

## Clinical Summary

### Clinical Problem

In the United States, in 2016, there will be approximately 373,970 new cases of breast cancer, melanoma, and head and neck cancers of the oral cavity (Table 1). Accurate staging at diagnosis in each of these diseases is critical to guiding therapy and is a strong determinant of long-term prognosis. Five-year survival rates among newly diagnosed patients are uniformly lower in patients with regional lymphatic spread of disease than in those with localized disease.<sup>1</sup>

**Table 1: Incidence and 5-year Survival of New Cancer Cases in the United States in 2016<sup>1</sup>**

	Breast cancer	Melanoma	Oral cavity*
New cases in 2016	249,260	76,380	48,330
5-year survival			
Localized disease	99%	98%	83%
Regional disease	85%	63%	62%

\*Also includes pharynx.

<sup>1</sup> American Cancer Society: Cancer Facts & Figures 2016 and Cancer Statistics Center. <http://cancerstatisticscenter.cancer.org>. Accessed March 28, 2016

Sentinel lymph node biopsy has been recognized as the standard of care in many patients with breast cancer and melanoma and is playing an increasingly larger role in the assessment of patients with head & neck cancers of the oral cavity. Commonly performed with blue dye and/or radiotracers, sentinel lymph node biopsy can help to assist in the localization of lymph nodes draining a primary tumor site and typically consists of imaging (lymphoscintigraphy) and/or intra-operative lymphatic mapping (ILM) using a gamma detection device.<sup>1-4</sup>

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By surgically removing and examining tumor-draining lymph nodes, doctors can sometimes determine if a cancer has spread. In breast cancer, sentinel lymph node biopsy is recommended for patients with early stage breast cancer (i.e. T1 or T2 tumors  $\leq 50$  mm in greatest diameter) and in select cases of ductal carcinoma in situ.<sup>2, 3</sup> In melanoma, sentinel lymph node biopsy is recommended for patients with intermediate-thickness melanoma (1-4 mm Breslow thickness) and may be recommended for patients with thick melanomas (T4 or  $>4$  mm) to assess the extent of disease and to facilitate regional control.<sup>4</sup> In patients with squamous cell carcinoma of the oral cavity, sentinel lymph node biopsy is recommended as an alternative to elective node dissection (END) for patients with early stage (i.e., T1 or T2, N0) oral cavity cancers in centers with expertise in the procedure.<sup>5</sup> Patients with floor-of-mouth tumors are traditionally a more challenging group of patients for sentinel lymph node identification and predictive accuracy because of the shine-through effect, a phenomenon in which radioactivity at the primary site obscures relevant radioactive nodes.<sup>4-9</sup>

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## **Lymphoseek**

**Description / Mechanism of Action:** As the first and only receptor-targeted lymphatic mapping agent, Lymphoseek<sup>®</sup> (technetium Tc 99m tilmanocept) injection has a unique design. It is a novel, soluble, synthetic molecule with a small diameter (7 nanometers) and carries multiple units of mannose, which have a high affinity for the CD206 receptor protein.<sup>10, 11</sup> The CD206 receptor, a molecular marker on the surface of activated macrophages and dendritic cells, is present in high concentration in lymph nodes.<sup>10, 12</sup>

**Indication:** Lymphoseek (technetium Tc 99m tilmanocept) injection 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 patients 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.<sup>10</sup>

**Recommended dose:** The recommended dose 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 initiation of intraoperative lymphatic mapping; complete these procedures within 15 hours after injection. The recommended total injection volume for each patient 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); or 1 mL administered in multiple syringes (0.2 mL to 0.5 mL).<sup>10</sup>

**Mechanism of Action:** Molecular lymphatic mapping with Lymphoseek occurs via a distinct mechanism of action that allows for identification of tumor-draining lymph nodes. The mannose units in tilmanocept have a high affinity for CD206 receptors on the cell surface of macrophages and dendritic cells, which are present in high

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concentrations within lymph nodes.<sup>10, 13</sup> Upon binding, there is rapid (within 10 minutes) uptake of Lymphoseek into lymph nodes followed by internalization of the mannose-receptor complex in macrophages. After Lymphoseek binds to the CD206 receptor, it is taken into macrophages where it persists in stable, non-digesting vesicles. Then, the CD206 receptor recycles to the cell surface allowing for Lymphoseek to accumulate in macrophages over time.<sup>14, 15</sup>

Non-clinical and early-phase clinical studies demonstrated that Lymphoseek exhibited rapid transit from the injection site,<sup>16-21</sup> accumulation in the lymph nodes draining a tumor,<sup>17, 20</sup> and retention in those lymph nodes, with minimal leakage into distal nodes.<sup>20-22</sup>

**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/hour. The drug half-life at the injection site ranged from 1.8 to 3.1 hours.<sup>10</sup>

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.<sup>10</sup>

**Clinical Data Summary:** To date, the safety and efficacy of Lymphoseek has been evaluated in Phase 1 & 2 clinical studies and in three Phase 3 clinical studies. Results of these studies as well as several investigator-initiated studies have been published. (Table 2)

**Table 2. Summary of Lymphoseek Clinical Trial Publications**

Reference	Study Phase	N <sup>1</sup>	Diagnosis
Wallace 2003 <sup>20</sup>	1	12	Breast cancer
Ellner 2003 <sup>18</sup>	1	24	Breast cancer
Wallace 2007 <sup>22</sup>	1	10	Breast cancer
Wallace 2009 <sup>23</sup>	1	11	Breast cancer
Wallace 2007 <sup>21</sup>	1	24	Melanoma
Leong 2011 <sup>24</sup>	2	78	Breast cancer and melanoma
Sondak 2013 <sup>11</sup>	3	154	Melanoma
Wallace 2013 <sup>25</sup>	3	148	Breast cancer
Agrawal 2015 <sup>26</sup>	3	85	Squamous cell head & neck cancer
Marcinow 2013 <sup>27</sup>	3	20	Squamous cell head & neck cancer
Tokin 2012 <sup>28</sup>	3	148	Breast cancer
Baker 2015 <sup>29</sup>	Investigator initiated	199	Breast cancer
Unkart 2015 <sup>30</sup>	Investigator initiated	52	Breast cancer

<sup>1</sup> N indicates total number of subjects evaluated; may include subjects receiving a comparator agent

**Phase 3 Studies in Breast Cancer and Melanoma:** Two open-label, multicenter, single-arm, within-subject active comparator phase 3 studies evaluated the safety and efficacy of Lymphoseek in patients with melanoma or breast cancer and no clinically evident nodal or metastatic disease. (Table 3) Eligible patients were at least 18 years of age, Eastern Cooperative Oncology Group performance status of 0-2, and candidates for surgical intervention.<sup>11, 25</sup> Patients were injected with Lymphoseek 50 mcg (0.5 to 2.0 mCi) from 15 minutes to 30 hours prior to the scheduled surgery; blue dye was injected, as a comparator, shortly prior to the initiation of 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 exam. All resected lymph nodes were sent for histopathology evaluation.<sup>10</sup>

**Table 3. Summary of Lymphoseek Phase 3 Studies<sup>10</sup>**

Study	N	Breast cancer, n (%)	Melanoma, n (%)	Median Age (range)	Percent female
NEO3-05	179	94 (53)	85 (47)	59 (20-90)	72%
NEO3-09	153	77 (50)	76 (50)	61 (26-88)	68%

The diagnostic efficacy of Lymphoseek was determined by comparison of the number and proportion of resected lymph nodes that contained a node tracer (Lymphoseek and/or blue dye) or neither tracer.<sup>10</sup> The criterion for intraoperative identification of lymph nodes draining a tumor were:

- *In vivo* visualization of blue dye in a node and/or its afferent lymphatic channel
- *In vivo* radioactive counts that exceeded the background count plus three times the standard deviation of the background (i.e. 3-sigma rule; corresponding to 99.7% confidence limits)
- Any palpable or enlarged abnormal node <sup>11, 25</sup>

Approximately 91% of patients from the two studies underwent preoperative lymphoscintigraphy to help identify nodal basins and to facilitate intraoperative identification of lymph nodes.<sup>10</sup> An analysis 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 breast cancer or melanoma patients imaged.<sup>31</sup> Over these two studies, 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 4)

**Table 4. Summary of Preoperative Lymphoscintigraphy Results<sup>10, 31</sup>**

	Melanoma	Breast Cancer	Head and Neck Cancer	Overall Results
Patients with Scintigraphic Hot Spot Identified	157/158; 99%	125/139; 90%	77/83; 93%	359/380; 95%
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%)**

\* Denominator equals total number of hot spots and/or hot nodes. Numerator equals the numbers where hot spots and hot nodes agreed in location.

\*\* 95% Confidence Intervals.

Lymphoseek was present in a greater proportion of resected lymph nodes versus blue dye in both diagnostic subpopulations in both studies (Table 5). Lymphoseek was present in 95% (range 89% to 100%) of resected and histopathology confirmed lymph nodes and blue dye was present in 64% (range 59% to 70%) of resected lymph nodes. (Results reported for Lymphoseek were independent of blue dye findings.) Significantly more resected lymph nodes were identified by Lymphoseek in comparison to blue dye. Lymphoseek localized an average of 2 lymph nodes per patient. Frequently more than one node must be detected for diagnostic evaluation.<sup>10</sup>

**Table 5. Summary of Intraoperative Lymphatic Mapping Results<sup>10</sup>**

Resected Lymph Nodes and Content of Lymphoseek and/or Blue Dye (BD) <sup>1</sup> (% , [95% CI])	Study One		Study Two	
	Melanoma (n=187)	Breast Cancer (n=192)	Melanoma (n=198)	Breast Cancer (n=181)
Lymphoseek Present % (95% CI)	93% (88%, 96%)	89% (83%, 93%)	99% (97%, 100%)	100% (98%, 100%)
BD Present % (95% CI)	65% (57%, 72%)	70% (63%, 77%)	59% (51%, 66%)	62% (55%, 70%)
Lymphoseek Only Present % (95% CI)	29% (23%, 37%)	26% (20%, 32%)	41% (34%, 48%)	38% (30%, 45%)

BD Only Present %(95% CI)	2% (0%, 5%)	7% (4%, 12%)	0% (0%, 2%)	0% (0%, 2%)
Neither Present %(95% CI)	6% (3%, 10%)	4% (2%, 8%)	1% (0%, 3%)	0% (0%, 2%)

BD – blue dye; CI – confidence interval

The percentages may not add to 100% due to rounding.

95% Confidence Intervals are based on Exact Binomial and represent the spread in the individual estimates

**Phase 3 Study in Squamous Cell Head & Neck Carcinoma:** Lymphoseek was evaluated in 83 patients with squamous cell carcinoma (T1-T4a, no clinically evident nodal or metastatic disease) of the oral cavity (n=79, including 20 patients with floor of mouth tumors), skin (n=5), and lip (n=1).<sup>10</sup> Diagnostic efficacy was determined by the patient level false negative rate (FNR) of sentinel lymph node detection by Lymphoseek as confirmed by pathologic assessment of lymph nodes removed during a required elective neck dissection. All patients from this study underwent preoperative lymphoscintigraphy to help identify nodal basins and to facilitate intraoperative identification of lymph nodes. (Table 4) At least one scintigraphic “hot spot” was identified in 93% of breast cancer or melanoma patients imaged, and there was 83% agreement on a nodal level.

Intraoperatively, 98% (81/83) of patients had at least one sentinel lymph node identified. Pathology-positive lymph nodes were found in 39 patients, all of whom had squamous cell carcinoma of the oral cavity. Only 2.6% of patients with pathology-positive lymph nodes were not identified by Lymphoseek (per patient FNR = 2.6%).

Lymphoseek also demonstrated a high negative predictive value—98% of patients identified as pathology-negative by Lymphoseek were confirmed as true negative by END.<sup>26, 32</sup>

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Sentinel lymph node biopsy may help determine whether the cancer has spread through the lymphatic system.

Such procedures also may allow for the option of more limited lymph node surgery in patients with sentinel nodes negative for cancer.<sup>26, 32</sup>

**Geriatric Use:** Of the 553 patients enrolled in clinical studies of breast cancer, melanoma, and squamous cell carcinoma of the oral cavity, skin and lip, 179 were age 65 years or older. Review of the clinical data, including evaluation of the frequency of adverse reactions, did not identify differences in safety or efficacy between elderly patients (65 to 90 years) and younger patients (18-65 years).<sup>10</sup>

**Safety Profile:** A total of 553 patients with either breast cancer, melanoma, or squamous cell carcinoma of the oral cavity, skin and lip have received Lymphoseek in open-label, single-arm clinical trials. No patients experienced serious adverse reactions. Injection site irritation (4 patients; 0.7%), and pain (1 patient; 0.2%) were reported.<sup>10</sup> In the post marketing setting, there have been no serious adverse events and less than 0.2% have had any adverse events reported in more than 75,000 injections since May 2013 product launch.<sup>31</sup>

## WARNINGS AND PRECAUTIONS

**Hypersensitivity Reactions:** Lymphoseek may pose a risk of hypersensitivity reactions due to its chemical similarity to dextran. Serious hypersensitivity reactions may 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, patients should be asked about prior hypersensitivity reactions to drugs, especially to dextran and modified forms of dextran. Resuscitation equipment and trained personnel should be immediately available at the time of administration.<sup>10</sup>

**Radiation Risks:** Any radiation-emitting product may increase the risk for cancer, especially in pediatric patients. Adherence to the dose recommendations and safe handling of Lymphoseek is required to minimize the risk for excessive radiation exposure to either patients or health care workers.<sup>10</sup>

**Product Description:** The active ingredient in Lymphoseek is technetium Tc 99m tilmanocept which forms when sodium pertechnetate Tc 99m solution is added to the Tilmanocept Powder vial. Technetium Tc 99m binds to the DTPA moieties of the tilmanocept molecule.<sup>10</sup>

Lymphoseek is supplied as a kit containing the necessary non-radioactive ingredients needed to produce technetium Tc 99m tilmanocept. Each kit contains five sets of two vials: a Tilmanocept Powder vial and a diluent vial. The Tilmanocept Powder vial contains 250 mcg of tilmanocept from which 50 mcg is intended for administration to the patient. The Tilmanocept Powder vial contains a sterile, non-pyrogenic, white to off-white powder that consists of 250 mcg tilmanocept, 20 mg trehalose dehydrate, 0.5 mg glycine, 0.5 mg ascorbate and 0.075 mg stannous chloride dehydrate. The contents of the vial are lyophilized and stored under nitrogen. The diluent vial contains 4.5 mL of sterile buffered saline consisting of 0.04% (w/v) potassium phosphate, 0.11% (w/v)

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sodium phosphate (heptahydrate), 0.50% (w/v) sodium chloride, and 0.40% (w/v) phenol with a pH of 6.8-7.2. It is used to dilute Lymphoseek after the radiolabeling procedures. The amount of diluents used is dependent on the total injection volume and the number of syringes for each patient.<sup>10</sup>

After radiolabeling with technetium Tc 99m, the constituted final product vial contains approximately 92.5 mBq (2.5 up to 10 mCi) and 250 mcg technetium Tc 99m tilmanocept in 0.5 mL to 5 mL total finished volume.<sup>10</sup>

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## Important Safety Information

In clinical trials with Lymphoseek, no serious hypersensitivity reactions were reported, however Lymphoseek may pose a risk of such reactions due to its chemical similarity to dextran. 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 administration, and patients observed for signs or symptoms of hypersensitivity following injection.

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

In clinical trials, no patients experienced serious adverse reactions and the most common adverse reactions were injection site irritation and/or pain (<1%).

Please visit [www.lymphoseek.com](http://www.lymphoseek.com) for Full Prescribing Information

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