CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202207Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 27, 2012
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA/Supplement#	NDA 202207
Applicant	Navidea Biopharmaceuticals, Inc. (former Neoprobe)
Date of Submission	August 10, 2011
PDUFA Goal Date	6/10/2012 (Extended to 9/10/2012 due to a major amendment submitted on 3/30/2012)
Proprietary Name / Established (USAN) names	Lymphoseek: Kit for the Preparation of Technetium Tc99m Tilmanocept for Injection / Tilmanocept (DTPA mannosyl dextran)
Dosage forms / Strength	18.5 MBq (0.5 mCi) / 50mcg by intradermal or subareolar injection, based on cancer type.
Proposed Indication(s)	(b) (4) localization of lymph nodes in patients with breast cancer or melanoma, (b) (4)
Recommended:	*Approval (pending the results of GMP inspections)*

1. Introduction

This Cross-Disciplinary Team leader (CDTL) review document addresses the New Drug Application (NDA) 202207 for Lymphoseek. Lymphoseek is a radioactive diagnostic drug (a technetium labeled dextran derivative, Tilmanocept) for preoperative injection at the surgical site and the subsequent intraoperative detection with a handheld gamma probe to (b) (4) localize lymph nodes draining the area of injection in the vicinity of the primary tumor in patients with breast cancer or melanoma.

The applicant's claim of effectiveness and safety of this drug has been primarily based on data from two confirmatory efficacy trials submitted with the application. The conclusions of the current review are based on the review of the relevant portions of the application and on examination of the primary review documents. During the review process, multiple review issues have arisen from various disciplines and are outlined in the body of this document. No significant disagreements have been encountered among individual reviewers or among disciplines.

2. Background

Tilmanocept is a macromolecule (~20 kDa) consisting of dextran and multiple units of diethylenetriaminepentaacetic acid (DTPA) and mannose, each synthetically attached to a dextran backbone. The mannose moiety acts as a substrate for mannose receptors on macrophages and dendritic cells residing in lymph nodes, and the DTPA serves as a "linker" for labeling with Tc 99m. The avidity of binding to specific receptors is proposed as a mechanism explaining this drug's purported specificity in selective binding to lymphatic tissue.

The product comes as a lyophilized powder to be radiolabeled with Tc 99m prior to administration for lymph node mapping by intradermal, subcutaneous, subareolar, or "peritumoral" injection. The intended mass dose of Lymphoseek is 50 mcg. Once radiolabeled, Lymphoseek has to be injected in close proximity to the primary tumor and localized intraoperatively utilizing a handheld gamma detection probe. The intended radioactivity dose, upon injection, is 18.5 MBq (0.5 mCi).

The generally termed clinical procedure for which Lymphoseek would be indicated is *intraoperative lymphatic mapping (ILM).* In clinical practice, the use of intraoperative lymphatic mapping is fairly well established for breast cancer and melanoma but is not as common in other types of cancer surgery.

There are currently two drugs approved in US for similar use. "Blue dye", also known as Vital Blue Dye (VBD), or Lymphazurin (isosulphan blue), is an optical imaging agent for the intraoperative delineation of lymphatic vessels draining the region of injection. The other drug is Tc-99m Sulfur Colloid (TcSC), a radiopharmaceutical used until recently off-label for lymphatic mapping but in 2011 approved for "localization of lymph nodes draining a primary tumor in patients with breast cancer when used with a handheld gamma counter". The application for use in melanoma is currently under review. In case of TcSC, efficacy supplements for both breast cancer and melanoma indication have been literature review based applications.

Development of Lymphoseek took place under IND 61757 and involved various interactions with the FDA including the End of Phase-2 meeting in 2007. The choices of VBD as a comparator and concordance with VBD in localizing lymph nodes as a primary efficacy endpoint were accepted as reasonable at the time. Assessing performance characteristics like sensitivity and specificity with extensive regional resection for nodal histopathology as a standard of truth was not considered to be practical given the surgical standard of care for melanoma and breast cancer. The accepted study design appeared reasonable for the ILM claim (b) (4)

3. CMC/Device

As described in the primary CMC review of the application, the active ingredient in Lymphoseek is technetium 99m Tilmanocept which forms when sodium pertechnetate Tc 99m solution is added to the Tilmanocept Powder vial. Technetium Tc 99m binds to the diethylenetriaminepentaacetic acid (DTPA) parts of the tilmanocept molecule. "Lymphoseek (Kit for the Preparation of Technetium Tc 99m Tilmanocept) Injection", as the drug product would be called in the labeling, includes a Tilmanocept Powder vial that contains the non-radioactive ingredients necessary to produce Technetium Tc 99m tilmanocept Injection. The kit also contains a Diluent vial. The Tilmanocept Powder vial contains a sterile, non-pyrogenic white to off-white, powder that consists of a mixture of 250 mcg tilmanocept and other ingredients (see the primary CMC review). The contents of the vial are lyophilized.

Prior to administration to the patient, a nuclear pharmacist would be preparing the injection by taking one lyophilized powder vial and radio-labeling with an amount of radioactivity as Sodium Pertechnetate Tc 99m Injection in isotonic saline after which the accompanying diluent is added. After radio-labeling the final product contains approximately 92.5 MBq (2.5 mCi). The overall patient mass dose in every case is 50 mcg corresponding to the radioactivity dose of 18.5 MBq, or 0.5 mCi. The remainder of 250 mcg is to be discarded. The maximum reconstitution volume is 5.0 mL. The volume of each injection, number of injections and amount of radioactivity varies depending on surgical circumstances. There could be anywhere from one to five injections, from 0.1 mL to 0.5 mL per injection, with up to 1 mL injected into a patient.

Multiple CMC deficiencies have been identified by the CMC review team requiring various Information Requests. As a result, the review clock has been extended for 3 months due to a major CMC amendment submitted on 3/31/2012. One of the recently remaining issues has been the analytical method used for the tilmanocept identification which is not considered to be suitable for establishing the quantity of tilmanocept in the drug product thus potentially making the drug potency assay data unreliable. There are also remaining multiple manufacturing deficiencies which have resulted in "withhold recommendations" from the Office of Compliance. The CMC review team does not recommend approval at this time.

4. Nonclinical Pharmacology/Toxicology

The single- and repeat-dose toxicology studies in appropriate animal species showed no evidence of potential toxicity of Technetium Tc 99m Tilmanocept. Studies to assess the carcinogenicity potential of tilmanocept have not been conducted. Tilmanocept was not found to be 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. Pharmacology-Toxicology reviewer recommends approval.

5. Clinical Pharmacology/Biopharmaceutics

Mechanism of action and dosing considerations are discussed elsewhere already. The clinical pharmacology reviewer also notes that, in a dose-ranging clinical study, injection site clearance rates are similar across all Lymphoseek doses (4 µg to 200 µg) with a mean elimination rate constant in the range of 0.222 to 0.396/hr. The drug half-life at the injection site ranges from 1.75 to 3.05 hours. (b) (4) but otherwise recommends approval.

6. Clinical Microbiology

Lymphoseek is not an antimicrobial therapeutic.

7. Clinical/Statistical- Efficacy

Efficacy of Lymphoseek was assessed in two similarly designed open-label, multicenter, single arm, within-subject active comparator trials of patients with melanoma or breast cancer (Study One and Study Two). Both clinical trials were titled "A Phase 3, Prospective, Open-Label, Multicenter Comparison Studies of Lymphoseek and Vital Blue Dye as Lymphoid Tissue Targeting Agents in Patients with Known Melanoma or Breast Cancer Who Are Undergoing Lymph Node Mapping". Both trials were prospective studies conducted in patients 18 years of age or older with known melanoma or breast cancer, who were candidates for surgical intervention and who prior to the nodal mapping procedure had no known nodal or metastatic disease.

All patients received a single dose of radioactively labeled Lymphoseek (50 mcg) and VBD prior to ILM. Lymphoseek was injected into patients at various times (up to 30 hours) prior to the scheduled surgery and blue dye was injected just shortly prior to initiation of the surgery. The definition of radioactively "hot" nodes to be found at surgery was pre-specified. ILM was performed using a handheld gamma detection probe and by visual inspection aided by VBD staining. It was followed by excision of lymph nodes identified by Lymphoseek, by blue dye or by the surgeon's visual examination and palpation. The primary objective of both studies was to determine the concordance between Lymphoseek and VBD in the intraoperative detection of lymph node(s) as confirmed by histopathology.

In Study One, of 179 patients who received Lymphoseek, 94 (53%) had known or suspected breast cancer and 85 (47%) 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. Thus both studies adequately represented the intended patient population.

In both studies, most of the subjects received the injection of Lymphoseek on the day of surgery and the dose was 0.5 mCi in 50mcg. In 38 subjects from Study One and 2 subjects

from Study Two, Lymphoseek was administered on the day prior to surgery and the dose was 2 mCi in 50 mcg. The exact timing of injection varied throughout.

The primary endpoint was the proportion of lymph nodes found by VBD which were also "hot" as identified by Lymphoseek, with the primary efficacy analysis having to show a statistical superiority over the pre-specified (0.9) threshold. As verified by clinical and statistical reviewers, *the applicant succeeded in the primary efficacy analyses in both clinical trials*. In both trials, based on the secondary analyses, the applicant also showed that VBD identified only a proportion of lymph nodes identified by Lymphoseek (estimated as 0.7 in Study One and 0.6 in Study Two).

FDA reviewers performed additional analyses based on the histopathologic confirmation of a finding of a lymph node as a standard of truth and recommended using the results of such analyses in the eventual labeling. These analyses therefore included lymph nodes that were identified neither by Lymphoseek nor by VBD (very small minority in Study One and none in Study Two). This reviewer notes some numerical discrepancies between the data cited by the primary clinical reviewer and those cited by the primary statistical reviewer. The explanation likely lies in that the clinical reviewer cites directly from the sponsor data whereas the statistical reviewer cites the data from the independent analyses. The overall conclusions are similar for both disciplines.

Various subgroup analyses were performed using type of cancer, demographics, dose, time and site of injection. No significant differences were found except for the time of injection in relation to surgery. Although the subgroup of patients in whom surgery was performed on the day after the Lymphoseek injection was small (see above) the relative detection rate for Lymphoseek appeared to have been significantly lower in the lymph nodes from this subgroup as compared to the whole group. Of note, the radioactivity dose was higher when surgery was planned on the day after the injection but the mass dose remained the same. An advantage that Lymphoseek seemed to have had over VBD in the whole group was lost in the next day surgery subgroup.

(b) (4)

(b) (4)

8. Safety

This reviewer agrees with the primary clinical reviewer's assessment that the safety database for Lymphoseek is small representing 531 patients from all the clinical studies and such a size of the safety population would be inadequate to evaluate adverse reactions occurring at incidence rates below 0.2%. However, it is also appropriately noted that within this small safety population, the safety profile of Lymphoseek appears acceptable. There were no deaths, no drop-outs related to adverse reactions to Lymphoseek, and no serious adverse reactions related to Lymphoseek. A particular attention during the review process was paid to hypersensitivity reactions because Lymphoseek is a dextran based product. However, no systemic anaphylactic or anaphylactoid reactions were observed in the clinical studies. According to the primary clinical reviewer, approximately 3% of patients experienced local allergic reactions, manifested as rash (1%), erythema (1%), skin irritation (0.4%), pruritus (0.4%), or urticaria (0.2%). Of note, these observations were confounded by the comparator blue dye known to cause hypersensitivity reactions (including anaphylactic reactions). Other adverse reactions such as injection site pain or irritation were uncommon and of mild severity. As a radioactive drug, Lymphoseek may increase the long term risk of cancer.

9. Advisory Committee Meeting

With ILM being a fairly well established procedure in clinical practice, no Advisory Committee meetings have been planned.

10. Pediatrics

The full account of the applicant's initial request for a waiver of pediatric studies is presented in the primary clinical review and reflected in the oncology consultation report. The applicant eventually revised the indication limiting it to patients with breast cancer and melanoma. Given that these conditions are rare in pediatric population the clinical team has recommended granting the full pediatric waiver.

11. Other Relevant Regulatory Issues

There are no other relevant regulatory issues at this time.

12. Labeling

The 8/12/11 cover letter to the original application lists the following indication:

(b) (4)

Thereafter, the applicant has revised it as such:

(b) (4)

In 7/09/12 correspondence, FDA has proposed the following wording to the indication: "Lymphoseek is indicated for use with a hand-held gamma counter to assist in the localization of lymph nodes draining a primary tumor in patients with breast cancer or melanoma".

At the time of this review, the labeling has not been finalized yet. Major revisions are being worked out to Dosage and Administration and Clinical Studies sections of the labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The Cross-Disciplinary Team Leader recommends approving Lymphoseek for use with a hand-held gamma counter to assist in the intraoperative localization of lymph nodes draining a primary tumor in patients with breast cancer or melanoma. The reviewer recognizes that the still outstanding CMC, labeling and manufacturing facilities' inspectional issues might necessitate a Complete Response in this review cycle.

- Risk Benefit Assessment

In assessing benefit of Lymphoseek the reviewer has considered several factors involving clinical utility and efficacy. Lymphoseek, once approved, would be useful in the Intraoperative Lymphatic Mapping, a current standard of care in breast cancer and melanoma. Although other drugs are used and/or approved for similar use Lymphoseek offers a theoretical advantage by potentially binding more specifically to lymphatic tissue. It is also possible that in clinical practice it will be used, as a radioactive modality, together with another modality like a blue dye or another optical agent.

The applicant has provided the substantial evidence of effectiveness based on the success of the pre-specified primary efficacy analyses in two adequate and well controlled clinical trials involving the use of Lymphoseek in patients with breast cancer and melanoma. Additional analyses carried out by the FDA reviewers confirmed and clarified effectiveness of Lymphoseek for intraoperative localization of lymph nodes.

Based on clinical trial data accumulated so far, a risk associated with the use of Lymphoseek appears to be minimal. However, a possibility of anaphylactic reactions remains to be of concern, especially in view of the limited safety database. Postmarketing pharmacovigilance should be sufficient in monitoring this risk,

Overall, given clearly established clinical utility of lymph node localization in intraoperative management of patients with breast cancer or melanoma and this drug's demonstrated effectiveness in being used for such a purpose coupled with an acceptable risk profile, the risk and benefit assessment favors the approval.

No additional postmarketing risk management activities or other clinical commitments are being sought at this time. There could be postmarketing CMC commitments depending on the conclusions of the still ongoing review. The nature of the outgoing comments to the applicant would depend on the resolution of the remaining CMC and labeling issues.

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ALEXANDER GOROVETS
07/30/2012