Lymphoseek (Tc 99m Tilmanocept)

Lymphoseek is a radioactive diagnostic agent indicated with or without scintigraphic imaging for:

- Lymphatic mapping using a handheld gamma counter to locate lymph nodes draining a primary tumor site in adult and pediatric patients age one month and older with solid tumors for which this procedure is a component of intraoperative management

- Guiding sentinel lymph node biopsy using a handheld gamma counter in patients with clinically node negative squamous cell carcinoma of the oral cavity, breast cancer or melanoma

- Lymphoseek is approved for subcutaneous, intradermal, subareolar, or peritumoral use.

Dosage and Administration

- Lymphoseek is supplied as a Kit and must be prepared by radiolabeling with Tc 99m and diluting with sterile 0.9% sodium chloride injection prior to use

- Aseptic technique must be used in drug preparation.

- radiation safety precautions must be observed during Lymphoseek preparation and handling.

- One must determine the total injection volume and number of sites to be injected for each patient before preparing Lymphoseek

- The recommended dose of Lymphoseek is 18.5 MBq (0.5 mCi) administered at least 15 minutes before initiating intraoperative lymphatic mapping or sentinel node biopsy procedures.

- One must 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.

Dosage Forms and Strengths

- The Kit for preparation of Lymphoseek contains five Tilmanocept Powder vials each containing 250 μg Tilmanocept, and is packaged either with five diluent vials each containing 4.5 mL of sterile buffered saline with phenol.

- After radiolabeling with 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 for injection

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 immediately available

Adverse Reactions

The most common adverse reactions (incidence < 1%) are injection site irritation and/ or pain

Use In Specific Populations

Lactation. To decrease radiation exposure to the breastfed child, advise a lactating woman to pump and discard breast milk after the administration of Lymphoseek for 24 hours.

Pregnancy

There are no available data on Lymphoseek use in pregnant women. Additionally, animal reproduction studies have not been conducted with technetium Tc 99m Tilmanocept. However, all radiopharmaceuticals have a potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. If considering Lymphoseek administration to a pregnant woman, inform the patient about the potential for adverse pregnancy outcomes based on the radiation dose from the drug and the gestational timing of exposure.
Lymphoseek may be administered to a patient as a single injection or as multiple

injections. The recommended total injection volume for each patient is

- 0.1 mL administered in a single syringe or
- 0.5 mL administered in multiple syringes (0.1 mL to 0.25 mL each) or
- mL administered in multiple syringes (0.2 mL to 0.5 mL each).

Radiolabeling Procedure

1. Inspect the Tilmanocept Powder vial for any damage. Do not use if vial integrity appears compromised. Do not vent the Tilmanocept Powder vial prior to or during radiolabeling.

2. Use Technetium Tc 99m pertechnetate, sodium injection solution from a technetium Tc 99m generator within 8 hours of its elution.

3. 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).

4. Assay the syringe for technetium Tc 99m activity in a dose calibrator

5. Record 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.

6. Aseptically add Technetium Tc 99m pertechnetate, sodium injection solution to the Tilmanocept Powder vial. Without withdrawing the needle, remove an equal volume of headspace gas. Do not vent.

7. Remove the needle, gently shake the vial to mix the contents, and then let it stand at room temperature for at least 15 minutes.

8. Aseptically add the supplied DILUENT for Lymphoseek or sterile 0.9% sodium chloride injection 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.

9. Each Lymphoseek vial, once radiolabeled and reconstituted, would contain sufficient amount to provide doses for up to four patients when prepared according to the instructions.

10. Store the radiolabeled Lymphoseek in radiation shielding at room temperature.

11. Use the radiolabeled Lymphoseek within 6 hours of preparation. Discard the unused radiolabeled Lymphoseek.

Quality Control of Radiolabeled Solution

1. Assay the reconstituted vial for total radioactivity using a dose calibrator.

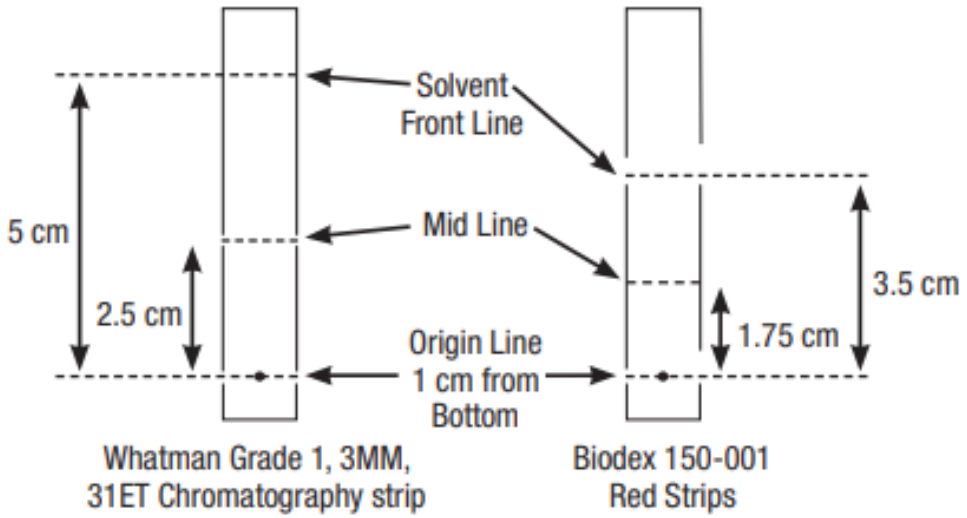
2. Record the technetium Tc 99m activity concentration, total volume, assay time and date, expiration time, and lot number on the shield label supplied with the Kit. Affix the label to the shield.

3. Determine the radiochemical purity of the radiolabeled product. Do not use if the radiochemical purity is less than 90%.

Determination of Radiochemical Purity of Radiolabeled Lymphoseek

1. 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).

d. 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).

e. Calculate the percent radiochemical purity (% RCP) as follows:

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

f. Do not use the Lymphoseek if the radiochemical purity is less than 90%.

Mapping and Sentinel Lymph Node Biopsy Following Injection of Lymphoseek

- Lymphoscintigraphy may be used to assist in planning the lymph node mapping procedures. In clinical studies, preoperative scintigraphic imaging was performed using planar imaging techniques and/or SPECT/CT to establish a map of nodal basins and to facilitate intraoperative identification of lymph nodes. Imaging was performed as early as immediately after injection and up to 21

- Use a handheld 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. The three sigma threshold (background radioactivity counts plus three times the square root of the mean background count) may be used as an estimate of the threshold for positive localization of Lymphoseek, as exemplified in Table 2.

Table 2. Examples of Three Sigma Threshold Values

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 mapping and sentinel node biopsy. Intraoperative lymphatic mapping and sentinel node biopsy using gamma detection of Lymphoseek within lymph nodes should be initiated no sooner than 15 minutes following injection. In clinical studies of breast cancer and melanoma, patients also received a concomitant blue dye tracer for comparative detection of lymph nodes. While most lymph nodes were detected with Lymphoseek, some were detected only with the blue dye tracer or only with palpation

Internal Radiation Dosimetry

• The radiation doses to organs and tissues of an adult patient weighing 70 kg given 18.5 MBq (0.5 mCi) of Lymphoseek are shown in Table 3. For pediatric patients, effective dose equivalent ranged from 355 microSv to 1,232 microSv.

Table 3. Estimated Absorbed Radiation Dose from 18.5 MBq (0.5 mCi) Lymphoseek in Adult Patients with Breast Cancer and Melanoma

Target Organ	Breast Cancer[a] mGy (rad)	Melanoma[b] mGy (rad)
brain	0.003 (0.0003)	0.0927 (0.0093)
breast (injection site)	1.659 (0.1659)	0.7903 (0.079)
gall bladder wall	0.0349 (0.0035)	0.0712 (0.0071)
lower large intestine wall	0.0123 (0.0012)	0.057 (0.0057)
small intestine	0.0101 (0.001)	0.0594 (0.0059)
stomach	0.0184 (0.0018)	0.0562 (0.0056)
upper large intestine wall	0.0125 (0.0012)	0.0582 (0.0058)
kidney	0.1863 (0.0186)	0.278 (0.0278)
liver	0.0324 (0.0032)	0.0929 (0.0093)
lungs	0.0374 (0.0037)	0.0599 (0.006)
muscle	0.0092 (0.0009)	0.0451 (0.0045)
ovaries	0.187 (0.0187)	0.2991 (0.0299)
red marrow	0.0127 (0.0013)	0.0507 (0.0051)
bone	0.0177 (0.0018)	0.0878 (0.0088)
spleen	0.0285 (0.0029)	0.0598 (0.006)
testes	0.0501 (0.005)	0.1043 (0.0104)
thymus	0.1168 (0.0117)	0.0577 (0.0058)
thyroid	0.088 (0.0088)	0.0464 (0.0046)
urinary bladder	0.0586 (0.0059)	0.1401 (0.014)
total body	0.0195 (0.0019)	0.0547 (0.0055)
Effective Dose Equivalent **males** **females**	**microSv** 296 330.2	**microSv** 202.4 251.1

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.

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

Pediatric Use

The safety and effectiveness of Lymphoseek have been established in pediatric patients 1 month of age and older. Use of Lymphoseek for this population is supported by evidence from adequate and well-controlled studies in adults with additional safety and diagnostic data from an open-label, single-arm trial in 23 pediatric patients with either melanoma, rhabdomyosarcoma, or other solid tumors who received Lymphoseek (18.5 MBq and 50 mcg) and underwent intraoperative lymphatic mapping, with or without additional use of preoperative scintigraphic imaging and/or blue. Review of the clinical data, including evaluation of the frequency of adverse reactions and localization of lymph nodes, has not identified differences in safety or efficacy between pediatric patients and older patients.

Geriatric Use

Of the 553 adult patients enrolled in clinical studies of breast cancer, melanoma, and squamous cell carcinoma (SCC) of oral cavity, skin, and lip, 179 (32%) 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 adult patients (18 to 65 years of age).11

Chemical Characteristics of Tilmanocept

The active ingredient in Lymphoseek, a radioactive diagnostic agent, is technetium Tc 99m Tilmanocept. Technetium Tc 99m binds to the diethylenetriaminepentaacetic acid (DTPA) moieties of the Tilmanocept molecule.

Mechanism of Action

Lymphoseek is a radioactive diagnostic agent that It accumulates in lymphatic tissue and selectively binds to mannose binding receptors (CD206) located on the surface of macrophages and dendritic cells. Tc 99m 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 Tc 99m.

Pharmacodynamics

1. In *in vitro* studies, technetium Tc 99m Tilmanocept exhibited binding to human mannose binding receptors with a high affinity.

2. In clinical studies, technetium Tc 99m Tilmanocept has been detectable in lymph nodes within 10 minutes and up to 30 hours after injection.

3. 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 1.8 to 3.1 hr.

4. 4. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

1. Studies to assess the carcinogenicity potential of Tilmanocept have not been conducted.

2. Tilmanocept was not mutagenic in vitro in the Ames bacterial mutation assay and in the in vitro mouse lymphoma test

3. Studies on reproductive fertility have not been conducted.

Overview of Clinical Studies

The efficacy and safety of Lymphoseek were assessed in three open-label, multicenter, single arm trials of adult patients with melanoma, breast cancer, or squamous cell carcinoma (SCC) of the oral cavity, skin, and lip and one open-label, multicenter, single arm trial of pediatric patients with melanoma, rhabdomyosarcoma, or other solid tumor. Prior to the lymph node mapping and sentinel lymph node biopsy procedures, patients had no known regional nodal or metastatic disease by standard clinical staging criteria.

An analysis of the four studies was performed to evaluate the agreement in location of lymph nodes identified by scintigraphic imaging and the handheld gamma counter. At least one scintigraphic “hot spot” was identified in 95% of patients imaged; the percentages were similar across tumor types and age groups. Overall, in the adult

patients, there was 84% agreement on a nodal level (when considering all missing observations as disagreement, as worst-case scenario) between the location of preoperative scintigraphic imaging hot spots and the intraoperative lymph node findings (Table 7)

Table 7. Location Agreement between Scintigraphic Imaging and Gamma Counter Findings in Adult Patients

	Melanoma	Breast Cancer	Head and Neck Cancer	Overall Results
Agreement of Hot Spot and Hot Node Location *	182/206; 88% (83%, 93%)**	116/147; 79% (70%, 88%)**	95/115; 83% (76%, 90%)**	393/468; 84% (81%, 87%)**

In Studies 1 and 2 in adult melanoma and breast cancer, 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 176 Study 1 patients and 152 Study 2 patients who received Lymphoseek at the dose of 0.5 to 2 mCi in 50 mcg administered 15 minutes to 30 hours prior to surgery. Table 8 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. Significantly more resected lymph nodes were identified by Lymphoseek in comparison to blue dye.

Table 8. Resected Lymph Nodes and Content of Lymphoseek (LS) and/or Blue Dye (BD) from Studies in Adult Breast Cancer and Melanoma

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	Melanoma	187	65%	93% (88% , 96%)	2% (0 , 5%)	29% (23% , 37%)	6% (3% , 10%)
	Breast Cancer	192	70% (63% , 77%)	89% (83% , 93%)	7% (4% , 12%)	26% (20% , 32%)	4% (2% , 8%)
Two	Melanoma	198	59% (51% , 66%)	99% (97% , 100%)	0 (0 , 2%)	41% (34% , 48%)	1% (0 , 3%)
	Breast Cancer	181	62% (55% , 70%)	100% (98% , 100%)	0 (0 , 2%)	38% (30% , 45%)	0 (0 , 2%)