

Lymphatic Mapping with A New Drug Lymphoseek (Technetium TC 99m Tilmanocept): A Receptor-Targeted Radiopharmaceutical

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ABSTRACT

Lymphoseek is a new radiopharmaceutical. It is used in lymphatic mapping procedure to assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer and melanoma. Lymphoseek was approved by the US Food and drug administration on 2013. Lymphoseek marketed by Nevidea Biopharmaceuticals, Inc. Lymphoseek binds to the mannose-binding protein (MBP) receptor (CD206) located on the surface of human dendritic cells and macrophages. The macromolecule of lymphoseek comprises a dextran backbone (10-kilodalton) to which multiple units of mannose and DTPA (diethylene triamine pentaacetic acid) are synthetically attached. The mannose act as a substrate for the CD206 receptor and DTPA serves as a chelating agent for labeling with Tc-99m. The injectable radioactivity dose of lymphoseek is 18.5 MBq and reported adverse reactions are pain and irritation in injection site. In clinical trials, 2.4 lymph nodes per patient have been found when the mapping procedure was performed 15 minutes to 15 hours with 50 mcg lymphoseek in injectable route.

Keywords: Lymphatic mapping, Radiopharmaceuticals, Lymphoseek, DTPA, Breast cancer.

INTRODUCTION

Lymph nodes are small round organs of the immune system, distributed widely throughout the body including in the neck, underarms, chest, abdomen, and groin. Lymph nodes are connected to lymph vessels. A clear fluid called lymph flows through lymph vessels and lymph nodes. Lymph nodes contain B-Lymphocytes, T-Lymphocytes and other types of immune system cells. Lymph nodes act as filters or traps for foreign particles and are important in the proper functioning of the immune system. They are packed tightly with the white blood cells called lymphocytes and macrophages¹.

Lymph nodes are also important in helping to determine whether cancer cells have developed the ability to spread to other parts of the body. Cancers of the lymph nodes are called lymphomas. There are ranges of lymphomas that differ in the specific cell type affected. They are lymphoblastic lymphoma, burkitts lymphoma, hodgkins lymphoma. Lymph nodes can be diagnosed by biopsy² whenever they are inflamed.

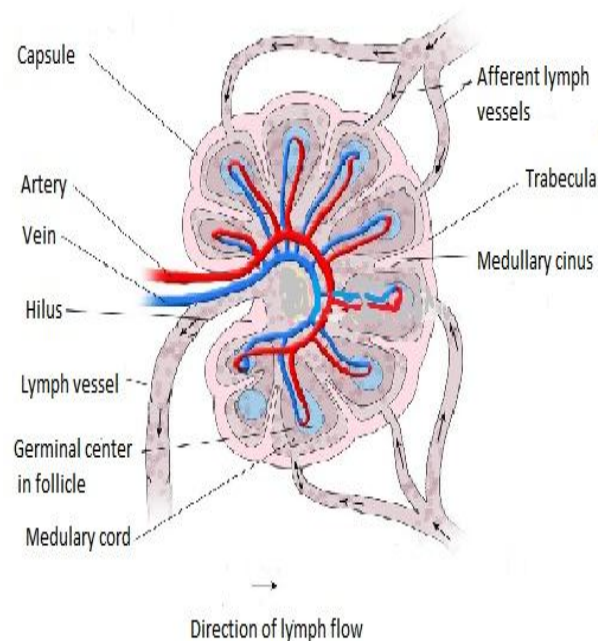


Fig. 1: Anatomy of lymph node (Source: Medical look.com)

Lymphatic mapping is a procedure in which lymph nodes that may contain tumor metastases are identified and biopsied to determine if cancer has spread beyond the primary tumor. It consists of Intraoperative Lymphatic Mapping (ILM) often accompanied by lymphoscintigraphy³. Lymphoscintigraphy is an imaging procedure routinely performed pre-operatively to provide guidance on the location of lymph nodes to be biopsied. ILM is a surgical procedure in which lymph nodes draining the area around a tumor are identified and biopsied to determine if cancer has spread to the lymph nodes. These nodes, commonly referred to as "Sentinel Lymph Nodes^{4, 5}," are removed and analyzed for the presence of malignant cells. Accurate staging of lymph nodes is critical, as it guides therapy decisions and determines patient prognosis and risk of recurrence. According to the American Cancer Society, approximately 232,000 new cases of breast cancer and 77,000 new cases of melanoma^{6, 7} are expected to be diagnosed in the United States in 2013.

There are various procedures^{8, 9} entailing the sentinel node detection:

- Preoperative planar lymphoscintigraphy
- Preoperative planar lymphoscintigraphy in conjunction with SPECT/CT [single photon emission CT (SPECT) with a low-dose CT]^{10,11}
- Intraoperative visual blue dye detection
- Intraoperative fluorescence detection (fluorescence image-guided surgery)
- Intraoperative gamma probe/Geiger meter-detection
- Postoperative scintigraphy of main specimen with planar acquisition

Advantages of lymph node mapping¹²⁻¹⁵

1. It can guide the surgeon to the appropriate therapy
2. Various aspect of cancer dissemination can be studied by using sentinel node biopsy such as cancer immunology, tumor biology pertaining to metastatic capacity
3. Reducing the risk of lymph edema
4. The main uses are in breast cancer and malignant melanoma surgery
5. It has been used in other tumor types such as colon cancer, penile cancer, urinary bladder cancer, prostate cancer, testicular cancer and renal cell cancer
6. Fewer side effects from surgery
7. The lymph system is left intact and is better able to transport fluid and fight infection.

8. Fewer risks of impairment of arm and shoulder movements.
9. With only a small amount of tissue being removed, it can be studied much more exhaustively in the laboratory for the presence of cancer.
10. Significant reduction in post-mastectomy pain.

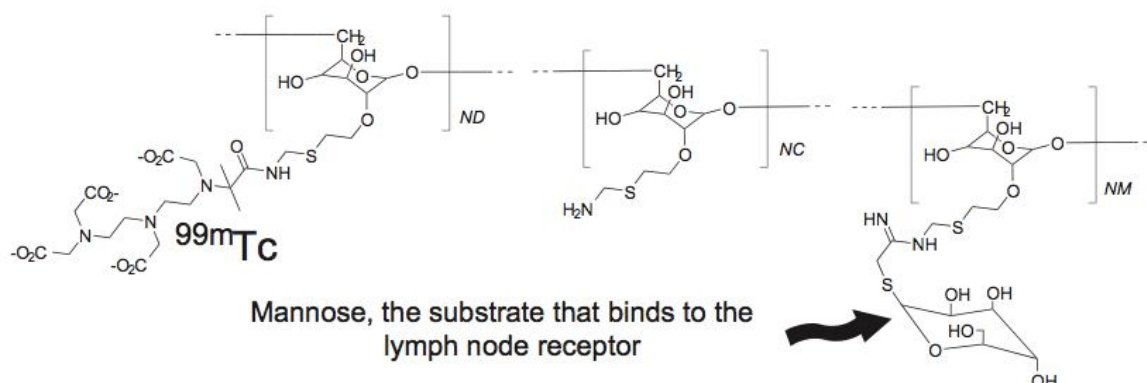
LYMPHOSEEK (TECHNETIUM Tc 99M TILMANOCEPT)

Lymphoseek was approved by the US Food and Drug Administration on 2013. Lymphoseek marketed by Navidea Biopharmaceuticals, Inc. (NYSE MKT: NAVB) is a biopharmaceutical company focused on the development and commercialization of precision diagnostics and radiopharmaceutical agents. Lymphoseek is a receptor targeted radiopharmaceutical¹⁶ use in lymphatic mapping procedures to assists in the localization of lymph nodes draining a primary tumor in patients with breast cancer and melanoma. Lymphoseek is designed to identify these lymph nodes which have the highest probability of harboring cancer and it can guide to the surgeon to the appropriate therapy¹⁷.

Tc 99m tilmanocept¹⁸ is the active ingredient in lymphoseek. For the preparation of this active ingredients technetium Tc 99m pertechnetate and sodium injection is added to the tilmanocept powder vial. Technetium Tc 99m binds to the DTPA (diethylene triamine pentaacetic acid) moieties of the tilmanocept molecule. Lymphoseek kit is distributed by Novida Biopharmaceutical, Inc. The kit contains-

- 1) Tilmanocept powder vials- It contains non-radioactive ingredients needed to produce technetium Tc 99m tilmanocept. It also contains a sterile, non-pyrogenic, white to off white powder that consist of a mixture of 250 mcg tilmanocept, 20 mg trehalose dehydrate, 0.5 mg glycine, 0.5 mg sodium ascorbate and 0.075 mg stannous chloride dehydrate.
- 2) Diluent for lymphoseek- It 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 P^H is 6.8-7.2

CHEMICAL STRUCTURE

Fig. 2: Molecular structure of lymphoseek¹⁹

The chemical name of lymphoseek [18] is technetium-^{99m}Tc, dextran 3-[(2-aminoethyl)thio]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.

Table 1: Chemical properties of lymphoseek¹⁸

Properties	
Molecular formula	[C ₆ H ₁₀ O ₅] _n . (C ₁₉ H ₂₈ N ₄ O ₉ S _{99m} Tc) _b . (C ₁₃ H ₂₄ N ₂ O ₅ S ₂) _c . (C ₅ H ₁₁ NS) _a
Trademark	Lymphoseek [®]
Sponsor	Neoprobe Corporation
Average molecular weight	15,281 to 23,454 g/mol

The chemical structure¹⁷ contains-

- 1) 3-8 conjugated DTPA molecules (b)
- 2) 12-20 conjugated mannose molecules (c)
- 3) 0-17 amine side chains (a)

MECHANISM OF ACTION: LYMPHOSEEK

A radioactive diagnostic agent lymphoseek binds to the mannose-binding protein (MBP) receptor (CD206) located on the surface of human dendritic cells and macrophages. The MBP receptor belongs to a class of collectins in the C-type lectin super family and binds to mannose-terminated glycoproteins. The receptor is found in high densities in lung macrophages, liver nonparenchymal and parenchymal cells, and lymphoid tissue or lymph nodes¹⁸.

The macromolecule of lymphoseek comprises a dextran backbone (10-kilodalton) to which multiple units of mannose and DTPA are

synthetically attached. The mannose acts as a substrate for the CD206 receptor and the diethylenetriamine pentaacetic acid (DTPA) serves as a chelating agent for labeling with Tc-^{99m}. The size of lymphoseek is small (7.1nm²) and it diffuses into lymphatic system easily and promotes rapid and reliable injection site clearance²⁰.

LYMPHOSEEK: ROUTE OF ADMINISTRATION AND LYMPHATIC MAPPING PROCEDURE BY INJECTION METHOD IN BREAST CANCER AND MELANOMA PATIENTS

In breast cancer patients' lymphoseek injected through intradrenal²¹, subcutaneous, subareolar, peritumoral routes. In melanoma patients lymphoseek injected through intradermal, subcutaneous routes.

Lymphoseek is injected¹⁸ at the site of primary tumor at least 15 minutes prior to intraoperative lymphatic mapping. Injected agents naturally follow the drainage path of the tumor to the nearest lymph nodes, called sentinel lymph nodes. These agents help to identify the correct SLNs in the vicinity of the tumor. The mapping procedure should not be continued more than 15 hours after lymphoseek injection.

Use a hand-held gamma counter to identify nodes that concentrated the injected radioactivity. Use the three sigma threshold as an estimate of the threshold for positive localization of lymphoseek. In clinical studies, patients also received a concomitant blue dye tracer to enhance the ability to detect lymph

nodes. Avoid injections into biopsy wound areas that show evidence of edema or inflammation.

- 1) If the SLNs show sign of malignancy, the surgeon removes additional regional lymph nodes.
- 2) If SLNs show no sign of malignancy, no additional lymph nodes are removed.

IMPORTANT SAFETY INFORMATION

No patients experienced serious adverse reactions during clinical trials. Injection site irritation and pain were reported adverse reactions. Serious hypersensitivity reactions have been associated with dextran and modified forms of dextran (such as iron dextran drugs).

Prior to the administration of Lymphoseek, patients should be asked about previous hypersensitivity reactions to drugs, in particular dextran and modified forms of dextran. Resuscitation equipment and trained personnel should be available at the time of Lymphoseek administration²².

RECOMMENDED DOSE

The radioactivity dose of lymphoseek is 18.5 MBq and mass dose¹⁸ is 50 mcg, administered at least 15 minutes prior to intraoperative lymphatic mapping. The recommended total injection volume for each patient is

- 1) 0.1 mL administered in a single syringe
- 2) 0.5 mL administered in a single syringe or in multiple syringes (0.1 mL to 0.25 mL each) or
- 3) 1 mL administered in multiple syringes (0.2 mL to 0.5 mL each)

PHARMACOKINETICS

In a clinical trial, eleven patients with breast cancer participated. Five patients injected 1.0 nmol of (99m) Tc-labelled lymphoseek intradermally. SLN mapping was performed on four subjects within 19 to 27 h. Six patients received an intradermal administration of [(99m)Tc]sulfur colloid (TcSc). SLN mapping was performed on five subjects within 18 to 26h. When an intradermal injection is employed, Lymphoseek demonstrated faster injection site clearance than unfiltered [(99m)Tc]sulfur colloid and persistent SLN accumulation for at least 24 h. Lymphoseek exhibited a significantly ($P < .001$) faster injection site clearance than TcSc. The mean Lymphoseek clearance half-time was 2.18 ± 1.09 h compared to 57.4 ± 92.8 h for TcSc. The mean sentinel lymph node uptake of Lymphoseek ($1.5 \pm 1.7\%$) and TcSc ($3.5 \pm 3.1\%$) was statistically equivalent ($P = .213$)²³.

STORAGE, SUPPLIED AND HANDLING¹⁸

Storage- Lymphoseek injection should be stored in controlled room temperature 22°C-25°C. Use reconstituted Lymphoseek within 6 hours of its preparation.

Supplied

The Lymphoseek (technetium Tc 99m tilmanocept) Injection supplied in five vials of Tilmanocept Powder, 250 mcg NDC 52579-1695-1, five vials of DILUENT for Lymphoseek NDC 52579-1649-1, five labels for shields and twenty-five labels for product vials and individual syringes. All the vials should be supplied with proper prescribing information.

Handling

For handling lymphoseek (technetium Tc 99m tilmanocept) Injection license is necessary from the U.S. Nuclear Regulatory Commission.

CLINICAL TRIALS

A single arm, multicenter, two open-label studies were performed in clinical trials of lymphoseek in patients with melanoma or breast cancer. 50 mcg lymphoseek was injected into patients at least 15 minutes prior to the scheduled surgery and blue dye²⁴ was injected shortly prior to irritation of the surgery.

153 patients were allocated to receive lymphoseek in study 1. It has been found that 94 (53%) were suspected breast cancer and 85 (48%) were suspected melanoma.

179 patients were allocated to receive lymphoseek in study 2. It has been found that 77 (50%) were suspected breast cancer and 76 (50%) were suspected melanoma.

Lymphoseek safety and efficacy were based upon comparisons of the number and proportion of tracer lymph nodes (Lymphoseek and/or blue dye) or neither tracer. 2.4 lymph nodes per patient has been found in both studies when the mapping procedure was performed 15 minutes to 15 hours with 50 mcg lymphoseek in injected route¹⁸.

LYMPHOSEEK MARKET OPPORTUNITY

Lymphoseek is the first radiopharmaceutical tracing agent¹⁶ for lymphatic mapping and gain market share quickly from the currently used off label agents due to the reduced costs to patients and health care providers from probable insurance reimbursement. The total worldwide market potential for lymphoseek is \$450 million USD. Approximately 43% of the opportunity is in

the US, 14% in EU, and the rest worldwide. Lymphoseek will be priced at or above sulphur colloid estimated by Navidea Biopharmaceuticals. There is a high degree of correlation between market opportunity and prevalence of each disease. Lymphoseek is used for lymphatic mapping²⁵ in patients with breast cancer, colon cancer, and prostate cancer etc²⁰.

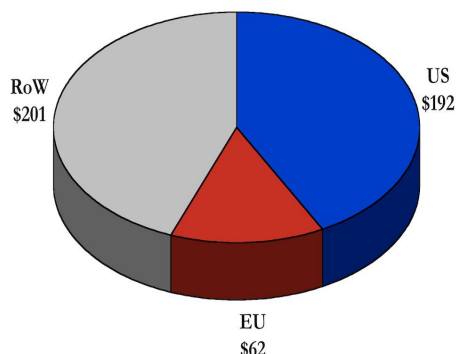


Fig. 3: Lymphoseek Worldwide Market Opportunity (Source: Company Reports & Life Sci Advisors)

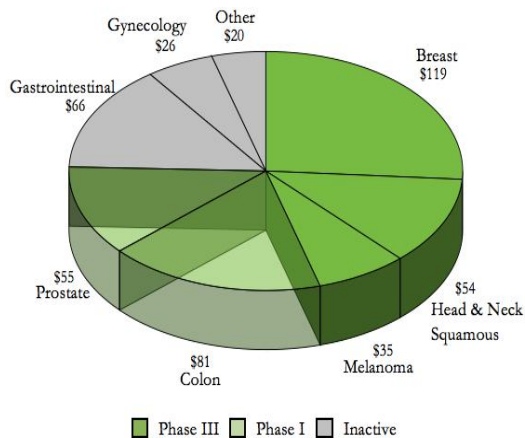


Fig. 4: Lymphoseek Worldwide Market Opportunity by Indication (Source: Company Reports & Life Sci Advisors)

SPECIAL POPULATIONS WITH SPECIAL CARE

Lymphoseek is a radiopharmaceutical. It crosses the placenta and cause fetal harm. The fetal harm depends on the lymphoseek dose and the stage of fetal development. Lymphoseek should be given to a pregnant woman only if clearly needed. Exercise caution when administering lymphoseek to a nursing mother.

Safety and effectiveness of lymphoseek in pediatric patients have not been established¹⁸.

CONCLUSION

Lymphoseek is a new receptor-targeted radio pharmaceutical and used in lymphatic mapping in patients with breast cancer and melanoma. In pharmacokinetic study, it has been found that the molecular receptor-binding agent lymphoseek demonstrated faster injection site clearance and equivalent primary sentinel node uptake and No patients experienced serious adverse reactions during clinical trials.

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