FDA Drug Designation and Approval

Generic Name: Satumomab pendetide

Trade Name: Oncoscint

URL:
https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=36789

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Home[3] Developing Products for Rare Diseases & Conditions[4]

Search Orphan Drug Designations and Approvals

Generic Name:	Satumomab pendetide
Trade Name:	Oncoscint CR/OV
Date Designated:	09/25/1989
Orphan Designation:	Detection of ovarian carcinoma.
Orphan Designation Status:	Designated/Approved
Sponsor:	Cytogen Corporation 600 College Road East Princeton, New Jersey 08540 United States *The sponsor address listed is the last reported by the sponsor to OOPD.*

Marketing approved:

1	**Generic Name:**	Satumomab pendetide
	Trade Name:	Oncoscint CR/OV
	Marketing Approval Date:	12/29/1992
	Approved Labeled Indication:	For determining the extent and location of extraphepatic malignant disease in patients with known colorectal and ovarian cancer.
	Exclusivity End Date:	12/29/1999
	Exclusivity Protected Indication* :	

*Exclusivity Protected Indications are shown for approvals from 01/01/2013 to the present.
*Data for the Date Designation Withdrawn or Revoked field are shown for designations withdrawn or revoked after 08/12/2013.

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FDA

U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

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FDA Drug Designation and Approval

Generic Name: Arcitumomab

Trade Name: CEA-Scan

URL:
https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=96596

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Home[3] Developing Products for Rare Diseases & Conditions[4]

Search Orphan Drug Designations and Approvals

Generic Name:	Arcitumomab
Date Designated:	05/10/1996
Orphan Designation:	Diagnosis and localization of primary, residual, recurrent and metastatic medullary thyroid carcinoma.
Orphan Designation Status:	Designated/Designation Withdrawn or Revoked
FDA Orphan Approval Status:	Not FDA Approved for Orphan Indication
Sponsor:	Immunomedics, Inc. 300 American Road Morris Plains, New Jersey 07950 United States *The sponsor address listed is the last reported by the sponsor to OOPD.*

*Exclusivity Protected Indications are shown for approvals from 01/01/2013 to the present.
*Data for the Date Designation Withdrawn or Revoked field are shown for designations withdrawn or revoked after 08/12/2013.

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2. http://www.addthis.com/bookmark.php
3. https://www.fda.gov/
4. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm

FDA CBER Product Approval Letter

Generic Name: Noferumomab

Trade Name: Verluma

URL:
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1996/nofedrk082096L.htm

Product Approval Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

August 20, 1996

Our Reference Nos: 94-0305 and 94-0308

Hermann Allgaier, Ph.D.
Dr. Karl Thomae GmbH
Birkendorfer StraBe 65
88397 Biberach an der Riss
GERMANY

Dear Dr. Allgaier:

This letter hereby issues Department of Health and Human Services Biologics License No. 1199, to Dr. Karl Thomae, GmbH, Biberach an der Riss, Germany, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture and import into this country for sale, barter, or exchange, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture and ship the product Noferumomab and associated components for the preparation of Technetium Tc 99m Nofetumomab Merpentan. Technetium Tc 99m Nofetumomab Merpentan is indicated for the detection of extensive stage disease in patients with biopsy-confirmed, previously untreated, small cell lung cancer.

Under this authorization, you are approved to manufacture Nofetumomab and the kit for the preparation of Technetium Tc 99m Nofetumomab Merpentan (hereafter known as the kit). Final containers of Nofetumomab will be manufactured, formulated, filled, and lyophilized at your facility in Biberach an der Riss, Germany. The nonbiological components of the kit will be provided by you and contract suppliers as specified in your license application. Isopropyl alcohol and phenthioate ligand will be supplied by you; the stannous gluconate complex glacial acetic/hydrochloric acid, sodium bicarbonate buffer and reaction and elution vials will be supplied by [---------- ----------] and the anion exchange column will be

supplied by [----------]. The final component containers will be labeled and packaged into the kit at your facility in Biberach an der Riss, Germany. The kit will be distributed by DuPont Radiopharmaceutical Division, DuPont Merck Pharmaceutical Company, Billerica, Massaachusetts under the trade name Verluma™. DuPont Radiopharmaceutical Division also acts on your behalf to receive adverse experience reports.

You are not currently required to submit samples of future lots of Nofetumomab or the kit to the Center for Biologics Evaluation and Research (CBER) for release under 21 CFR 610.2 by the Director, CBER. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for the dosage formulation of Nofemmomab shall be 24 months from the date of manufacture when stored at [----------]. The date of manufacture shall be defined as the date of final sterile filtration of the formulated bulk. The formulated Nofetumomab bulk may be stored for up to 18 months at [----------]. The dating period for the kit shall be 24 months or less, dependent upon the shortest expiration date of any component in the kit when stored at [----------]. The dating periods of the non-biological vialed components when stored at [----------] shall be: [----------] for isopropyl alcohol [----------] for phenthioate ligand. [----------] for glacial acetic/hydrochloric acid, [----------] for stannous gluconate complex. [----------] for sodium bicarbonate buffer, [----------] for anion exchange column, and for the reaction and elution vials. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

We acknowledge your written commitment of April 15, 1996 including:

1. To submit within six months of licensure a labeling supplement that proposes modifications to the package insert based upon the results of the combined analysis of the fully audited data from the 77 patients in the readministration study and the data submitted in your product license application.

2. To perform and submit the results of an analysis (with supporting clinical data) to assess the safety and efficacy of the product in a subset of human-anti-mouse- antibody (HAMA) - negative patients who were readministered the product, and if necessary to develop a protocol to assess the safety and efficacy of the product in HAMA - negative patients.

3. To submit a plan for identification of patients who are or have been HAMA positive based upon HAMA test results at your central laboratory, and to propose a clinical protocol to evaluate the safety and efficacy of your product in this patient population.

4. To provide an educational program for physician and technologist instruction in Technetium Tc 99m Nofetumomab Merpentan image interpretation which will include an educational manual, consultant physician(s), and training sessions at national scientific meetings.

We also acknowledge your commitment of June 28, 1996 to perform and submit on an annual basis, trend analysis on release tests for lots of Nofeturnomab, and lots of the kit including nonbiological components.

We also acknowledge your commitment of August 19, 1996 to have available at the time of market launch, mutually agreed upon training for the radiopharmacist in the use of the kit to prepare the product.

Any changes in the manufacturing, testing, packaging or labeling of Nofetumomab, the kit, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12. Any addition or

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deletion of contract suppliers involved in the production of the kit will require the submission of appropriate supporting data in order to ensure continued compliance with the approved standards for the manufacture of the kit.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). These requirements became effective on December 27, 1994. All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Bioiogics Evaluation and Research.

Please acknowledge receipt of the enclosed biologics license to the Director, Division of Application Review and Policy (HFM-585), Center for Biologics Evaluation and Research.

Sincerely yours,

--- signature ---
Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research

--- signature ---
Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment Licensing and Product Surveillance
Center for Biologics Evaluation and Research

Last Updated: 1/14/2001

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Date created: September 25, 2003

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FDA Product Approval Information

Generic Name: Capromab Pendetide

Trade Name: ProstaScint

URL:
https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1996/capcyt102896L.htm

Product Approval Information - Licensing Action

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

28 OCT 1996

Our Reference No. 95-0041 and 95-0087

Mr. Michael A Trapani
Cytogen Corporation
600 College Road East
Princeton, NJ 08540

Dear Mr. Trapani:

Your biologics license application for Capromab Pendetide is approved effective this date. Cytogen Corporation, Princeton, New Jersey is hereby authorized to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce Capromab Pendetide under Department of Health and Human Services BiologicsLicense No. 1164.

Capromab Pendetide is indicated for the preparation of lndium In 111 Capromab Pendetide to be used as a diagnostic imaging agent in newly diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation, who are at high risk for pelvic lymph node metastases, and in post-prostatectomy patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.

In accordance with approved labeling, your product will bear the tradename ProstaScint, and will be marketed as a single dose kit containing a 1 mL vial of Capromab Pendetide solution and a 1 mL vial of sodium acetate buffer solution.

You are not currently required to submit samples of future lots of Capromab Pendetide to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated product. The bulk Capromab antibody may be stored for up to 36 months at 2-8°C or -70°C. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

We acknowledge your written commitment of October 25, 1996 to submit a galley proof of the package insert for review and approval prior to implementation.

Any changes in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). These requirements became effective on December 27, 1994. All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

--- signature ---
Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research

--- signature ---
Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment Licensing and Product Surveillance
Center for Biologics Evaluation and Research

Last Updated: 1/18/2001

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Date created: September 25, 2003

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FDA Drug Label

Generic Name: ibritumomab tiuxetan

Trade Name: Zevalin

URL: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125019s227lbl.pdf

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For current labeling information, please visit https://www.fda.gov/drugsatfda

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEVALIN safely and effectively. See full prescribing information for ZEVALIN.

ZEVALIN® (ibritumomab tiuxetan) injection, for intravenous use
Initial U.S. Approval: 2002

WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS
See full prescribing information for complete boxed warning.

- **Serious Infusion Reactions, some fatal, may occur within 24 hours of rituximab infusion. (5.1)**
- **Prolonged and Severe Cytopenias occur in most patients. (5.2)**
- **Severe Cutaneous and Mucocutaneous Reactions, some fatal, reported with Zevalin therapeutic regimen. (5.3, 6.2)**
- **Do not exceed 32 mCi (1184 MBq) of Y-90 Zevalin. (2.2)**

----------INDICATIONS AND USAGE----------
Zevalin is a CD20-directed radiotherapeutic antibody administered as part of the Zevalin therapeutic regimen indicated for the treatment of adult patients with:

- relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) (1.1).
- previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy (1.2).

----------DOSAGE AND ADMINISTRATION----------

- **Day 1**: Administer rituximab 250 mg/m^2 intravenous infusion. (2.2)
- **Day 7, 8, or 9**:
  Administer rituximab 250 mg/m^2 intravenous infusion. (2.2)
  - If platelets at least 150,000/mm^3: Within 4 hours after rituximab infusion, administer 0.4 mCi/kg (14.8 MBq per kg) Y-90 Zevalin intravenous infusion.
  - If platelets 100,000 to 149,000/mm^3 in relapsed or refractory patients: Within 4 hours after rituximab infusion, administer 0.3 mCi/kg (11.1 MBq per kg) Y-90 Zevalin intravenous infusion.

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 3.2 mg per 2 mL in a single-dose vial. (3)

----------CONTRAINDICATIONS----------
None.

----------WARNINGS AND PRECAUTIONS----------

- Serious Infusion Reactions: Immediately discontinue rituximab and Y-90 Zevalin. (5.1, 6.1)
- Prolonged and Severe Cytopenias: Do not administer Zevalin to patients with ≥ 25% lymphoma marrow involvement or impaired bone marrow reserve. (5.2, 6.1)
- Severe Cutaneous and Mucocutaneous Reactions: Discontinue rituximab and Zevalin infusions if patients develop severe cutaneous or mucocutaneous reactions. (5.3, 6.2)
- Development of Leukemia and Myelodysplastic Syndrome: Monitor patients for hematological toxicity including secondary malignancies. (5.4, 6.1)
- Extravasation: Monitor for extravasation and terminate infusion if it occurs. Resume infusion in another limb. (5.5, 6.2)
- Immunization: Do not administer live viral vaccines to patients who recently received Zevalin. (5.6)
- Embryo-fetal Toxicity: May cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.8, 8.1, 8.3)

----------ADVERSE REACTIONS----------
Common adverse reactions (≥ 10%) in clinical trials were: cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Spectrum Pharmaceuticals, Inc. at 1-866-298-8433 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

- Monitor patients receiving medications that interfere with platelet function or coagulation more frequently for thrombocytopenia. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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1.1 Relapsed or Refractory, Low-grade or Follicular NHL
1.2 Previously Untreated Follicular NHL
2 DOSAGE AND ADMINISTRATION
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2.3 Directions for Preparation of Radiolabeled Y-90 Zevalin Doses
2.4 Procedure for Determining Radiochemical Purity
2.5 Radiation Dosimetry
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*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFUSION REACTIONS, PROLONGED AND SEVERE CYTOPENIAS, and SEVERE CUTANEOUS AND MUCOCUTANEOUS REACTIONS

Serious Infusion Reactions: Deaths have occurred within 24 hours of rituximab infusion, an essential component of the Zevalin therapeutic regimen. These fatalities were associated with hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock. Most (80%) fatalities occurred with the first rituximab infusion [*see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*]. **Discontinue rituximab and Y-90 Zevalin infusions in patients who develop severe infusion reactions.**

Prolonged and Severe Cytopenias: Y-90 Zevalin administration results in severe and prolonged cytopenias in most patients. Do not administer Y-90 Zevalin to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve [*see Warnings and Precautions (5.2)* and *Adverse Reactions (6.1)*].

Severe Cutaneous and Mucocutaneous Reactions: Severe cutaneous and mucocutaneous reactions, some fatal, can occur with the Zevalin therapeutic regimen. Discontinue rituximab and Y-90 Zevalin infusions in patients experiencing severe cutaneous or mucocutaneous reactions [*see Warnings and Precautions (5.3)* and *Adverse Reactions (6.2)*].

Dosing: The dose of Y-90 Zevalin should not exceed 32.0 mCi (1184 MBq) [*see Dosage and Administration (2.2)*].

1 INDICATIONS AND USAGE

1.1 Relapsed or Refractory, Low-grade or Follicular NHL

Zevalin is indicated for the treatment of adult patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL).

1.2 Previously Untreated Follicular NHL

Zevalin is indicated for the treatment of previously untreated follicular NHL in adult patients who achieve a partial or complete response to first-line chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing Schedule

- Administer the Zevalin therapeutic regimen as outlined below.
- Initiate the Zevalin therapeutic regimen following recovery of platelet counts to 150,000/mm^3 or more at least 6 weeks, but no more than 12 weeks, following the last dose of first-line chemotherapy.
- Only administer rituximab /Zevalin in facilities where immediate access to resuscitative measures is available.

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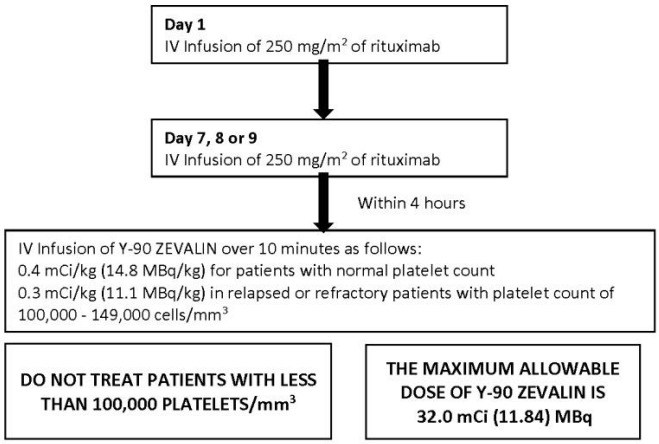
Overview of Dosing Schedule



2.2 Zevalin Therapeutic Regimen Dosage and Administration

Day 1:

- Premedicate with acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to rituximab infusion.
- Administer rituximab 250 mg/m^2 intravenously at an initial rate of 50 mg/hr. In the absence of infusion reactions, escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. Do not mix or dilute rituximab with other drugs.
- Immediately stop the rituximab infusion for serious infusion reactions and discontinue the Zevalin therapeutic regimen [*see Boxed Warning* and *Warnings and Precautions (5.1)*].
- Temporarily slow or interrupt the rituximab infusion for less severe infusion reactions. If symptoms improve, continue the infusion at one-half the previous rate.

Day 7, 8 or 9:

- Premedicate with acetaminophen 650 mg orally and diphenhydramine 50 mg orally prior to rituximab infusion.
- Administer rituximab 250 mg/m^2 intravenously at an initial rate of 100 mg/hr. Increase rate by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr, as tolerated. If infusion reactions occurred during rituximab infusion on Day 1 of treatment, administer rituximab at an initial rate of 50 mg/hr and escalate the infusion rate in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
- Administer Y-90 Zevalin injection through a free flowing intravenous line within 4 hours following completion of rituximab infusion. Use a 0.22 micron low-protein-binding in-line filter between the syringe and the infusion port. After infusion, flush the line with at least 10 mL of normal saline.
  - **If platelet count at least 150,000/mm^3**, administer Y-90 Zevalin over 10 minutes as an intravenous infusion at a dose of Y-90 0.4 mCi per kg (14.8 MBq per kg) actual body weight.
  - **If platelet count 100,000 to 149,000/mm^3**, in relapsed or refractory patients, administer Y-90 Zevalin over 10 minutes as an intravenous infusion at a dose of Y-90 0.3 mCi per kg (11.1 MBq per kg) actual body weight.
  - Do not administer more than 32 mCi (1184 MBq) Y-90 Zevalin dose regardless of the patient's body weight.
- Monitor patients closely for evidence of extravasation during the infusion of Y-90 Zevalin. Immediately stop infusion and restart in another limb if any signs or symptoms of extravasation occur [see Warnings and Precautions (5.5)].

2.3 Directions for Preparation of Radiolabeled Y-90 Zevalin Doses

A clearly-labeled kit is required for preparation of Yttrium-90 (Y-90) Zevalin. Follow the detailed instructions for the preparation of radiolabeled Zevalin [*see Dosage and Administration (2.4)*].

Required materials not supplied in the kit:

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1. Yttrium-90 Chloride Sterile Solution
2. Three sterile 1 mL plastic syringes
3. One sterile 3 mL plastic syringe
4. Two sterile 10 mL plastic syringes with 18-20 G needles
5. ITLC silica gel strips
6. 0.9% Sodium Chloride aqueous solution for the chromatography solvent
7. Developing chamber for chromatography
8. Suitable radioactivity counting apparatus
9. Filter, 0.22 micrometer, low-protein-binding
10. Appropriate acrylic shielding for reaction vial and syringe for Y-90

Method:

1. Allow contents of the refrigerated Y-90 Zevalin kit (Zevalin vial, 50 mM sodium acetate vial, and formulation buffer vial) to reach room temperature.
2. Place the empty reaction vial in an appropriate acrylic shield.
3. Determine the amount of each component needed:
   a. Calculate volume of Y-90 Chloride equivalent to 40 mCi based on the activity concentration of the Y-90 Chloride stock.
   b. The volume of 50 mM Sodium Acetate solution needed is 1.2 times the volume of Y-90 Chloride solution determined in step 3.a, above.
   c. Calculate the volume of formulation buffer needed to bring the reaction vial contents to a final volume of 10 mL.
4. Transfer the calculated volume of 50 mM Sodium Acetate to the empty reaction vial. Coat the entire inner surface of the reaction vial by gentle inversion or rolling.
5. Transfer 40 mCi of Y-90 Chloride to the reaction vial using an acrylic shielded syringe. Mix the two solutions by gentle inversion or rolling.
6. Transfer 1.3 mL of Zevalin (ibritumomab tiuxetan) to the reaction vial. **Do not shake or agitate the vial contents.**
7. Allow the labeling reaction to proceed at room temperature for 5 minutes. A shorter or longer reaction time may adversely alter the final labeled product.
8. **Immediately** after the 5-minute incubation period, transfer the calculated volume of formulation buffer from step 3.c. to the reaction vial. Gently add the formulation buffer down the side of the reaction vial. If necessary, withdraw an equal volume of air to normalize pressure.
9. Measure the final product for total activity using a radioactivity calibration system suitable for the measurement of Y-90.
10. Using the supplied labels, record the date and time of preparation, the total activity and volume, and the date and time of expiration, and affix these labels to the shielded reaction vial container.
11. Patient Dose: Calculate the volume required for a Y-90 Zevalin dose [*see Dosage and Administration (2.2)*]. Withdraw the required volume from the reaction vial. Assay the syringe in the dose calibrator suitable for the measurement of Y-90. The measured dose must be within 10% of the prescribed dose of Y-90 Zevalin and **must not exceed 32 mCi (1184 MBq)**. Using the supplied labels, record the patient identifier, total activity and volume and the date and time of expiration, and affix these labels to the syringe and shielded unit dose container.
12. Determine Radiochemical Purity [*see Dosage and Administration (2.4)*].
13. Store Yttrium-90 Zevalin at 2-8°C (36-46°F) until use and administer within 8 hours of radiolabeling. Immediately prior to administration, assay the syringe and contents using a radioactivity calibration system suitable for the measurement of Y-90.

2.4 Procedure for Determining Radiochemical Purity

Use the following procedures for radiolabeling Y-90 Zevalin:

1. Place a small drop of Y-90 Zevalin at the origin of an ITLC silica gel strip.

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2. Place the ITLC silica gel strip into a chromatography chamber with the origin at the bottom and the solvent front at the top. Allow the solvent (0.9% NaCl) to migrate at least 5 cm from the bottom of the strip. Remove the strip from the chamber and cut the strip in half. Count each half of the ITLC silica gel strip for one minute (CPM) with a suitable counting apparatus.
3. Calculate the percent RCP as follows:

$$\% \text{ RCP} = \frac{\text{CPM bottom half}}{\text{CPM bottom half} + \text{CPM top half}} \times 100$$

4. Repeat the ITLC procedure if the radiochemical purity is <95%. If repeat testing confirms that radiochemical purity is <95%, do not administer the Y-90 Zevalin dose.

2.5 Radiation Dosimetry

During clinical trials with Zevalin, estimations of radiation-absorbed doses for Y-90 Zevalin were performed using sequential whole body images and the MIRDOSE 3 software program. The estimated radiation absorbed doses to organs and marrow from a course of the Zevalin therapeutic regimen are summarized in Table 1. Absorbed dose estimates for the lower large intestine, upper large intestine, and small intestine have been modified from the standard MIRDOSE 3 output to account for the assumption that activity is within the intestine wall rather than the intestine contents.

Table 1. Estimated Radiation Absorbed Doses from Y-90 Zevalin

	Y-90 Zevalin cGy /mCi (mGy/MBq)	
Organ	**Median**	**Range**
Spleen[a]	34.78 (9.4)	6.66 - 74.00 (1.8 - 20.0)
Liver[a]	17.76 (4.8)	10.73 - 29.97 (2.9 - 8.1)
Lower Large Intestinal Wall[a]	17.39 (4.7)	11.47 - 30.34 (3.1 - 8.2)
Upper Large Intestinal Wall[a]	13.32 (3.6)	7.40 - 24.79 (2.0 - 6.7)
Heart Wall[a]	10.73 (2.9)	5.55 - 11.84 (1.5 - 3.2)
Lungs[a]	7.4 (2)	4.44 - 12.58 (1.2 -3.4)
Testes[a]	5.55 (1.5)	3.70 - 15.91 (1.0 - 4.3)
Small Intestine[a]	5.18 (1.4)	2.96 - 7.77 (0.8 - 2.1)
Red Marrow[b]	4.81 (1.3)	2.22 - 6.66 (0.6 - 1.8)
Urinary Bladder Wall[c]	3.33 (0.9)	2.59 - 4.81 (0.7 - 1.3)
Bone Surfaces[b]	3.33 (0.9)	1.85 - 4.44 (0.5 - 1.2)
Total Body[c]	1.85 (0.5)	1.48 - 2.59 (0.4 - 0.7)
Ovaries[c]	1.48 (0.4)	1.11 - 1.85 (0.3 - 0.5)
Uterus[c]	1.48 (0.4)	1.11 - 1.85 (0.3 - 0.5)

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Adrenals[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Brain[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Breasts[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Gallbladder Wall[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Muscle[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Pancreas[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Skin[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Stomach[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Thymus[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Thyroid[c]	1.11 (0.3)	0.74 - 1.85 (0.2 - 0.5)
Kidneys[a]	0.37 (0.1)	0.00 - 1.11 (0.0 - 0.3)

a) Organ region of interest
b) Sacrum region of interest
c) Whole body region of interest

3 DOSAGE FORMS AND STRENGTHS

Injection: 3.2 mg ibritumomab tiuxetan per 2 mL as a clear, colorless solution, that may contain translucent particles, in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infusion Reactions

Rituximab, alone or as a component of the Zevalin therapeutic regimen, can cause severe, including fatal, infusion reactions. These reactions typically occur during the first rituximab infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Temporarily slow or interrupt the rituximab infusion for less severe infusion reactions. Immediately discontinue rituximab and Y-90 Zevalin administration for severe infusion reactions. Only administer rituximab/Zevalin in facilities where immediate access to resuscitative measures is available [*see Boxed Warning* and *Dosage and Administration (2.2)*]. See also prescribing information for rituximab.

5.2 Prolonged and Severe Cytopenias

Cytopenias with delayed onset and prolonged duration, some complicated by hemorrhage and severe infection, are the most common severe adverse reactions of the Zevalin therapeutic regimen. When used according to recommended doses, the incidences of severe thrombocytopenia and neutropenia are greater in patients with mild baseline thrombocytopenia ($\geq$ 100,000 but $\leq$ 149,000/mm^3) compared to those with normal pretreatment platelet counts. Severe cytopenias persisting more than 12 weeks following administration can occur. Monitor complete blood counts (CBC) and platelet counts following the Zevalin therapeutic regimen weekly until levels recover or as clinically indicated. [*see Boxed Warning* and *Adverse Reactions (6.1)*].

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Do not administer the Zevalin therapeutic regimen to patients with ≥ 25% lymphoma marrow involvement and/or impaired bone marrow reserve. Monitor patients for cytopenias and their complications (e.g., febrile neutropenia, hemorrhage) for up to 3 months after use of the Zevalin therapeutic regimen. Avoid using drugs which interfere with platelet function or coagulation following the Zevalin therapeutic regimen.

5.3 Severe Cutaneous and Mucocutaneous Reactions

Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis, some fatal, were reported in post-marketing experience. The time to onset of these reactions was variable, ranging from a few days to 4 months after administration of the Zevalin therapeutic regimen. Discontinue the Zevalin therapeutic regimen in patients experiencing a severe cutaneous or mucocutaneous reaction [*see Boxed Warning* and *Adverse Reactions (6.2)*].

5.4 Risk of Developing Myelodysplastic Syndrome, Leukemia, and Other Malignancies

The radiation dose resulting from therapeutic exposure to Y-90 radiolabeled Zevalin may result in secondary malignancies.

Myelodysplastic syndrome (MDS) and/or acute myelogenous leukemia (AML) were reported in 5.2% (11/211) of patients with relapsed or refractory NHL enrolled in clinical studies and 1.5% (8/535) of patients included in the expanded-access trial, with median follow-up of 6.5 and 4.4 years, respectively. Among the 19 reported cases, the median time to the diagnosis of MDS or AML was 1.9 years following treatment with the Zevalin therapeutic regimen; however, the cumulative incidence continues to increase [*see Adverse Reactions (6.1)*].

Among 204 patients receiving Y-90 Zevalin following first-line chemotherapy, 26 (12.7%) patients in the Zevalin arm developed a second primary malignancy compared to 14 (6.8%) of patients in the control arm. Seven patients (3.4%, 7/204) were diagnosed with MDS/AML after receiving Zevalin, compared to one patient (0.5%, 1/205) in the control arm, with a median follow-up of 7.3 years. Deaths due to second primary malignancy included 8 (3.9%) patients in the Zevalin arm compared to 3 (1.5%) patients in the control arm. Deaths due to MDS/AML included five (2.5%) patients in the Zevalin arm compared to no patients in the control arm.

Monitor patients for hematological toxicity including development of MDS or AML.

5.5 Extravasation

Monitor patients closely for evidence of extravasation during Zevalin infusion. Immediately terminate the infusion if signs or symptoms of extravasation occur and restart in another limb [*see Dosage and Administration (2.2)*].

5.6 Risks of Immunization

The safety of immunization with live viral vaccines following the Zevalin therapeutic regimen has not been studied. Do not administer live viral vaccines to patients who have recently received Zevalin. The ability to generate an immune response to any vaccine following the Zevalin therapeutic regimen has not been studied.

5.7 Radionuclide Precautions

During and after radiolabeling Zevalin with Y-90, minimize radiation exposure to patients and to medical personnel, consistent with institutional good radiation safety practices and patient management procedures.

5.8 Embryo-Fetal Toxicity

Based on its radioactivity, Y-90 Zevalin may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for a minimum of twelve months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Serious Infusion Reactions [*see Boxed Warning* and *Warnings and Precautions (5.1)*].
- Prolonged and Severe Cytopenias [*see Boxed Warning* and *Warnings and Precautions (5.2)*].
- Severe Cutaneous and Mucocutaneous Reactions [*see Boxed Warning* and *Warnings and Precautions (5.3)*].
- Leukemia and Myelodysplastic Syndrome [*see Warnings and Precautions (5.4)*].

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The reported safety data reflects exposure to Zevalin in 349 patients with relapsed or refractory, low-grade, follicular or transformed NHL across 5 trials (4 single arm and 1 randomized) and in 206 patients with previously untreated follicular NHL in a randomized trial (FIT study) who received any portion of the Zevalin therapeutic regimen. The safety data reflect exposure to Zevalin in 270 patients with relapsed or refractory NHL with platelet counts ≥150,000/ mm^3 who received 0.4 mCi/kg (14.8 MBq/kg) of Y-90 Zevalin (Group 1 in Table 4), 65 patients with relapsed or refractory NHL with platelet counts of ≥100,000 but ≤ 149,000/mm^3 who received 0.3 mCi/kg (11.1 MBq/kg) of Y-90 Zevalin (Group 2 in Table 4), and 204 patients with previously untreated NHL with platelet counts ≥150,000/ mm^3 who received 0.4 mCi/kg (14.8 MBq/kg) of Y-90 Zevalin; all patients received a single course of Zevalin.

The most common adverse reactions of Zevalin are cytopenias, fatigue, nasopharyngitis, nausea, abdominal pain, asthenia, cough, diarrhea, and pyrexia.

The most serious adverse reactions of Zevalin are prolonged and severe cytopenias (thrombocytopenia, anemia, lymphopenia, neutropenia) and secondary malignancies.

Because the Zevalin therapeutic regimen includes the use of rituximab, see prescribing information for rituximab.

Table 2 displays selected adverse reaction incidence rates in patients who received any portion of the Zevalin therapeutic regimen (n=206) or no further therapy (n=203) following first-line chemotherapy (FIT study).

Table 2.

Per-Patient Incidence (%) of Selected[a] Adverse Reactions Occurring in ≥ 5% of Patients with Previously Untreated Follicular NHL Treated with the Zevalin Therapeutic Regimen

	Zevalin (n=206)		Observation (n=203)	
	All Grades[b]	Grade[b] 3-4	All Grades[b]	Grade[b] 3-4
	%	%	%	%
Gastrointestinal Disorders				
Abdominal pain	17	2	13	<1
Diarrhea	11	0	3	0
Nausea	18	0	2	0
Body as a Whole				
Asthenia	15	1	8	<1
Fatigue	33	1	9	0
Influenza-like illness	8	0	3	0
Pyrexia	10	3	4	0
Musculoskeletal				
Myalgia	9	0	3	0
Metabolism				
Anorexia	8	0	2	0
Respiratory, Thoracic & Media				
Cough	11	<1	5	0
Pharyngolaryngeal pain	7	0	2	0
Epistaxis	5	2	<1	0
Nervous System				
Dizziness	7	0	2	0
Vascular				
Hypertension	7	3	2	<1
Skin & Subcutaneous				
Night sweats	8	0	2	0
Petechiae	8	2	0	0

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Pruritus	7	0	1	0
Rash	7	0	<1	0
Infections & Infestations				
Bronchitis	8	0	3	0
Nasopharyngitis	19	0	10	0
Rhinitis	8	0	2	0
Sinusitis	7	<1	<1	0
Urinary tract infection	7	<1	3	0
Blood and Lymphatic System				
Thrombocytopenia	62	51	1	0
Neutropenia	45	41	3	2
Anemia	22	5	4	0
Leukopenia	43	36	4	1
Lymphopenia	26	18	9	5

a) Between-group difference of ≥5%

b) NCI CTCAE version 2.0

Table 3 shows hematologic toxicities in 349 Zevalin-treated patients with relapsed or refractory, low-grade, follicular or transformed B-cell NHL. Grade 2-4 hematologic toxicity occurred in 86% of Zevalin-treated patients.

Table 3.
Per-Patient Incidence (%) of Hematologic Adverse Reactions in Patients with Relapsed or Refractory Low-grade, Follicular or Transformed B-cell NHL[a] (N = 349)

	All Grades %	Grade 3-4 %
Thrombocytopenia	95	63
Neutropenia	77	60
Anemia	61	17
Ecchymosis	7	<1

a) Occurring within the 12 weeks following the first rituximab infusion of the Zevalin therapeutic regimen

Prolonged and Severe Cytopenias

Patients in clinical studies were not permitted to receive hematopoietic growth factors beginning 2 weeks prior to administration of the Zevalin therapeutic regimen.

The incidence and duration of severe hematologic toxicity in previously treated NHL patients (N=335) and in previously untreated patients (FIT study) receiving Y-90 Zevalin are shown in Table 4.

Table 4.
Severe Hematologic Toxicity in Patients Receiving Zevalin

Baseline Platelet Count	**Group 1 (n=270) ≥ 150,000/mm^3**	**Group 2 (n=65) ≥100,000 but ≤ 149,000/mm^3**	**FIT study (n=204) ≥ 150,000/mm^3**
Y-90 Zevalin Dose	**0.4 mCi/kg (14.8 MBq/kg)**	**0.3 mCi/kg (11.1 MBq/kg)**	**0.4 mCi/kg (14.8 MBq/kg)**
ANC			
Median nadir (per mm^3)	800	600	721
Per Patient Incidence ANC <1000/mm^3	57%	74%	65%
Per Patient Incidence ANC <500/mm^3	30%	35%	26%

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Median Duration (Days)[a] ANC <1000/mm^3	22	29	29
Median Time to Recovery[b]	12	13	15
Platelets			
Median nadir (per mm^3)	41,000	24,000	42,000
Per Patient Incidence Platelets <50,000/mm^3	61%	78%	61%
Per Patient Incidence Platelets <10,000/mm^3	10%	14%	4%
Median Duration (Days)[c] Platelets <50,000/mm^3	24	35	26
Median Time to Recovery[b]	13	14	14

a) Day from last ANC ≥1000/mm^3 to first ANC ≥1000/mm^3 following nadir, censored at next treatment or death

b) Day from nadir to first count at level of Grade 1 toxicity or baseline

c) Day from last platelet count ≥50,000/mm^3 to day of first platelet count ≥50,000/mm^3 following nadir, censored at next treatment or death

Cytopenias were more severe and more prolonged among eleven (5%) patients who received Zevalin after first-line fludarabine or a fludarabine-containing chemotherapy regimen as compared to patients receiving non-fludarabine-containing regimens. Among these eleven patients, the median platelet nadir was 13,000/mm^3 with a median duration of platelets below 50,000/mm^3 of 56 days and the median time for platelet recovery from nadir to Grade 1 toxicity or baseline was 35 days. The median ANC was 355/mm^3, with a median duration of ANC below 1,000/mm^3 of 37 days and the median time for ANC recovery from nadir to Grade 1 toxicity or baseline was 20 days.

The median time to cytopenia was similar across patients with relapsed/refractory NHL and those completing first-line chemotherapy, with median ANC nadir at 61-62 days, platelet nadir at 49-53 days, and hemoglobin nadir at 68-69 days after Y-90-Zevalin administration.

Information on hematopoietic growth factor use and platelet transfusions is based on 211 patients with relapsed/refractory NHL and 206 patients following first-line chemotherapy. Filgrastim was given to 13% of patients and erythropoietin to 8% with relapsed or refractory disease; 14% of patients receiving Zevalin following first-line chemotherapy received granulocyte-colony stimulating factors and 5% received erythopoiesis-stimulating agents. Platelet transfusions were given to approximately 22% of all Zevalin-treated patients. Red blood cell transfusions were given to 20% of patients with relapsed or refractory NHL and 2% of patients receiving Zevalin following first-line chemotherapy.

Infections

In relapsed or refractory NHL patients, infections occurred in 29% of 349 patients during the first 3 months after initiating the Zevalin therapeutic regimen and 3% developed serious infections (urinary tract infection, febrile neutropenia, sepsis, pneumonia, cellulitis, colitis, diarrhea, osteomyelitis, and upper respiratory tract infection). Life-threatening infections were reported in 2% (sepsis, empyema, pneumonia, febrile neutropenia, fever, and biliary stent-associated cholangitis). From 3 months to 4 years after Zevalin treatment, 6% of patients developed infections; 2% were serious (urinary tract infection, bacterial or viral pneumonia, febrile neutropenia, perihilar infiltrate, pericarditis, and intravenous drug-associated viral hepatitis) and 1% were life-threatening infections (bacterial pneumonia, respiratory disease, and sepsis).

When administered following first-line chemotherapy (Table 2), Grade 3-4 infections occurred in 8% of Zevalin treated patients and in 2% of controls and included neutropenic sepsis (1%), bronchitis, catheter sepsis, diverticulitis, herpes zoster, influenza, lower respiratory tract infection, sinusitis, and upper respiratory tract infection.

Leukemia and Myelodysplastic Syndrome

Among 746 patients with relapsed/refractory NHL, 19 (2.6%) patients developed MDS/AML with a median follow-up of 4.4 years. The overall incidence of MDS/AML among the 211 patients included in the clinical studies was 5.2% (11/211), with a median follow-up of 6.5 years and median time to development of MDS/AML of 2.9 years. The cumulative Kaplan-Meier estimated incidence of MDS/secondary leukemia in this patient population was 2.2% at 2 years and 5.9% at 5 years. The incidence of MDS/AML among the 535 patients in the expanded access programs was 1.5% (8/535) with a median follow-up of 4.4 years and median time to development of MDS/AML of 1.5 years. Multiple cytogenetic abnormalities were described, most commonly involving chromosomes 5 and/or 7. The risk of MDS/AML was not associated with the number of prior treatments (0-1 versus 2-10).

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Among 204 patients receiving Y-90-Zevalin following first-line treatment, 7 (3%) patients developed MDS/AML between approximately 2 to 7 years after Zevalin administration [*see Warnings and Precautions (5.4)*].

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of the Zevalin therapeutic regimen in hematologic malignancies. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to the Zevalin therapeutic regimen.

- Cutaneous and mucocutaneous reactions: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous dermatitis, and exfoliative dermatitis [*see Boxed Warning* and *Warnings and Precautions (5.3)*].
- Infusion site erythema and ulceration following extravasation [*see Warnings and Precautions (5.5)*].
- Radiation injury in tissues near areas of lymphomatous involvement within a month of Zevalin administration.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of antibodies to the Zevalin therapeutic regimen in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

HAMA and HACA response data on 446 patients from 8 clinical studies conducted over a 10-year time period are available. Overall, 11/446 (2.5%) had evidence of either HAMA formation (N=8) or HACA formation (N=4). Six of these patients developed HAMA/HACA after treatment with Zevalin and 5 were HAMA/HACA positive at baseline. Of the 6 who were HAMA/HACA positive, only one was positive for both. Furthermore, in 6 of the 11 patients, the HAMA/HACA reverted to negative within 2 weeks to 3 months. No patients had increasing levels of HAMA/HACA at the end of the studies.

Only 6/446 patients (1.3%) had developed evidence of antibody formation after treatment with Zevalin, and of these, many either reverted to negative or decreased over time. This data demonstrates that HAMA/HACA develop infrequently, are typically transient, and do not increase with time.

7 DRUG INTERACTIONS

Patients receiving medications that interfere with platelet function or coagulation should have more frequent laboratory monitoring for thrombocytopenia. No formal drug interaction studies have been performed with Zevalin.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its radioactivity, Y-90 Zevalin may cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. Immunoglobulins are known to cross the placenta. There are no available data on Zevalin use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Advise women of childbearing potential to use adequate contraception for a minimum of twelve months. Inform women who become pregnant while receiving Zevalin of the potential fetal risks.

The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

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There are no data on the presence of Zevalin or its metabolites in human milk, the effects of Zevalin on the breastfed child, or its effects on milk production. Because human IgG is excreted in human milk, it is expected that Zevalin would be present in human milk. Due to the potential for serious adverse reactions in a breastfeeding child from Zevalin, advise lactating women to avoid breastfeeding during treatment with the Zevalin therapeutic regimen and for 6 months after the last dose.

8.3 Females and Males of Reproductive Potential

Zevalin may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Conduct pregnancy testing in females of reproductive potential prior to treatment with Zevalin.

Contraception

Females

Based on its radioactivity, Y-90 Zevalin may cause fetal harm. Advise females of reproductive potential to use effective contraceptive methods during treatment and for 12 months after the last dose of the Zevalin therapeutic regimen *[see Clinical Pharmacology (12.1)]*.

Males

Based on its radioactivity, Y-90 Zevalin may cause fetal harm. Advise males with female partners of reproductive potential to use effective contraceptive methods during treatment and for 12 months after the final dose of the Zevalin therapeutic regimen *[see Clinical Pharmacology (12.1)]*.

Infertility

Based on its radioactivity, there is a potential risk that the Zevalin therapeutic regimen could cause toxic effects on the male and female gonads *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of Zevalin have not been established in pediatric patients.

8.5 Geriatric Use

Of 349 patients with relapsed/refractory NHL treated with the Zevalin therapeutic regimen in clinical studies, 38% (132 patients) were age 65 years and over, while 12% (41 patients) were age 75 years and over.

Of 414 patients enrolled in the FIT study (Zevalin following first-line chemotherapy) 206 patients received Zevalin. Of these patients 14% (29 patients) were 65 years and over, while 2% (4 patients) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Severe cytopenias which may require stem cell support have occurred at doses higher than the recommended maximum total dose of 32 mCi (1184 MBq).

11 DESCRIPTION

Zevalin (ibritumomab tiuxetan) is the immunoconjugate resulting from a stable thiourea covalent bond between the monoclonal antibody ibritumomab and the linker-chelator tiuxetan [N-[2-bis(carboxymethyl)amino]-3-(p-isothiocyanatophenyl)-propyl]-[N-[2-bis(carboxymethyl)amino]-2-(methyl)-ethyl]glycine. This linker-chelator provides a high affinity, conformationally restricted chelation site for Yttrium-90. The approximate molecular weight of ibritumomab tiuxetan is 148 kD. The antibody moiety of Zevalin is ibritumomab, a murine IgG_1 kappa monoclonal antibody directed against the CD20 antigen.

Ibritumomab tiuxetan is a clear, colorless, sterile, pyrogen-free, preservative-free solution that may contain translucent particles. Each single-use vial includes 3.2 mg of ibritumomab tiuxetan in 2 mL of 0.9% Sodium Chloride.

Physical/Radiochemical Characteristics of Y-90

Yttrium-90 decays by emission of beta particles, with a physical half-life of 64.1 hours (2.67 days). The product of radioactive decay is non-radioactive Zirconium-90. The range of beta particles in soft tissue (χ_{90}) is 5 mm. Radiation emission data for Y-90 are summarized in Table 5.

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Table 5.
Principal Y-90 Radiation Emission Data

Radiation	Mean % per Disintegration	Mean Energy (keV)
Beta minus	100	750-935

External Radiation

The exposure rate for 1 mCi (37 MBq) of Y-90 is 8.3 x 10^{-3} C/kg/hr (32 R/hr) at the mouth of an open Y-90 vial.

To allow correction for physical decay of Y-90, the fractions that remain at selected intervals before and after the time of calibration are shown in Table 6.

Table 6.
Physical Decay Chart: Y-90 Half-life 2.67 Days (64.1 Hours)

Calibration Time (Hrs.)	Fraction Remaining	Calibration Time (Hrs.)	Fraction Remaining
-36	1.48	0	1.00
-24	1.30	1	0.99
-12	1.14	2	0.98
-8	1.09	3	0.97
-7	1.08	4	0.96
-6	1.07	5	0.95
-5	1.06	6	0.94
-4	1.04	7	0.93
-3	1.03	8	0.92
-2	1.02	12	0.88
-1	1.01	24	0.77
0	1.00	36	0.68

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ibritumomab tiuxetan binds specifically to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35). The apparent affinity (K_D) of ibritumomab tiuxetan for the CD20 antigen ranges between approximately 14 to 18 nM. The CD20 antigen is expressed on pre-B and mature B lymphocytes and on > 90% of B-cell non-Hodgkin's lymphomas (NHL). The CD20 antigen is not shed from the cell surface and does not internalize upon antibody binding.

The chelate tiuxetan, which tightly binds Y-90, is covalently linked to ibritumomab. The beta emission from Y-90 induces cellular damage by the formation of free radicals in the target and neighboring cells.

Ibritumomab tiuxetan binding was observed *in vitro* on lymphoid cells of the bone marrow, lymph node, thymus, red and white pulp of the spleen, and lymphoid follicles of the tonsil, as well as lymphoid nodules of other organs such as the large and small intestines.

12.2 Pharmacodynamics

In clinical studies, administration of the Zevalin therapeutic regimen resulted in sustained depletion of circulating B cells. At four weeks, the median number of circulating B cells was zero (range, 0-1084/mm^3). B-cell recovery began at approximately 12 weeks following treatment, and the median level of B cells was within the normal range (32 to 341/mm^3) by 9 months after treatment. Median serum levels of IgG and IgA remained within the normal range throughout the period of B-cell depletion. Median IgM serum levels dropped below normal (median 49 mg/dL, range 13-3990 mg/dL) after treatment and recovered to normal values by 6-months post therapy.

12.3 Pharmacokinetics

Pharmacokinetic and biodistribution studies were performed using In-111 Zevalin (5 mCi [185 MBq] In-111, 1.6 mg ibritumomab tiuxetan). In an early study designed to assess the need for pre-administration of unlabeled antibody, only

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18% of known sites of disease were imaged when In-111 Zevalin was administered without unlabeled ibritumomab. When preceded by unlabeled ibritumomab (1.0 mg/kg or 2.5 mg/kg), In-111 Zevalin detected 56% and 92% of known disease sites, respectively. These studies were conducted with a Zevalin therapeutic regimen that included unlabeled ibritumomab.

In pharmacokinetic studies of patients receiving the Zevalin therapeutic regimen, the mean effective half-life for Y-90 activity in blood was 30 hours, and the mean area under the fraction of injected activity (FIA) vs. time curve in blood was 39 hours. Over 7 days, a median of 7.2% of the injected activity was excreted in urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutogenicity studies have not been conducted. However, radiation is a potential carcinogen and mutagen.

No animal studies have been performed to determine the effects of Zevalin on fertility in males or females. In clinical studies, the Zevalin therapeutic regimen results in a significant radiation dose to the testes: the radiation dose to the ovaries has not been established [*see Dosage and Administration (2.5*)]. There is a potential risk that the Zevalin therapeutic regimen could cause toxic effects on the male and female gonads. Effective contraceptive methods should be used during treatment and for up to 12 months following the Zevalin therapeutic regimen.

13.2 Animal Toxicology and/or Pharmacology

Animal reproductive toxicology studies of the Zevalin therapeutic regimen have not been conducted. Because the Zevalin therapeutic regimen includes the use of rituximab, also see prescribing information for rituximab.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-grade or Follicular Lymphoma

A study to evaluate the efficacy and safety of Zevalin (referred to as Study 106-06) was a single arm study of 54 patients with relapsed follicular lymphoma, who were refractory to rituximab treatment. Patients had a World Health Organization (WHO) Performance Status (PS) 0-2, <25% bone marrow involvement by NHL, no prior bone marrow transplantation, and acceptable hematologic, renal, and hepatic function. Refractoriness to rituximab was defined as failure to achieve a complete or partial response or time-to-disease-progression (TTP) of < 6 months. The main efficacy outcome measure of the study was the overall response rate (ORR) using the International Workshop Response Criteria (IWRC). Other efficacy outcome measures included time-to-disease-progression (TTP) and duration of response (DR). Table 7 summarizes efficacy data from Study 106-06.

Another study to evaluate the efficacy and safety of Zevalin (referred to as Study 106-04) was a randomized (1:1), open-label, multicenter study comparing the Zevalin therapeutic regimen with rituximab. The trial was conducted in 130 patients with relapsed or refractory low-grade or follicular non-Hodgkin's lymphoma (NHL); no patient had received prior rituximab. Patients had histologically confirmed NHL requiring therapy, a WHO PS 0-2, <25% bone marrow involvement by NHL, no prior bone marrow transplantation, and acceptable hematologic function. Sixty-four patients received the Zevalin therapeutic regimen, and 66 patients received rituximab given as an IV infusion at 375 mg per m^2 weekly times 4 doses. The main efficacy outcome measure of the study was ORR using the IWRC. The ORR was significantly higher for patients receiving the Zevalin therapeutic regimen (83% vs. 55%, $p<0.001$). Time-to-disease-progression was not significantly different between study arms. Table 7 summarizes efficacy data from Study 106-04.

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Table 7.
Summary of Efficacy Data[a]

	Study 106-06	Study 106-04	
	Zevalin therapeutic regimen N = 54	**Zevalin therapeutic regimen N = 64**	**Rituximab N = 66**
Overall Response Rate (%)	74	83	55
Complete Response Rate[b] (%)	15	38	18
Median DR[c,d] (Months) [Range[e]]	6.4 [0.5-49.9+]	14.3 [1.8-47.6+]	11.5 [1.2-49.7+]
Median TTP[c,f](Months) [Range[e]]	6.8 [1.1-50.9+]	12.1 [2.1-49.0+]	10.1 [0.7-51.3+]

a) IWRC: International Workshop Response Criteria
b) CRu and CR: Unconfirmed and confirm complete response
c) Estimated with observed range
d) Duration of response: interval from the onset of response to disease progression
e) "+" indicates an ongoing response
f) Time to Disease Progression: interval from the first infusion to disease progression

A single-arm study to evaluate the efficacy and safety of Zevalin (referred to as Study 106-05) was conducted in 30 patients, of whom 27 had relapsed or refractory low-grade, follicular NHL and a platelet count 100,000 to 149,000/mm^3. Patients with ≥ 25% lymphomatous marrow involvement, prior myeloablative therapy with stem cell support, prior external beam radiation to > 25% of active marrow or neutrophil count <1,500/mm^3 were ineligible for Study 106-05. All patients received Y-90 Zevalin [0.3 mCi per kg (11.1 MBq per kg)]. Objective, durable clinical responses were observed [89% ORR (95% CI: 70-97%) with a median duration of response of 11.6 months (range: 1.0-42.4+ months)].

14.2 Follicular, B-Cell NHL Upon Completion of First-Line Chemotherapy

The FIT (First-line Indolent Trial) study (NCT00185393) was a multi-center, randomized, open-label study conducted in patients with follicular NHL with a partial (PR) or complete response (CR/CRu) upon completion of first-line chemotherapy. Randomization was stratified by center and response to first-line therapy (CR or PR). Key eligibility criteria were <25% bone marrow involvement, no prior external beam radiation or myeloablative therapy, and recovery of platelets to normal levels. Patients were randomized to receive Zevalin (n=208) or no further therapy (n=206). Y-90 Zevalin was administered at least 6 weeks but no more than 12 weeks following the last dose of chemotherapy. The main efficacy outcome measure was progression-free survival (PFS) assessed by study investigators using the International Workshop to Standardize Response Criteria for non-Hodgkin's Lymphoma (1999).

Among the 414 patients, 49% were male, 99% were Caucasian, 12% were ≥65 years old, 83% had a WHO performance status of 0, and 65% had Stage IV disease. Thirty-nine (9.5%) patients received single agent chlorambucil, 22 (5%) patients received fludarabine or a fludarabine-containing regimen, 294 (71%) patients received cyclophosphamide-containing combination chemotherapy [CHOP (31%); CHOP-like (15%); CVP/COP (26%)] and 59 (14%) patients received rituximab-containing combination chemotherapy as first-line treatment.

Progression-free survival was significantly prolonged among Zevalin-treated patients compared to those receiving no further treatment [median PFS 38 months vs. 18 months; HR 0.46 (95% CI: 0.35, 0.60) p<0.0001 Cox model stratified by response to first-line therapy and initial treatment strategy (immediate vs. watch-and-wait)]. The number of patients who died was too small to permit a reliable comparison on survival.

The results for PFS are presented in Figure 1.

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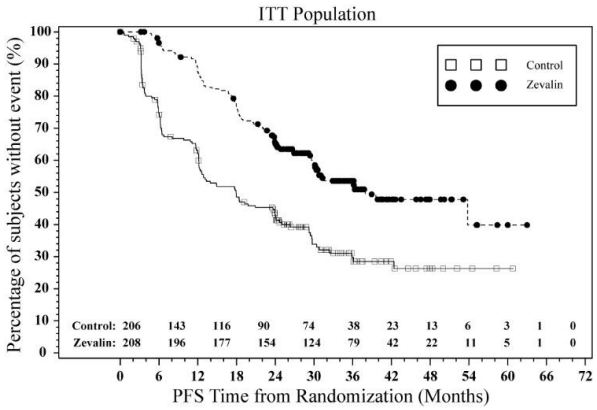
Figure 1. FIT Study: Kaplan-Meier Estimator for Investigator-Assessed Progression Free Survival Time



16 HOW SUPPLIED/STORAGE AND HANDLING

A kit is used for preparing Y-90 radiolabeled Zevalin (NDC 68152-103-03). The contents of all vials are sterile, pyrogen-free, contain no preservatives, and are not radioactive. The kit contains four identification labels and the following four vials:

1. One (1) Zevalin vial containing 3.2 mg ibritumomab tiuxetan in 2 mL 0.9% Sodium Chloride as a clear, colorless solution.
2. One (1) 50 mM Sodium Acetate Vial containing 13.6 mg Sodium Acetate trihydrate in 2 mL Water for Injection, USP as a clear, colorless solution.
3. One (1) Formulation Buffer Vial containing 750 mg Albumin (Human), 76 mg Sodium Chloride, 28 mg Sodium Phosphate Dibasic Dodecahydrate, 4 mg Pentetic Acid, 2 mg Potassium Phosphate Monobasic and 2 mg Potassium Chloride in 10 mL Water for Injection, pH 7.1 as a clear yellow to amber colored solution.
4. One (1) empty Reaction Vial.

Yttrium-90 Chloride Sterile Solution is shipped directly from the supplier upon placement of an order for the Y-90 Zevalin kit.

Rituximab must be ordered separately.

Storage

Store the kit at 2-8°C (36-46°F). Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To contact a healthcare professional for severe signs and symptoms of infusion reactions.
- To take premedications as prescribed [*see Dosage and Administration (2.2)* and *Warnings and Precautions (5.1)*].
- To report any signs or symptoms of cytopenias (bleeding, easy bruising, petechiae or purpura, pallor, weakness or fatigue) [*see Warnings and Precautions (5.2)*].
- To avoid medications that interfere with platelet function, except as directed by a healthcare professional [*see Warnings and Precautions (5.2)*].
- To seek prompt medical evaluation for diffuse rash, bullae, or desquamation of the skin or oral mucosa [*see Warnings and Precautions (5.3)*].
- To immediately report symptoms of infection (e.g. pyrexia) [*see Adverse Reactions (6.2)*].
- That immunization with live viral vaccines is not recommended for 12 months following the Zevalin therapeutic regimen [*see Warnings and Precautions (5.6)*].
- To use effective contraceptive methods during treatment and for a minimum of 12 months following Zevalin therapy [*see Warnings and Precautions (5.8)*], *Use in Specific Populations (8.1, 8.3) and Nonclinical Toxicology (13.1)]*.

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- To discontinue breastfeeding during and for 6 months after the last dose of Zevalin treatment [*see Use In Specific Populations (8.2)*].

Zevalin® (ibritumomab tiuxetan)
Manufactured for:
Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618

U.S. License No. 1832

Zevalin® is a registered trademark of Spectrum Pharmaceuticals, Inc. and its subsidiaries.

Protected by U.S. Patent Nos. 5,736,137, 5,776,456, 5,843,439, 6,207,858, 6,399,061, 6,682,734, 6,994,840, 7,229,620, 7,381,560, 7,422,739 and other patents and patents pending.

FDA Information: Withdrawn Cancer Accelerated Approvals

URL: https://www.fda.gov/drugs/resources-information-approved-drugs/resources-information-approved-drugs/withdrawn-cancer-accelerated-approvals

Withdrawn | Cancer Accelerated Approvals

This listing includes accelerated approvals (/drugs/nda-and-bla-approvals/accelerated-approval-program) (AAs) for malignant hematology and oncology indications that have been subsequently withdrawn, and are therefore, no longer FDA-approved. Please refer to Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/) for the latest approvals and prescribing information for specific products. Visit the ongoing (/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated-approvals) or verified (/drugs/resources-information-approved-drugs/verified-clinical-benefit-cancer-accelerated-approvals) AA indication pages for more information.

Withdrawn indications are not listed until FDA publishes a Federal Register notice to that effect or updates product labeling.

Drug Name	Accelerated Approval (AA) Indication	Accelerated Approval Date	Withdrawal Date [1]
Tazverik (tazemetostat)	Treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection (https://wayback.archive-it.org/7993/20201222063544/https:/www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tazemetostat-advanced-epithelioid-sarcoma) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)	1/23/2020	6/22/2026
Tazverik (tazemetostat)	Treatment of adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least 2 prior systemic therapies. Treatment of adult patients with R/R FL who have no satisfactory alternative treatment options (https://wayback.archive-it.org/7993/20201222062826/https:/www.fda.gov/drugs/fda-granted-accelerated-approval-tazemetostat-follicular-lymphoma) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)	6/18/2020	6/22/2026
Xpovio (selinexor)	Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma (FL), after at least 2 lines of systemic therapy. (https://wayback.archive-it.org/7993/20201222062817/https:/www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-selinexor-relapsedrefractory-diffuse-large-b-cell-lymphoma) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)	6/22/2020	4/30/2026

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Drug Name	Accelerated Approval (AA) Indication	Accelerated Approval Date	Withdrawal Date [1]
Trodelvy (sacituzumab govitecan-hziy)	Treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-sacituzumab-govitecan-advanced-urothelial-cancer)	4/13/2021	11/22/2024
Exkivity (mobocertinib)	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy	9/15/2021	7/15/2024
Truseltiq (infigratinib)	Treatment of adult patients with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangement as detected by an FDA approved test (/drugs/resources-information-approved-drugs/withdrawn-fda-grants-accelerated-approval-infigratinib-metastatic-cholangiocarcinoma)	5/28/2021	5/16/2024
Aliqopa (copanlisib)	Treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies	9/14/2017	3/18/2024
Pepaxto (melphalan flufenamide)	In combination with dexamethasone for the treatment of adult patients with relapsed or refractory (R/R) multiple myeloma (MM) who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD-38 directed monoclonal antibody (/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-melphalan-flufenamide-relapsed-or-refractory-multiple-myeloma)	2/26/2021	2/23/2024
Gavreto (pralsetinib)	Treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic RET-mutant medullary thyroid cancer (MTC) who require systemic therapy	12/1/2020	7/20/2023
Imbruvica (ibrutinib)	Adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy	11/13/2013	5/18/2023
Imbruvica (ibrutinib)	Adult patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy	1/18/2017	5/18/2023
Blenrep (belantamab mafodotin-blmf)	Adults patients with relapsed or refractory (R/R) multiple myeloma (MM) who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent (/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-belantamab-mafodotin-blmf-multiple-myeloma)	8/5/2020	2/6/2023

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Drug Name	Accelerated Approval (AA) Indication	Accelerated Approval Date	Withdrawal Date [1]
Tecentriq (atezolizumab)	Patients with locally advanced or metastatic urothelial carcinoma (mUC) who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 as determined by an FDA approved test or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status	4/17/2017	12/2/2022
Ukoniq (umbralisib)	Adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen	2/5/2021	5/31/2022
Ukoniq (umbralisib)	Adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy	2/5/2021	5/31/2022
Marqibo (vincristine sulfate liposomal)	Adults with Philadelphia (PH) chromosome negative (-) ALL in second relapse or greater relapsed or whose disease has progressed following 2 or greater treatment lines of anti-leukemia therapies	8/9/2012	5/2/2022
Farydak (panobinostat)	In combination with bortezomib (BTZ) and dexamethasone (DEX) for the treatment of patients with multiple myeloma (MM) who have received at least 2 prior regimens, including BTZ and an immunomodulatory agent.	2/23/2015	3/24/2022
Zydelig (idelalisib)	For the treatment of relapsed follicular B-cell Non-Hodgkin Lymphoma (FL) in patients who have received at least 2 prior systemic therapies and relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies	7/23/2014	2/18/2022
Keytruda (pembrolizumab)	For patients with recurrent or locally advanced or metastatic gastric or GEJ adenocarcinoma whose tumors express PD-L1 [CPS ≥1] as determined by an FDA-approved test, with disease progression on/after two or more prior lines of therapy including fluoropyrimidine and platinum containing chemotherapy and if appropriate, HER2/NEU targeted therapy	9/22/2017	2/4/2022
Copiktra (duvelisib)	Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after at least 2 prior systemic therapies	9/24/2018	12/17/2021
Keytruda (pembrolizumab)	Metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy	6/17/2019	3/30/2021
Tecentriq (atezolizumab)	In combination with paclitaxel protein-bound for unresectable locally advanced or metastatic triple-negative breast cancer whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells of any intensity covering = 1% of the tumor area), as determined by an FDA-approved test. (/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative)	3/8/2019	10/6/2021

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Drug Name	Accelerated Approval (AA) Indication	Accelerated Approval Date	Withdrawal Date [1]
Opdivo (nivolumab)	Metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy	8/16/2018	12/29/2020
Opdivo (nivolumab)	Hepatocellular carcinoma previously treated with sorafenib	9/22/2017	7/23/2021
Imfinzi (durvalumab)	Locally advanced or metastatic urothelial carcinoma that progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	5/1/2017	2/19/2021
Lartruvo (olaratumab)	In combination with doxorubicin for adults with soft tissue sarcoma with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery	10/19/2016	2/25/2020
Tecentriq (atezolizumab)	Locally advanced or metastatic urothelial carcinoma that progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	5/18/2016	4/13/2021
Istodax (romidepsin)	Peripheral T-cell lymphoma in patients who have received at least one prior therapy	6/16/2011	7/30/2021
Oforta (fludarabine phosphate)	For adults with B-cell CLL that has not responded to or progressed during or after treatment with at least one standard alkylating agent containing regimen	12/18/2008	12/31/2011
Avastin (bevacizumab)	In combination with paclitaxel for patients who have not received chemotherapy for metastatic HER2 negative breast cancer	2/22/2008	11/18/2011
Bexxar (tositumomab and iodine i 131 tositumomab)	For patients with relapsed or refractory low-grade follicular or transformed CD20+ NHL who have not received rituximab	12/22/2004	10/23/2013
Iressa (gefitinib)	As monotherapy for locally advanced or metastatic NSCLC after failure of platinum-based and docetaxel chemotherapy	5/5/2003	4/25/2012
Mylotarg (gemtuzumab ozogamicin)	For patients with CD33+ AML in first relapse 60 years of age or older and not candidates for cytotoxic chemotherapy	5/17/2000	11/28/2011
Celebrex (celecoxib)	To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis patients, as an adjunct to usual care	12/23/1999	6/8/2012

1 Withdrawal date indicates either the effective date published by the Federal Register or the date the product label was updated, whichever date came first.

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EMA Medicine Authorization Status

Generic Name: Arcitumomab

Trade Name: CEA-Scan

URL: https://www.ema.europa.eu/en/medicines/human/EPAR/cea-scan

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

English

← Medicines

CEA-Scan

arcitumomab

Medicine Human

Withdrawn

This medicine's authorisation has been withdrawn

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Application under evaluation

CHMP opinion

European Commission decision

Overview

On 4 October 1996 the European Commission granted a marketing authorisation for the whole European Union to Immunomedics GmbH, for Cea-Scan (arcitumomab), for the following indication:

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"CEA-Scan is indicated only in patients with histologically-demonstrated carcinoma of the colon or rectum for imaging of recurrence and/or metastases. CEA-Scan is employed, in the above mentioned patients, as an adjunct to standard non-invasive imaging techniques, such as ultrasonography or CT scan, in the following situations:

- Patients with evidence of recurrence and/or metastatic carcinoma of the colon or rectum, who are undergoing an evaluation for extent of disease, such as prior to surgical resection and/or other therapy.
- Patients with suspected recurrence and/or metastatic carcinoma of the colon or rectum in association with rising levels of carcinoembryonic antigen (CEA)."

CEA-Scan has been marketed in Austria, Belgium, Czech Republic, Cyprus, Finland, France , Germany, Greece, Hungary, Ireland, Italy, Luxemburg, Malta, the Netherlands, Poland, Portugal, Spain, Sweden and United Kingdom.

On 30 August 2005, the Marketing Authorisation Holder notified the European Commission of its decision to voluntarily withdraw the Marketing Authorisation for CEA-Scan for commercial reasons.

On 27 September 2005 the European Commission adopted the decision withdrawing the Marketing Authorisation for the medicinal product for human use "CEA-Scan". Pursuant to this decision the European Public Assessment Report for CEA-Scan has been removed from the EMA website.

Product information

26/09/2005

This medicine's product information is available in all **official EU languages**.
Select 'available languages' to access the language you need.

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Product information documents contain:

- summary of product characteristics (annex I);
- manufacturing authorisation holder responsible for batch release (annex IIA);
- conditions of the marketing authorisation (annex IIB);
- labelling (annex IIIA);
- package leaflet (annex IIIB).

Product details

Name of medicine

CEA-Scan

Active substance

arcitumomab

International non-proprietary name (INN) or common name

arcitumomab

Therapeutic area (MeSH)

- Radionuclide Imaging
- Colorectal Neoplasms

Anatomical therapeutic chemical (ATC) code

V09IA01

Pharmacotherapeutic group

Diagnostic radiopharmaceuticals

Therapeutic indication

CEA-Scan is indicated only in patients with histologically-demonstrated carcinoma of the colon or rectum for imaging of

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recurrence and/or metastases. CEA-Scan is employed for diagnostic use only, in the above mentioned patients, as an adjunct to standard non-invasive imaging techniques, such as ultrasonography or CT scan, in the following situations:

- Patients with evidence of recurrence and/or metastatic carcinoma of the colon or rectum, who are undergoing an evaluation for extent of disease, such as prior to surgical resection and/or other therapy, or
- Patients with suspected recurrence and/or metastatic carcinoma of the colon or rectum in association with rising levels of carcinoembryonic antigen (CEA).

Authorisation details

EMA product number

EMEA/H/C/000041

Marketing authorisation holder

Immunomedics GmbH
Otto-Röhm-Straße 69
D-64293 Darmstadt
Germany

Marketing authorisation issued

04/10/1996

Withdrawal of marketing authorisation

27/09/2005

Revision

6

This page was last updated on 16/11/2005

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EMA Medicine Authorization Status

Generic Name: igovmab

Trade Name: Indimacis 125

URL:
https://www.ema.europa.eu/en/medicines/human/EPAR/indimacis-125

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

English

← Medicines

Indimacis 125

igovomab

Medicine Human

Withdrawn

This medicine's authorisation has been withdrawn

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Application under evaluation

CHMP opinion

European Commission decision

Overview

The marketing authorisation for Indimacis 125 has been withdrawn at the request of the marketing authorisation holder.

Product information

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31/12/2009

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- manufacturing authorisation holder responsible for batch release (annex IIA);
- conditions of the marketing authorisation (annex IIB);
- labelling (annex IIIA);
- package leaflet (annex IIIB).

Product details

Name of medicine

Indimacis 125

Active substance

igovomab

International non-proprietary name (INN) or common name

igovomab

Therapeutic area (MeSH)

- Radionuclide Imaging
- Ovarian Neoplasms

Product details

V09IB03

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Pharmacotherapeutic group

Diagnostic radiopharmaceuticals

Therapeutic indication

Positive diagnosis of relapsing ovarian adenocarcinoma when serum CA 125 is increased without positive results of ultrasound or computerised tomography scan.

Authorisation details

EMA product number

EMEA/H/C/000065

Marketing authorisation holder

CIS bio international
B.P. 32
91192 Gif-sur-Yvette Cedex
France

Marketing authorisation issued

04/10/1996

This page was last updated on 31/12/2009

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EMA Medicine Authorization Status

Generic Name: sulesomab

Trade Name: LeukoScan

URL: https://www.ema.europa.eu/en/medicines/human/EPAR/leukoscan

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

English

← Medicines

LeukoScan

sulesomab

Medicine Human

Withdrawn

This medicine's authorisation has been withdrawn

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Application under evaluation

CHMP opinion

European Commission decision

Overview

On 30 January 2018, the European Commission withdrew the marketing authorisation for LeukoScan (sulesomab) in the European Union (EU). The withdrawal was at the request of the marketing authorisation holder, Immunomedics GmbH, which notified the European Commission of its decision to

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permanently discontinue the marketing of the product for commercial reasons.

LeukoScan was granted marketing authorisation in the EU on 14 February 1997 for diagnostic imaging in suspected osteomyelitis. The marketing authorisation was initially valid for a 5-year period. It was subsequently renewed for an additional 5-year period in year 2002. It was then granted unlimited validity in 2007.

The European Public Assessment Report (EPAR) for LeukoScan is updated accordingly to reflect the fact that the marketing authorisation is no longer valid.

LeukoScan : EPAR - Summary for the public

English (EN) (516.27 KB - PDF)
First published: 13/08/2007
Last updated: 09/02/2018

View

Other languages (21)

Product information

LeukoScan : EPAR - Product Information

English (EN) (611.18 KB - PDF)
First published: 13/08/2007
Last updated: 09/02/2018

View

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Other languages (24)

Latest procedure affecting product information:IAIN/0024/G

18/01/2017

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- package leaflet (annex IIIB).

LeukoScan : EPAR - All Authorised presentations

English (EN) (466.59 KB - PDF)

First published: 21/10/2005

Last updated: 09/02/2018

View

Product details

Name of medicine

LeukoScan

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Active substance

sulesomab

International non-proprietary name (INN) or common name

sulesomab

Therapeutic area (MeSH)

- Osteomyelitis
- Radionuclide Imaging

Anatomical therapeutic chemical (ATC) code

VO4D

Pharmacotherapeutic group

Diagnostic agents

Therapeutic indication

This medicinal product is for diagnostic use only.

LeukoScan is indicated for diagnostic imaging for determining the location and extent of infection/inflammation in bone in patients with suspected osteomyelitis, including patients with diabetic foot ulcers.

LeukoScan has not been employed to diagnose osteomyelitis in patients with sickle cell anaemia.

Authorisation details

EMA product number

EMEA/H/C/000111

Marketing authorisation holder

Immunomedics GmbH

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Otto-Röhm-Straße 69
D-64293 Darmstadt
Germany

Marketing authorisation issued

14/02/1997

Withdrawal of marketing authorisation

30/01/2018

Revision

7

Assessment history

Expand section Collapse section

Changes since initial authorisation of medicine

Initial marketing authorisation documents

This page was last updated on 09/02/2018

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EMA Medicine Authorization Status

Generic Name: votumumab

Trade Name: HumaSPECT

URL:
https://www.ema.europa.eu/en/medicines/human/EPAR/humaspect

EUROPEAN MEDICINES AGENCY
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English

← Medicines

HumaSPECT

votumumab

Medicine Human

Withdrawn

This medicine's authorisation has been withdrawn

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Application under evaluation

CHMP opinion

European Commission decision

Overview

On 25 September 1998, the European Commission granted a marketing authorisation for HumaSPECT (votumumab) for the whole European Union to Organon Teknika. The marketing authorisation was subsequently transferred to KS Biomedix Ltd. HumaSPECT is indicated in patients with histologically proven

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carcinoma of the colon or rectum for imaging of recurrence and/or metastases.

HumaSPECT is not marketed anywhere in the world. On 22 September 2003, KS Biomedix Ltd notified the European Commission of its decision not to renew the marketing authorisation for HumaSPECT for commercial reasons. Alternatives are available in Europe, since other radiopharmaceutical agents are used for this indication.

On 24 September 2003, the marketing authorisation for HumaSPECT expired. Consequently, the European Public Assessment Report for HumaSPECT has been removed from this website.

Product information

24/09/2003

This medicine's product information is available in all **official EU languages**.
Select 'available languages' to access the language you need.

Product information documents contain:

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- package leaflet (annex IIIB).

Product details

Name of medicine

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HumaSPECT

Active substance

votumumab

International non-proprietary name (INN) or common name

votumumab

Therapeutic area (MeSH)

- Ultrasonography
- Colorectal Neoplasms
- Tomography, X-Ray Computed

Anatomical therapeutic chemical (ATC) code

V09IX

Pharmacotherapeutic group

Diagnostic radiopharmaceuticals

Therapeutic indication

After reconstitution with sodium pertechnetate [^{99m}Tc] solution, HumaSPECT [^{99m}Tc] is indicated in patients with histologically proven carcinoma of the colon or rectum for imaging of recurrence and/or metastases. HumaSPECT [^{99m}Tc] is employed, in the above mentioned patients, as an adjunct to standard non invasive imaging techniques, such as ultrasonography or CT scan, in the following situations.
• Patients with evidence of recurrence and/or metastatic carcinoma of the colon or rectum, who are undergoing an evaluation for extent of disease, such as prior to surgical resection and/or other therapy.
• Patients with suspected recurrence and/or metastatic carcinoma of the colon or rectum in association with rising levels of carcinoembryonic antigen (CEA).

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Authorisation details

EMA product number

EMEA/H/C/000145

Marketing authorisation holder

KS Biomedix Limited
KS Biomedix
Unit 7, Romans Business Park
East Street
Farnham, Surrey GU9 7SX
United Kingdom

Marketing authorisation issued

25/09/1998

Withdrawal of marketing authorisation

24/09/2003

This page was last updated on 23/02/2004

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