease. The topline results will be presented as a late breaker at the 128th Annual Meeting of the American Academy of Ophthalmology (AAO) during Retina Subspecialty Day on Friday, October 18, in Chicago.

"These data clearly indicate a clinically meaningful trend in slowing the growth rate of GA lesions, which is extremely encouraging," said Seemi Khan, M.D., M.P.H., M.B.A., Chief Medical Officer of Alkeus Pharmaceuticals. "The SAGA data represent the first clinical demonstration that slowing vitamin A dimerization could be beneficial in the treatment of GA secondary to AMD. Results from SAGA build upon the positive data from TEASE-1, a study of gildeuretinol in Stargardt disease. We look forward to discussing these results with the U.S. Food and Drug Administration to determine the optimal path forward. We extend our gratitude to the patients, investigators and trial sites for their participation in this study."

SAGA was a 24-month, double-masked, randomized, placebo-controlled trial to investigate the safety, pharmacokinetics, tolerability and efficacy in patients with GA secondary to AMD. The study enrolled 198 patients. The primary efficacy endpoint was the growth rate of GA lesions from baseline to 24 months as assessed by Fundus Autofluorescence (FAF). The first key secondary endpoint was the change in LLVA at 24 months.

"I am highly encouraged by the results of an oral treatment that showed a significant reduction of the growth rate of GA, as well as its effect on visual acuity," said David S. Boyer, M.D., a retina

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specialist with Retina-Vitreous Associates Medical Group of Los Angeles, and a principal investigator in SAGA. "The patient population afflicted with GA is in desperate need of an oral treatment to slow disease progression. I'm extremely excited by these data and believe this is a significant advancement of our scientific understanding of the GA disease mechanism."

GA is a serious, progressive condition that causes irreversible loss of central vision. It is estimated that the median time of progression to legal blindness is slightly over six years. There is no oral therapy approved by the FDA to treat GA. The prevalence of GA in the United States is estimated to be over 1 million people, with 160,000 new cases occurring each year.

"These results reinforce the potential of gildeuretinol as an oral therapy for the treatment of macular degenerative diseases," said Michel Dahan, President and CEO of Alkeus Pharmaceuticals. "We are driven by our mission to positively impact the lives of the many people around the world living with degenerative eye diseases. Patients, parents and children, and their treating physicians are waiting for treatment options to preserve sight. We will continue to work diligently to bring oral gildeuretinol to those in need starting with individuals impacted by Stargardt disease, subject to regulatory approval."

About Gildeuretinol Acetate (ALK-001)

Gildeuretinol acetate (ALK-001) is a novel molecule created as a specialized form of deuterated vitamin A designed to reduce the dimerization of vitamin A without disrupting vision. In preclinical studies, gildeuretinol decreased vitamin A dimerization down to the normal rate and prevented retinal degeneration and loss of visual function in animals with Stargardt disease. A randomized, placebo-controlled, double-masked clinical trial of gildeuretinol in late-stage Stargardt patients (TEASE-1) showed clinically and statistically significant slowing of the growth of retinal lesions over two years of treatment. Additional clinical trials of gildeuretinol in Stargardt disease are ongoing. Gildeuretinol has received breakthrough therapy designation and orphan drug designation for Stargardt disease from the U.S. Food and Drug Administration. A Phase 2/3 study (SAGA) of gildeuretinol in approximately 200 patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) has been completed and topline data has been accepted as a late-breaking abstract at the 128th Annual Meeting of the American Academy of Ophthalmology (AAO) being held October 18-21 in Chicago.

About Alkeus Pharmaceuticals

Alkeus Pharmaceuticals, Inc. is a private biopharmaceutical company with headquarters in Cambridge, Mass., backed by institutional investors led by Bain Capital Life Sciences. Founded in 2010, Alkeus is developing therapies for serious diseases of the eye with high unmet need. Alkeus' breakthrough-designated lead candidate, gildeuretinol acetate (ALK-001), is currently being

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evaluated in clinical trials for the treatment of Stargardt disease and for geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

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Alkeus Pharmaceuticals Presents Positive Interim Data Showing Gildeuretinol Halted Stargardt Disease Progression

- All three patients treated for two years or more have remained free of symptoms and disease progression while taking gildeuretinol.
- TEASE-3 is the first clinical trial in early-stage Stargardt disease, a leading cause of inherited blindness in children and young adults.
- Data to be presented today at 11:30 a.m. PST during the J.P. Morgan Healthcare Conference at The Westin St. Francis San Francisco, Golden Gate room, 32nd floor of the Tower Building.

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CAMBRIDGE, Mass., Jan. 10, 2024 – Alkeus Pharmaceuticals, Inc. today announced positive interim data showing gildeuretinol halted Stargardt disease progression for up to six years. In its ongoing TEASE-3 clinical trial in early-stage Stargardt disease, the first three teenage patients enrolled in TEASE-3 and treated with oral gildeuretinol acetate remained asymptomatic and free of disease progression for their treatment duration ranging between two (one patient) and six years (two patients). In the absence of treatment, the patients were projected to begin experiencing vision loss within two years, following the same disease trajectory as that of their respective older siblings with identical genetic mutations who had not been treated with gildeuretinol.

"The data show the potential of gildeuretinol acetate to arrest Stargardt disease when treatment is started early," said Leonide Saad, Ph.D., President and CEO of Alkeus Pharmaceuticals. "These early results of TEASE-3, together with the results of TEASE-1 in more advanced disease, recently presented at the American Academy of Ophthalmology, show great promise for all patients. We look forward to submitting a new drug application for gildeuretinol acetate in the treatment of Stargardt disease."

Alkeus will present an update at 11:30 a.m. PST today during the J.P. Morgan Healthcare Conference at The Westin St. Francis San Francisco, Golden Gate room, 32nd floor of the Tower Building.

"I am encouraged by the results of the different TEASE trials," said Michael B. Gorin, M.D., Ph.D., Departments of Ophthalmology and Human Genetics at the David Geffen School of Medicine at UCLA. "Both the initial TEASE-1 study and this smaller cohort of early-stage Stargardt patients show clinical benefits from gildeuretinol. However, the dramatic preservation of vision in these younger patients highlights the need to consider the impact of therapies at different stages of the condition. Usually, such asymptomatic or minimally symptomatic individuals are excluded from clinical trials. Being able to compare even this small number of individuals with the severity of disease in their older, untreated siblings who share the same genetic etiology, as well as the same dietary and environmental exposures, allows us to draw meaningful insights into the potential of this medication to preserve sight."

TEASE-3, the first clinical trial in early-stage Stargardt disease, is an open-label study of gildeuretinol. Participants have early signs of disease visible on retinal imaging, but have not begun experiencing symptoms of vision loss. Fundus autofluorescence (FAF) imaging and other outcome measures were used to assess the extent to which gildeuretinol affects disease progression. Year-over-year progression was assessed, as well as age-matched comparison to each participant's untreated sibling with Stargardt disease and identical mutations. The primary endpoint is a measure of progression after the first two years of treatment. After the initial two-

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year treatment, patients can continue to receive gildeuretinol for extended periods. TEASE-3 has enrolled a total of five patients to date with no signs of disease progression while on treatment.

Stargardt disease is a leading genetic cause of blindness in children and young adults, with an estimated 30,000 people affected in the U.S. and more than 150,000 worldwide. There is no approved treatment. In individuals with Stargardt disease, the ABCA4 protein is defective. Loss of the protein results in the accelerated dimerization of vitamin A, forming toxic by-products that irreversibly damage the retina, resulting in progressive vision loss.

"Stargardt is a very serious blinding disease that progressively robs the patient of their central vision and unfortunately has no approved treatment," said Jason Menzo, Chief Executive Officer at the Foundation Fighting Blindness. "An efficacious and safe oral therapy that could slow or perhaps stop disease progression for this patient population would be welcomed by those living with Stargardt disease."

About the TEASE Trials

The TEASE trials consist of four independent clinical studies of gildeuretinol (ALK-001) in Stargardt disease, denoted as TEASE-1, TEASE-2, TEASE-3 and TEASE-4. The TEASE-1 study was a randomized, triple-masked, placebo-controlled trial in 50 randomized patients with Stargardt disease. Gildeuretinol met its prespecified primary efficacy endpoint showing a 21% reduction in the growth rate of retinal atrophic lesions ($p<0.001$, square root units, 28% effect for untransformed areas) against untreated patients. Gildeuretinol was well-tolerated. The TEASE-2 trial is an ongoing, fully enrolled, randomized, triple-masked, placebo-controlled trial in 80 patients with Stargardt disease, expected to read out topline data in 2025. TEASE-3 is an open-label study designed to assess gildeuretinol in early-stage Stargardt patients. TEASE-4 is an open-label extension study.

About Gildeuretinol Acetate (ALK-001)

Gildeuretinol acetate (ALK-001) is a novel molecule created as a specialized form of deuterated vitamin A designed to reduce the dimerization of vitamin A without disrupting vision. In preclinical studies, gildeuretinol decreased vitamin A dimerization to the normal rate seen in unaffected individuals and prevented retinal degeneration and blindness in animals with Stargardt disease. In addition to the TEASE trials, a Phase 3 study of gildeuretinol in 200 patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD) has recently been completed and is expected to read out topline data in 2024. Gildeuretinol has received breakthrough therapy designation and orphan drug designation by the U.S. Food and Drug Administration.

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Alkeus Pharmaceuticals Announces Presentation of a TEASE-3 Study Update Showing Progression Stalled in Early-Stage Stargardt Disease Patients Treated with Gildeuretinol

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Data in early-stage patients presented at the 42nd ASRS Annual Scientific Meeting

CAMBRIDGE, Mass., July 18, 2024 – Alkeus Pharmaceuticals, Inc. today announced the presentation of interim data from its TEASE-3 study demonstrating that early-stage Stargardt disease patients treated with gildeuretinol acetate showed no disease progression and remained asymptomatic while on therapy ranging between two and six years. The study update was presented during the 42nd American Society of Retina Specialists (ASRS) Annual Scientific Meeting, being held July 17-20 in Stockholm, Sweden.

"Interim results from the TEASE-3 study of gildeuretinol in early-stage Stargardt patients indicate the potential value of treating patients with confirmed disease-causing ABCA4 genetic mutations as early as possible before the disease causes progressive loss of central vision," said Seemi Khan, M.D., M.P.H., M.B.A., Chief Medical Officer of Alkeus Pharmaceuticals. "There is high unmet need in this disease area with no existing treatment, and we look forward to sharing additional results from this encouraging study in the future as we work to advance our development program, which has the potential to be the first therapy for Stargardt disease."

TEASE-3, the first clinical trial in early-stage Stargardt disease, is an open-label study of gildeuretinol in genetically confirmed patients with early signs of disease visible on retinal imaging, but who have not begun experiencing symptoms of vision loss. Each TEASE-3 study participant has a sibling who was previously diagnosed with Stargardt disease, has identical gene mutations and has experienced irreversible vision loss. The primary endpoint of disease progression over two years is assessed by retinal imaging and functional outcome measures. After the initial two-year treatment period, patients continue to receive gildeuretinol while enrolled in an open label long-term extension study. The TEASE-3 study has enrolled a total of six patients, who receive gildeuretinol as a once-a-day pill.

"The TEASE-3 study has been a unique opportunity to evaluate gildeuretinol in a small group of presymptomatic children for whom we had clinical history information regarding the course of Stargardt disease in older siblings," said Michael B. Gorin, M.D., Ph.D., of the Departments of Ophthalmology and of Human Genetics at the David Geffen School of Medicine at UCLA. "We were able to assess the ability of the medication to stall vision loss in these children as compared to the age-matched data of their genetically-matched Stargardt siblings. The dramatic delay of vision and photoreceptor loss in this small cohort is an exciting advancement in the therapy for ABCA4-related Stargardt disease and suggests that the clinical benefits may be greater at the earliest stages of this condition."

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Stargardt disease is a serious cause of blindness in children and young adults, with an estimated 30,000 people affected in the U.S. and more than 150,000 worldwide. There is no approved treatment. In individuals with Stargardt disease, the ABCA4 protein is defective. This defect in the protein results in the accelerated dimerization of vitamin A, forming toxic by-products that irreversibly damage the retina, resulting in progressive vision loss.

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For further information, please contact:

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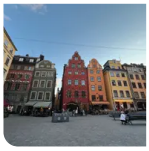


University of Arkansas for Medical Sciences receives $2.2 million grant to study efferocytosis in retinopathy

By Martin David Harp

September 23rd 2024

Efferocytosis' role in retinopathy is largely unknown despite knowledge of the process in other diseases.



The sights of Stockholm

By Sydney M Crago

September 23rd 2024



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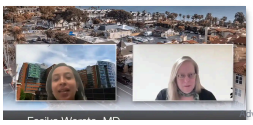


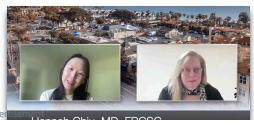
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The CHMP will recommend SB15, biosimilar to aflibercept (Eylea), for marketing authorisation by the European Commission

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EURETINA 2024: Yousif Subhi, MD, PhD, on the "things that matter" in macular degeneration and central serous chorioretinopathy

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Yousif Subhi, MD, PhD, delivered the Ophthalmologica Lecture, "Things That Matter: An Evidence-Based Approach to AMD and CSC."

EURETINA 2024: Andrea Govetto, MD, PhD, says it takes teamwork to understand macular edema

By Hattie Hayes
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We spoke with Andrea Govetto, MD, PhD, winner of the inaugural Ramin Tadayoni Award at EURETINA

Spotlight on GA: Promoting early detection and treatment

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EURETINA 2024: Phase 1 HELIOS trial for OTX-TKI

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Veeral S. Sheth, MD, MBA, FASRS, FACS, discussed the outcome of the Phase 1 HELIOS trial of OTX-TKI at from this year's EURETINA congress being held in Barcelona, Spain, which takes place September 19-22, 2024.

EURETINA 2024: Unraveling the genetic spectrum of combined retinal dystrophy and hearing impairment

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Researchers in Portugal investigated Usher syndrome, Senior-Loker syndrome and other ciliopathies

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EURETINA 2024: Ricardo Leitão Guerra, MD, MSc, FICO, speaks about multimodal

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imaging
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Why having a set process for diagnostic imaging is crucial to patient outcomes

The unique role of the retina optometrist
By Betty Zhang, OD
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Zhang's journey as the first retina optometrist in Colorado

EURETINA 2024: Subretinal gene therapy improves function and structure in patients with Bothnia Dystrophy
By Lynda Charters
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Bothnia Dystrophy generally presents during early childhood; patients have night blindness, progressive visual loss, and subsequent legal blindness.

EURETINA 2024: Ocular involvement among patients with COVID-19 infection or vaccination
By Lynda Charters
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A case series illuminates neuro-ophthalmologic manifestations, retinal vascular involvement and other pathologies

Opthea completes process performance qualification (PPQ)
By Sydney M Crago
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The PPQ campaign consisted of the production of 3 successful consecutive commercial-scale drug substance batches required for the validation of Opthea's manufacturing process.

Alkeus Pharmaceuticals shares results of SAGA study of oral gildeuretinol acetate for GA
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Oral gildeuretinol demonstrated a clinically meaningful reduction in the GA lesion

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growth rate at 24 months in the SAGA study.

EURETINA 2024: Cardio-ocular syndrome and retinal microvasculature changes in acute heart failure

By Lynda Charters

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The research team used spectral-domain OCT and OCT angiography imaging to study the changes in the retinal microvasculature in patients

EURETINA 2024: Efficacy results and patient preference findings from the Pagoda trial

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Dr Margaret A. Chang shares data on the port delivery system with ranibizumab, and her strategy for making the most of conferences

4DMT shares data from Phase 1/2 PRISM clinical trial, 4FRONT Phase 3 study design

By Sydney M Crago

September 18th 2024

4D Molecular Therapeutics has announced data based on the longest interim follow-up from Phase 1/2 PRISM clinical trial and 4FRONT Phase 3 study design.

Opthea makes changes to leadership and hires senior roles

By Sydney M Crago

September 18th 2024

Opthea Limited has made changes to the company's executive leadership in its and notable hires in senior roles.

OCT-based AI analysis brings changes in GA and therapeutic responses into sharp focus

By Lynda Charters

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Atsena Therapeutics receives Orphan Drug Designation from FDA for ATSN-201 gene therapy to treat X-linked retinoschisis

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By David Hutton
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The announcement marks the second FDA designation for ATSN-201, which previously received Rare Pediatric Disease designation.

ANI Pharmaceuticals completes acquisition of Alimera Sciences
By David Hutton
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The acquisition strengthens the company's rare disease segment, and adds 2 durable commercial assets, Iluvien and Yutiq with significant growth potential, expanding ANI's foothold in strategic therapeutic area of ophthalmology.

The current state of gene therapy in managing neovascular macular degeneration
By Veeral Sheth, MD, MBA, FAS, FASRS
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Gene therapy offers a promising alternative by potentially providing long-lasting effects from a single treatment.

The future of retina care
By Marta Stevanovic, MD, MSc
September 17th 2024

Retina is a rapidly advancing field with promising research, technology, and treatment areas. Two stand out as particularly exciting.

Social factors associated with diabetic retinopathy visit adherence
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