

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202207Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lymphoseek safely and effectively. See full prescribing information for Lymphoseek.

Lymphoseek (technetium Tc 99m tilmanocept) Injection for subcutaneous, intradermal, or peritumoral administration. Initial U.S. Approval: 2013

INDICATIONS AND USAGE

Lymphoseek (technetium Tc 99m tilmanocept) Injection is a radioactive diagnostic agent indicated for lymphatic mapping with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma. (1)

DOSAGE AND ADMINISTRATION

- Lymphoseek is supplied as a Kit and must be prepared by radiolabeling with technetium Tc 99m and diluting with the supplied diluent prior to use. (2.3)
- Use aseptic technique and radiation safety precautions during Lymphoseek preparation and handling. For each patient, the total injection volume and the number of sites to be injected should be known before preparing Lymphoseek. (2.1, 2.3)
- Administer 18.5 MBq (0.5 mCi) of Lymphoseek at least 15 minutes before initiating intraoperative lymphatic mapping. Complete lymphatic mapping within 15 hours of Lymphoseek injection. (2.2, 2.3)
- Recommended administration routes are intradermal, subcutaneous, and peritumoral injections. (2.3)
- Each radiolabeled Lymphoseek vial contains sufficient amount to provide doses for up to four patients when prepared according to the instructions. (3) The radiolabeled Lymphoseek is to be used within 6 hours of its preparation.

DOSAGE FORMS AND STRENGTHS

The Kit for preparation of Lymphoseek contains five Tilmanocept Powder vials each containing 250 mcg tilmanocept and five DILUENT for Lymphoseek vials containing 4.5 mL of sterile buffered saline. After radiolabeling with technetium Tc 99m and dilution, Lymphoseek contains approximately 92.5 MBq (2.5 mCi) and 250 mcg of technetium Tc 99m tilmanocept in 0.5 mL to 5 mL total volume. (3)

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CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Hypersensitivity: Ask patients about prior reactions to drugs, especially dextran or modified forms of dextran. Observe for hypersensitivity signs and symptoms following Lymphoseek injection. Have resuscitation equipment and trained personnel available at the time of Lymphoseek administration. (5.1)

ADVERSE REACTIONS

In clinical trials, the most common adverse reactions, injection site irritation and/or pain, occurred in < 1% of patients. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Navidea Biopharmaceuticals, Inc. at 1-800-476-5270 or www.lymphoseek.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if clearly needed. (8.1)
- Nursing mothers: Express and discard milk for at least 4 hours following administration of Lymphoseek. (8.3)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2013

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Lymphoseek (technetium Tc 99m tilmanocept) Injection is indicated for lymphatic mapping with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor site in patients with breast cancer or melanoma.

2 DOSAGE AND ADMINISTRATION

2.1 Radiation Safety – Drug Handling

Lymphoseek is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure. [see *Warnings and Precautions (5.2)*] Use waterproof gloves, effective radiation shielding, and appropriate safety measures when preparing and handling Lymphoseek.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclides, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

2.2 Recommended Dose

The recommended dose of Lymphoseek is 18.5 MBq (0.5 mCi) as a radioactivity dose and 50 mcg as a mass dose, administered at least 15 minutes prior to initiating intraoperative lymphatic mapping. The recommended total injection volume for each patient (Table 1) is 0.1 mL administered in a single syringe; 0.5 mL administered in a single syringe or in multiple syringes (0.1 mL to 0.25 mL each); or 1 mL administered in multiple syringes (0.2 mL to 0.5 mL each).

2.3 Drug Preparation and Administration

General Considerations:

- Kit for the preparation of Lymphoseek contains five sets of two vials: a Tilmanocept Powder vial and a DILUENT for Lymphoseek vial.
 - Tilmanocept Powder vial contains 250 mcg of tilmanocept from which 50 mcg is intended for administration to a patient.
 - The DILUENT for Lymphoseek vial contains 4.5 mL of sterile buffered saline. It is used to dilute Lymphoseek after the radiolabeling procedure. The amount of diluent used varies, depending on the total injection volume and the number of syringes used for each patient.
- The vial components of the Kit for the preparation of Lymphoseek are sterile, non-pyrogenic, and are intended solely for use in the preparation of Lymphoseek (technetium Tc 99m tilmanocept) Injection. Do not administer the unprepared vial components of the Kit directly to a patient.
- Follow aseptic procedures during preparation and administration.
- Follow appropriate radiation safety precautions during preparation and administration. Use radiation shielding for radiolabeled Lymphoseek to prevent radiation exposure.

Drug Preparation Instructions:

Lymphoseek may be administered to a patient as a single injection or as multiple injections. Prior to preparation of Lymphoseek, determine the planned injection technique and the number of injections that will be used for a given patient. For each injection prepare a separate syringe. Based on the planned

number of injection syringes and the planned total injection volume per patient, determine (from Table 1 below) the Reconstituted Vial Volume of radiolabeled Lymphoseek.

Table 1. Preparation of Lymphoseek for Administration

Planned Number of Injections for a Patient	Total Injection Volume Per Patient	Reconstituted Vial Volume of Radiolabeled Lymphoseek
1 syringe x 0.1 mL	0.1 mL	0.5 mL
5 syringes x 0.1 mL or 2 syringes x 0.25 mL or 1 syringe x 0.5 mL	0.5 mL	2.5 mL
5 syringes x 0.2 mL or 4 syringes x 0.25 mL or 2 syringes x 0.5 mL	1 mL	5 mL

Each Lymphoseek vial, once reconstituted and radiolabeled, would contain sufficient amount to provide doses for up to four patients when prepared according to the instructions. The radiolabeled Lymphoseek is to be used within 6 hours of its preparation. Discard the unused radiolabeled Lymphoseek.

Once the Reconstituted Vial Volume is established, use the following steps to prepare radiolabeled Lymphoseek:

- a. Prior to radiolabeling, inspect the Tilmanocept Powder vial for any damage. Do not use if vial integrity appears compromised.
- b. For radiolabeling, use Technetium Tc 99m pertechnetate, sodium injection solution from a technetium Tc 99m generator within 8 hours of its elution.
- c. Do not vent the Tilmanocept Powder vial prior to or during radiolabeling.
- d. Using a sterile syringe, aseptically draw approximately 92.5 MBq (2.5 mCi) of Technetium Tc 99m pertechnetate sodium injection solution in either about 0.35 mL volume (for 0.5 mL Reconstituted Vial Volume) or about 0.7 mL volume (for 2.5 mL or 5 mL Reconstituted Vial Volume). Assay the syringe for technetium Tc 99m activity in a dose calibrator.
- e. Prior to reconstitution, write the radioactivity amount, the Reconstituted Vial Volume, date and time, expiration time and lot number in the space provided on the radioactive product vial label and affix it to the Tilmanocept Powder vial. Place the vial in a radiation shield and sanitize the septum with alcohol wipe.
- f. Aseptically add Technetium Tc 99m pertechnetate, sodium injection solution (from step d above) to the Tilmanocept Powder vial. Without withdrawing the needle, remove an equal volume of headspace gas. Do not vent.
- g. Remove the needle, gently shake the vial to mix the contents, and then let it stand at room temperature for at least 15 minutes.
- h. Aseptically add the supplied DILUENT for Lymphoseek to the radiolabeled product in the Tilmanocept Powder vial to bring the volume to the Reconstituted Vial Volume of 0.5 mL, 2.5 mL, or 5 mL prior to filling the patient dose in syringe(s). To normalize pressure, withdraw an equal volume of headspace gas.
- i. Assay the reconstituted vial for total radioactivity using a dose calibrator. Write the technetium Tc 99m activity concentration, total volume, assay time and date, expiration time, and lot number on the shield label supplied with the Kit. Affix the label to the shield.

- j. Determine the radiochemical purity of the reconstituted product as described in 2.4. Do not use if the radiochemical purity is less than 90%.
- k. Withdraw the required volume of the reconstituted product into the required number of syringes. Assay the syringe(s) in a dose calibrator. Write the radioactivity amount, date and time of assay, volume, and expiration time (this is not to exceed 6 hours from preparation time) on the supplied syringe label and affix it to the syringe(s).
- l. Store the reconstituted product at room temperature in a shield. Use within the expiry time on the label.

Route of Administration and Injection Method:

The route of administration depends on the type of cancer and the planned injection technique. Inject Lymphoseek into a patient at least 15 minutes prior to intraoperative lymphatic mapping; do not delay mapping more than 15 hours after Lymphoseek injection. Table 2 shows the route of administration options.

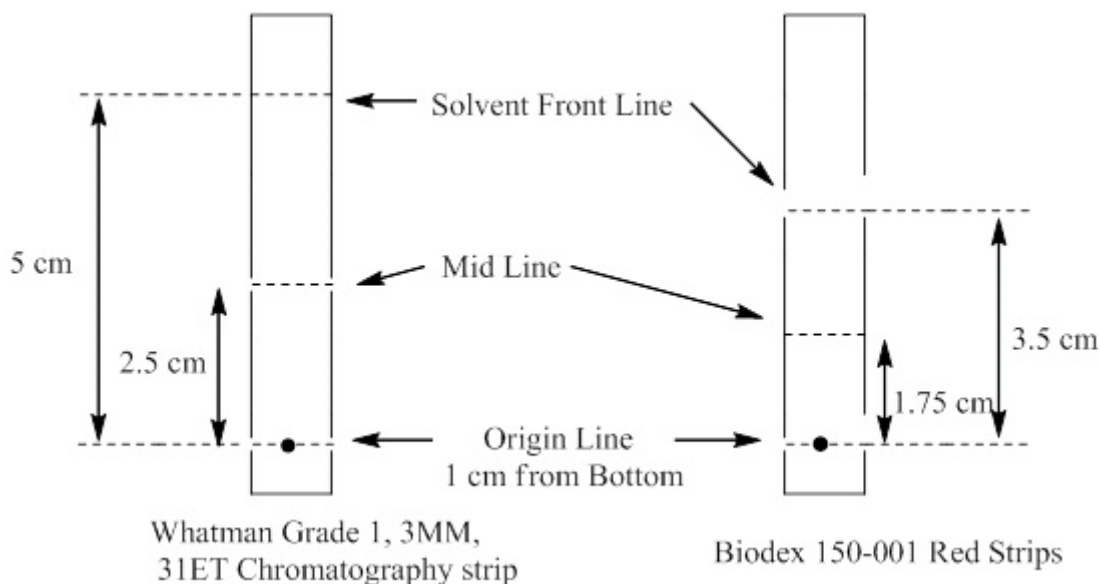
Table 2. Lymphoseek Administration Routes

Cancer Type	Route of Administration
Breast Cancer	intra-dermal, subcutaneous, subareolar, peritumoral
Melanoma	intra-dermal, subcutaneous

2.4 Determination of Radiochemical Purity of Radiolabeled Lymphoseek

Determine radiochemical purity of the reconstituted radiolabeled Lymphoseek by Instant Thin Layer Chromatography (ITLC) using either Whatman Grade 1, 3MM, 31ET Chr or Biodex 150-001 Red Strips (cellulose chromatography paper) using the following method:

- a. Mark the chromatographic strip for origin, mid and solvent front lines with a pencil as shown below:



- b. Apply a small drop (3 - 10 microliters) of the reconstituted product at the center of the origin line chromatography strip. Let the product spot dry.
- c. Place the strip into a chromatography chamber containing 1 mL of acetone as the developing solvent. Allow the solvent to migrate to the solvent front line (5 cm from the bottom of the Whatman strips and 3.5 cm for the Biodex strip). Remove the strip from the chamber, let it dry and cut it in half. Count each half of the strip with a suitable radioactivity counting apparatus (dose calibrator or multichannel analyzer).
- d. Calculate the percent radiochemical purity (% RCP) as follows:

$$\% \text{ RCP} = \frac{\text{Counts (activity) in bottom half}}{\text{Counts(activity) in bottom half} + \text{Counts(activity) in top half}} \times 100$$

- e. Do not use the reconstituted Lymphoseek if the radiochemical purity is less than 90%.

2.5 Lymphatic Mapping Procedures Following Injection of Lymphoseek

- Lymphoscintigraphy may be considered to help plan the lymph node mapping procedures. In clinical studies, preoperative lymphoscintigraphy was performed in most patients; the extent to which lymphoscintigraphy contributed to the success of the mapping procedures was not established. [see *Clinical Studies (14)*]
- Use a hand-held gamma counter to identify nodes that concentrated the injected radioactivity.
- For intraoperative lymphatic mapping, first measure the background radioactivity counts from tissue at least 20 centimeters distal to the injection site. Use the three sigma threshold (background radioactivity counts plus three times the square root of the mean background count) as an estimate of the threshold for positive localization of Lymphoseek, as exemplified in Table 3.

Table 3. Example of Estimates of the Three Sigma Threshold Value

Background Count ^a (cpm)	Threshold Value (cpm)
5	12
10	20
15	27
20	34
25	40
30	47
35	53
40	59

^a Average of three 2-second counts or one 10-second count

- Lymphoseek is intended to supplement palpation, visual inspection, and other procedures important to lymph node localization. Intraoperative lymphatic mapping by gamma detection of Lymphoseek within lymph nodes should be initiated no sooner than 15 minutes following injection of the final product. In clinical studies, patients also received a concomitant blue dye tracer to enhance the ability to detect lymph nodes. While most lymph nodes were detected with Lymphoseek, some were detected only with the blue dye tracer or only with palpation. [see *Clinical Studies (14)*]

- The lymphatic system architecture and function may be changed by prior surgery, radiation, edema, inflammation or metastatic disease, and may result in changes to lymph node localization by a radiopharmaceutical or other tracers, including colorimetric agents. Avoid injections into biopsy wound areas that show evidence of edema or inflammation.

2.6 Radiation Dosimetry

The radiation doses to organs and tissues of an average patient (70 kg) per 18.5 MBq (0.5 mCi) of Lymphoseek are shown in Table 4 and Table 5.

Table 4. Estimated Absorbed Radiation Dose from 50 mcg Lymphoseek in Patients with Breast Cancer^a

Estimated Radiation Absorbed Dose for Breast Cancer, mGy (rad)	
Target Organ	18.5 MBq (0.5 mCi) Tc 99m Dose for Lymphoseek
brain	0.003 (0.0003)
breast (injection site)	1.659 (0.1659)
gall bladder wall	0.0349 (0.0035)
lower large intestine wall	0.0123 (0.0012)
small intestine	0.0101 (0.001)
stomach	0.0184 (0.0018)
upper large intestine wall	0.0125 (0.0012)
kidney	0.1863 (0.0186)
liver	0.0324 (0.0032)
lungs	0.0374 (0.0037)
muscle	0.0092 (0.0009)
ovaries	0.187 (0.0187)
red marrow	0.0127 (0.0013)
bone	0.0177 (0.0018)
spleen	0.0285 (0.0029)
testes	0.0501 (0.005)
thymus	0.1168 (0.0117)
thyroid	0.088 (0.0088)
urinary bladder	0.0586 (0.0059)
total body	0.0195 (0.0019)
Effective Dose Equivalent (males, microSv)	296
Effective Dose Equivalent (females, microSv)	330.2

^a Calculated from data of 18 patients with breast cancer who received four peritumoral injections of 4 mcg, 20 mcg, and 100 mcg doses of Lymphoseek.

Table 5. Estimated Absorbed Radiation Dose from 50 mcg Lymphoseek in Patients with Melanoma^a

Estimated Radiation Absorbed Dose for Melanoma, mGy (rad)	
Target Organ	18.5 MBq (0.5 mCi) Tc 99m Dose for Lymphoseek
brain	0.0927 (0.0093)
breast (injection site) ^b	0.7903 (0.079)
gall bladder wall	0.0712 (0.0071)
lower large intestine wall	0.057 (0.0057)
small intestine	0.0594 (0.0059)
stomach	0.0562 (0.0056)
upper large intestine wall	0.0582 (0.0058)
kidney	0.278 (0.0278)
liver	0.0929 (0.0093)
lungs	0.0599 (0.006)
muscle	0.0451 (0.0045)
ovaries	0.2991 (0.0299)
red marrow	0.0507 (0.0051)
bone	0.0878 (0.0088)
spleen	0.0598 (0.006)
testes	0.1043 (0.0104)
thymus	0.0577 (0.0058)
thyroid	0.0464 (0.0046)
urinary bladder	0.1401 (0.014)
total body	0.0547 (0.0055)
Effective Dose Equivalent (males, microSv)	202.4
Effective Dose Equivalent (females, microSv)	251.1

^a Calculated from data of 18 patients with melanoma who received four intradermal injections of 20 mcg, 100 mcg, and 200 mcg doses of Lymphoseek.

^b Due to the differences in injection sites among patients with melanoma, the injection site was assumed to be the breast for the purposes of this calculation, as it represents the nearest anatomical construct for the skin from the anatomical sites appropriately included in the estimates.

The Effective Dose Equivalents for other technetium Tc 99m-based evaluations are: 1) bone scan = 4,000 microSv; 2) thyroid scan = 1,000 microSv; and 3) lung scan = 1,000 microSv.

3 DOSAGE FORMS AND STRENGTHS

The Kit for preparation of Lymphoseek contains five Tilmanocept Powder vials each containing 250 mcg tilmanocept and five DILUENT for Lymphoseek vials each containing 4.5 mL of sterile buffered saline. After radiolabeling with technetium Tc 99m, the diluted Lymphoseek contains approximately 92.5 MBq (2.5 mCi) and 250 mcg technetium Tc 99m tilmanocept in 0.5 mL to 5 mL total volume.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Lymphoseek may pose a risk of hypersensitivity reactions due to its chemical similarity to dextran. [*see Description (11)*] Serious hypersensitivity reactions have been associated with dextran and modified forms of dextran (such as iron dextran drugs). In clinical trials, no serious hypersensitivity reactions were reported.

Before administering Lymphoseek, ask patients about prior reactions to drugs, especially to dextran and modified forms of dextran. Have resuscitation equipment and trained personnel immediately available at the time of Lymphoseek administration.

5.2 Radiation Risks

Any radiation-emitting product may increase the risk for cancer, especially in pediatric patients. Adhere to the dose recommendations and ensure safe handling to minimize the risk for excessive radiation exposure to either the patient or health care workers.

6 ADVERSE REACTIONS

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.

In clinical trials, 542 patients received Lymphoseek. No patients experienced serious adverse reactions.

Injection site irritation (3 of 542 patients; 0.6%) and pain (1 of 542 patients; 0.2%) were reported. Other adverse reactions were uncommon, of mild severity and short duration.

7 DRUG INTERACTIONS

In animal studies, locally injected anesthetics have been reported to reduce lymphatic flow. Co-injection (mixture) of local anesthetics with Lymphoseek is not recommended and may impair the lymph nodal mapping.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate or well-controlled studies of Lymphoseek in pregnant women.

Unbound technetium crosses the placenta. All radiopharmaceuticals, including Lymphoseek, have a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development and the radiopharmaceutical dose. No reproduction and developmental studies have been conducted with Lymphoseek. Lymphoseek should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Lymphoseek is excreted in human milk. Based on the clearance of the drug, advise patients to express and discard milk for at least four hours after administration of Lymphoseek.

Exercise caution when administering Lymphoseek to a nursing mother.

8.4 Pediatric Use

Safety and effectiveness of Lymphoseek in pediatric patients have not been established.

8.5 Geriatric Use

Of the 468 patients enrolled in breast cancer and melanoma clinical studies, 136 patients were aged 65 or older. Review of the clinical data, including evaluation of the frequency of adverse reactions, has not identified differences in safety or efficacy between elderly patients (65 to 90 years of age) and younger patients (18 to 65 years of age).

8.6 Females of Reproductive Potential

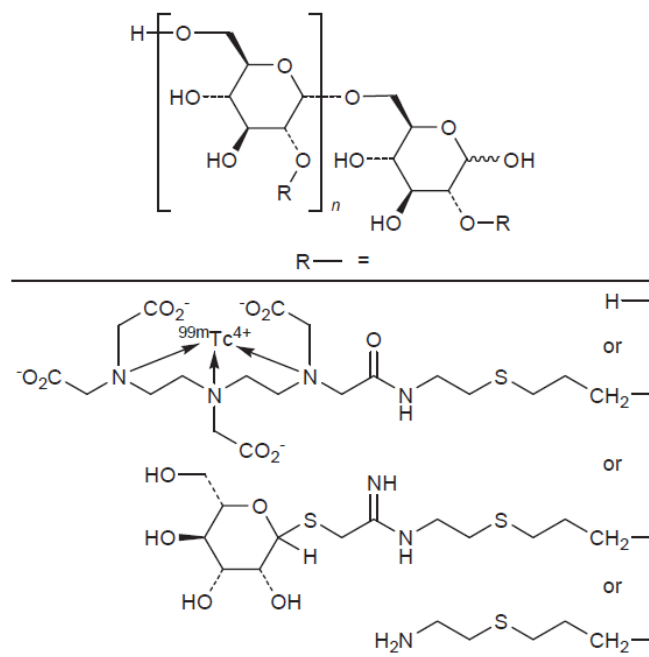
In females of reproductive potential, any Lymphoseek administration should be performed within the ten days following the onset of menses or a pregnancy test should be performed within 48 hours prior to the administration.

11 DESCRIPTION

The active ingredient in Lymphoseek is technetium Tc 99m tilmanocept. The active ingredient is formed when Technetium Tc 99m pertechnetate, sodium injection is added to the Tilmanocept Powder vial.

Technetium Tc 99m binds to the diethylenetriaminepentaacetic acid (DTPA) moieties of the tilmanocept molecule.

Chemically, technetium Tc 99m tilmanocept consists of technetium Tc 99m, dextran 3-[(2-aminoethylthio)propyl 17-carboxy-10,13,16- tris(carboxymethyl)-8-oxo-4-thia-7,10,13,16-tetraazaheptadec-1-yl 3-[[2-[[1-imino-2-(D- mannopyranosylthio) ethyl]amino]ethyl]thio]propyl ether complexes. The molecular formula of technetium Tc 99m tilmanocept is $[C_6H_{10}O_5]_n.(C_{19}H_{28}N_4O_9S^{99m}Tc)_b.(C_{13}H_{24}N_2O_5S_2)_c.(C_5H_{11}NS)_a$. It contains 3-8 conjugated DTPA (diethylenetriamine pentaacetic acid) molecules (b); 12-20 conjugated mannose molecules (c) with 0-17 amine side chains (a) remaining free. The calculated average molecular weight of tilmanocept ranges from 15,281 to 23,454 g/mol. Technetium Tc 99m tilmanocept has the following structural formula:



Lymphoseek (technetium Tc 99m tilmanocept) Injection is supplied as a Kit. The Kit includes Tilmanocept Powder vials which contain the necessary non-radioactive ingredients needed to produce technetium Tc 99m tilmanocept. The Kit also contains DILUENT for Lymphoseek. The diluent contains a preservative and is specifically formulated for Lymphoseek. No other diluent should be used.

The Tilmanocept Powder vial contains a sterile, non-pyrogenic, white to off-white powder that consists of a mixture of 250 mcg tilmanocept, 20 mg trehalose dihydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate, and 0.075 mg stannous chloride dihydrate. The contents of the vial are lyophilized and are under nitrogen.

The DILUENT for Lymphoseek contains 4.5 mL sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v) sodium phosphate (heptahydrate), 0.5% (w/v) sodium chloride, and 0.4% (w/v) phenol. The pH is 6.8 – 7.2.

11.1 Physical Characteristics

Technetium Tc 99m decays by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 6.

Table 6. Principal Radiation Emission Data

Radiation	Mean % Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

From: Kocher, D.C. Radioactive decay data tables. DOE/TIC-11026, 108 (1981).

11.2 External Radiation

The linear mass energy absorption attenuation coefficient for Tc 99m is 18.986 cm⁻¹. The first half-value layer is 0.037 cm of lead (Pb). The use of a 0.25 cm thick standard radiation lead shield will attenuate the radiation emitted by millicurie amounts of technetium Tc 99m by a factor of about 100. A range of values for the relative attenuation of the radiation of technetium Tc 99m that results with various thicknesses of lead shielding are displayed in Table 7.

Table 7. Radiation Attenuation by Lead Shielding

Shield Thickness, cm of lead (Pb)	Coefficient of Attenuation
0.037	0.5
0.12	10 ⁻¹
0.24	10 ⁻²
0.36	10 ⁻³
0.49	10 ⁻⁴

To correct for physical decay of the radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 8.

Table 8. Physical Decay Chart; Tc 99m, Half-Life of 6.02 Hours

Hours	Fraction Remaining
0	1
1	0.891
3	0.708
6	0.501
12	0.251
15	0.178

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lymphoseek is a radioactive diagnostic agent. It accumulates in lymphatic tissue and selectively binds to mannose binding receptor (CD206) located on the surface of macrophages and dendritic cells.

Lymphoseek (tilmanocept) is a macromolecule consisting of multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose, each covalently attached to a 10 kDa dextran backbone. The mannose acts as a ligand for the receptor, and the DTPA serves as a chelating agent for labeling with technetium Tc 99m.

12.2 Pharmacodynamics

In *in vitro* studies, Lymphoseek exhibited binding to human mannose binding receptor with a primary binding site affinity of $K_d = 2.76 \times 10^{-11}$ M.

In clinical studies, Lymphoseek has been detectable in lymph nodes within 10 minutes and up to 30 hours after injection. It is recommended that intraoperative lymphatic mapping be conducted between 15 minutes and 15 hours following injection.

12.3 Pharmacokinetics

In dose-ranging clinical studies, injection site clearance rates were similar across all Lymphoseek doses (4 to 200 mcg) with a mean elimination rate constant in the range of 0.222 to 0.396/hr, resulting in a drug half-life at the injection site of 1.75 to 3.05 hours.

The amount of the accumulated radioactive dose in the liver, kidney, and bladder reached a maximum 1 hour post administration of Lymphoseek and was approximately 1% to 2% of the injected dose in each tissue.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies to assess the carcinogenicity potential of tilmanocept have not been conducted. Tilmanocept was not mutagenic *in vitro* in the Ames bacterial mutation assay and in the *in vitro* mouse lymphoma test, and was negative in the *in vivo* micronucleus test in mice.

Studies on reproductive fertility have not been conducted.

14 CLINICAL STUDIES

Lymphoseek safety and efficacy were assessed in two open-label, multicenter, single arm, within-subject active comparator trials of patients with melanoma or breast cancer. Prior to the nodal mapping procedure, the patients had no nodal or metastatic disease by standard tumor staging criteria. Diagnostic efficacy was determined by the number of histology-confirmed lymph nodes detected by Lymphoseek. Lymphoseek (50 mcg; 0.5 mCi) was injected into patients at least 15 minutes prior to the scheduled surgery, and blue dye was injected shortly prior to initiation of the surgery. Intraoperative lymphatic mapping was performed using a hand-held gamma detection probe followed by excision of lymph nodes identified by Lymphoseek, blue dye, or the surgeon's visual and palpation examination. The resected lymph nodes were evaluated for histopathology.

In Study One, of 179 patients who received Lymphoseek, 94 (53%) had known or suspected breast cancer and 85 (48%) had known or suspected melanoma. The median age was 59 years (range 20 to 90 years) and most (72%) were women.

In Study Two, of 153 patients who received Lymphoseek, 77 (50%) had known or suspected breast cancer and 76 (50%) had known or suspected melanoma. The median age was 61 years (range 26 to 88 years) and most (68%) were women.

Approximately 94% of patients from the two studies underwent preoperative lymphoscintigraphy to help identify nodal basins and to facilitate intraoperative identification of lymph nodes.

Efficacy analyses were based upon comparisons of the number and proportion of resected lymph nodes that contained a lymph node tracer (Lymphoseek and/or blue dye) or neither tracer. Evaluable lymph nodes were resected from 138 Study One patients and 150 Study Two patients who received Lymphoseek at the dose of 0.5 mCi in 50 mcg administered 15 minutes to 15 hours prior to surgery. Table 9 shows the distribution of resected lymph nodes by the presence or absence of a tracer. Most of the resected lymph nodes were identified by either Lymphoseek (LS) or blue dye (BD) or both.

Table 9. Resected Lymph Nodes and Content of Lymphoseek (LS) and/or Blue Dye (BD)

Study	Tumor	Nodes n	BD Present % (95% CI)	LS Present % (95% CI)	Only BD Present % (95% CI)	Only LS Present % (95% CI)	Neither BD nor LS Present % (95% CI)
One	M	155	64% (56% , 71%)	94% (89% , 97%)	1% (0 , 4%)	30% (23% , 38%)	6% (3% , 11%)
	B	154	70% (62% , 77%)	95% (90% , 98%)	5% (2% , 9%)	29% (22% , 37%)	1% (0 , 4%)
Two	M	196	59% (51% , 66%)	100% (98% , 100%)	0 (0 , 2%)	41% (34% , 49%)	0 (0 , 2%)
	B	180	62% (55% , 69%)	100% (98% , 100%)	0 (0 , 2%)	38% (31% , 45%)	0 (0 , 2%)

M = melanoma; B = breast cancer; The percents may not add to 100% due to rounding.
95% Confidence Intervals are based on Exact Binomial and represent the spread in the individual estimates.

Among all patients in both studies, Lymphoseek localized an average of 2.4 lymph nodes per patient (range 1 to 11) when the mapping procedure was performed 15 minutes to 15 hours following injection of the drug.

16 HOW SUPPLIED/STORAGE AND HANDLING

The Kit for the Preparation of Lymphoseek (technetium Tc 99m tilmanocept) Injection includes:

- Five vials of Tilmanocept Powder, 250 mcg NDC 52579-1695-1
- Five vials of DILUENT for Lymphoseek NDC 52579-1649-1
- Prescribing information
- Five labels for shields
- Twenty-five labels for product vials and individual syringes

Storage

Store Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) Injection in the original packaging at USP controlled room temperature 20°C - 25°C (68°F - 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Store reconstituted Lymphoseek in radiation shielding at room temperature.

Use reconstituted Lymphoseek within 6 hours of its preparation.

Handling

This Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) Injection is approved for distribution to persons licensed by the U.S. Nuclear Regulatory Commission to use byproduct material identified in 10 CFR 35.200 or under an equivalent license issued by an Agreement State.

17 PATIENT COUNSELING INFORMATION

Instruct patients to inform their physician or healthcare provider if they:

- are pregnant or breast feeding, or
- have had prior reactions to dextran, dextran containing compounds, or tilmanocept, or
- are sensitive to a technetium-containing contrast agents.

Inform nursing mothers to express and discard milk for at least four hours following administration of Lymphoseek (technetium Tc 99m tilmanocept) Injection.

Kit for the preparation of Lymphoseek (technetium Tc 99m tilmanocept) Injection is distributed by Navidea Biopharmaceuticals, Inc., Dublin, OH 43017

Lymphoseek is a registered trademark of Navidea Biopharmaceuticals, Inc.

Revision date: 02/2013

6-D001712C

NDC 52579-1695-1
Tilmanocept Powder for
Preparation of Lymphoseek
(technetium Tc 99m tilmanocept) Injection
250 mcg Tilmanocept per Vial

LOT:

EXP:

6-L001642D

Administer only after radiolabeling with technetium Tc 99m.
See insert for content, preparation and administration instructions.
Store at controlled room temperature, 20°C – 25°C (68°F – 77°F).

Distributed by: Navidea Biopharmaceuticals, Inc.
Dublin, OH 43017

Sterile
Rx Only

FPO
DATA
MATRIX

NDC 52579-1649-1

Rx Only

23001105-N02

DILUENT for Lymphoseek

For diluting radiolabeled Lymphoseek
only

Not for direct administration

See package insert for preparation and
administration instructions.

Single Use Vial - Discard unused portion.

Contents: 4.5 mL non-pyrogenic, aqueous
solution of 0.04% w/v Potassium Phosphate,
0.11% w/v Sodium Phosphate (Heptahydrate),
0.50% w/v Sodium Chloride, and 0.4C% w/v
Phenol.

Store at controlled room temperature, 20°C -
25°C (68°F - 77°F), in original package;
excursions permitted to 15°C to 30°C (59°F
to 86°F.)

Distributed by:
Navidea Biopharmaceuticals, Inc.
Dublin, OH 43017

Lot No.
Exp. Date



NDC: 52579-1600-5

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection

250 mcg Tilmanocept per Vial

Each sterile, non-pyrogenic, lyophilized Tilmanocept Powder vial contains:

Tilmanocept	250 mcg
Trehalose, Dihydrate	20 mg
Glycine	0.5 mg
Sodium Ascorbate	0.5 mg
Sulfurous Chloride, Dihydrate	0.075 mg

The Tilmanocept Powder vials are sealed under nitrogen at the time of manufacture, and contain no preservatives.

DILUENT for Lymphoseek contains:
 Each vial contains 4.5 mL sterile, non-pyrogenic, aqueous solution of:

Potassium Phosphate	0.04% w/v
Sodium Phosphate-7H ₂ O	0.11% w/v
Sodium Chloride	0.50% w/v
Phenol	0.40% w/v

Rx Only
 For Customer Service call: 1-800-476-5270
 Web site: www.lymphoseek.com

Navidea 7-0901561E

Lot:
Exp:



Kit for Preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection
 All parts, Radionuclide and/or diluent used by persons who are certified by state, federal, or local health and/or radiation authorities and whose activities and training have been approved by the appropriate governmental agency authorized to license the use of nuclear.

NDC: 52579-1600-5

Kit for the preparation of Lymphoseek® (technetium Tc 99m tilmanocept) Injection

250 mcg Tilmanocept per Vial


- Contents:**
- Five vials of Tilmanocept Powder, 250 mcg NDC 52579-1695-1
 - Five vials of DILUENT for Lymphoseek NDC 52579-1649-1
 - Prescribing Information
 - Five Radioassay Information shield labels
 - Twenty-five labels for product vials and individual syringes

Use within 6 hours after reconstitution.
 Store at controlled room temperature, 20°C-25°C (68°F-77°F), in original package; excursions permitted to 15°C to 30°C (59°F to 86°F).


Distributed by Navidea Biopharmaceuticals Inc.
 Dublin, OH 43017

Rx Only

Storage Conditions:
 Store at controlled room temperature, 20°C-25°C (68°F-77°F), in original package; excursions permitted to 15°C to 30°C (59°F to 86°F).

 CAUTION RADIOACTIVE MATERIAL Rx Only	_____	Lymphoseek[®]
	MBq (mCi) Tc 99m/mL	(technetium Tc 99m tilmanocept) Injection
	_____	Store at controlled room temperature, 20°C – 25°C (68°F – 77°F).
	Volume (mL)	

_____	Time/Date	
_____	Expiration Time	Lot No. 6-L001694B

 CAUTION RADIOACTIVE MATERIAL Rx Only	Shield Label	
	Lymphoseek (technetium Tc 99m tilmanocept) Injection	
	_____	Contents:
	MBq (mCi) Tc 99m/mL	Techetium Tc 99m pertechnetate, sodium Tilmanocept 50 mcg Trehalose, Dihydrate 4 mg Glycine 0.1 mg Sodium Ascorbate 0.1 mg Stannous Chloride, Dihydrate 0.015 mg Buffered Saline with phenol q.s.
	_____	Store at controlled room temperature, 20°C - 25°C(68°F - 77°F). Discard Unused Portion
	Volume (mL)	

_____	Time/Date	
_____	Expiration Time	Lot No.
		6-L001592D

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHAW T CHEN
03/13/2013