CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202207Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 5, 2013
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	202207
Applicant Name	Navidea Biopharmaceuticals, Inc.
Date of Submission	Second cycle submission on 10/31/2012 First cycle submission on 08/10/2011
PDUFA Goal Date	April 30, 2013
Proprietary Name / Established (USAN) Name	Lymphoseek/technetium Tc 99m tilmanocept
Dosage Forms / Strength	A solution prepared in the nuclear pharmacy from the Kit for preparation of Lymphoseek/the dose is 50 mcg containing 92.5 MBq (b) (4) administered according to the planned lymphatic mapping technique (intradermal, subcutaneous or peritumoral); the volume injected varies with the mapping technique as described in the proposed labeling.
Proposed Indication(s)	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.
Action/Recommended Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Ye, MD
Statistical Review	& Jyoti Zalkikar, PhD
Pharmacology Toxicology Review	Olayinka Dina, PhD
CMC Review/OBP Review	Ravindra Kasliwal, PhD
Microbiology Review	John Metcalfe, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Gene Williams, PhD (TL)
DDMAC/DPP	James Dvorsky
DSI	Jong Hoon Lee, MD
CDTL Review	Alex Gorovets, MD
OSE/DMEPA	Jibril Abdus-Samad, PharmD & Todd Bridges, PharmD (TL)
Pediatric and Maternal Health	Jeanine Best, MSN and Upasana Bhatnagar, MD
Project Manager	Alberta Davis-Warren

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication renamed as DPP, Division of Professional Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
DSI=Division of Scientific Investigations
CDTL=Cross-Discipline Team Leader
TL = Team Leader
CMC = chemistry, manufacturing and controls

1. Introduction:

This is a second cycle review for Lymphoseek, a diagnostic radiopharmaceutical. The first cycle review was completed with resolution of all issues except for facility inspectional items. Labeling and all clinical/statistical/clinical pharmacology/nonclinical toxicology matters were resolved during the first cycle. During this second cycle, the facility inspectional issues were resolved and the drug is now recommended for approval.

For ease of review within a single document, here I am largely reiterating comments from my original review. The only update pertains to the chemistry, manufacturing and control (CMC) section; here I cite the resolved facility inspection issues. The review team is also recommending that a pending Citizen's Petition (CP) be addressed prior to (or at the time of) the approval. The team has completed a consult pertaining to this CP, and the team has explicitly stated that the Lymphoseek approval is unrelated to the CP concern. Specifically, the CP expressed concern that FDA not approve drugs for sentinel lymph node detection unless certain criteria were met. Lymphoseek is not indicated for sentinel lymph node detection; hence, the CP concern does not apply to Lymphoseek.

Lymphoseek was shown in clinical studies to be useful in the intraoperative identification of lymph nodes among patients with breast cancer or melanoma. Lymphoseek contains radioactive technetium complexed with tilmanocept, a mannosylated dextran molecule. The mannose components are thought to facilitate binding to mannose receptors on macrophages and dendritic cells within lymph nodes. Following injection of Lymphoseek, a surgeon uses a gamma probe to detect the radioactive signal that identifies a Lymphoseek-tagged lymph node.

The applicant performed two phase 3 clinical studies that achieved the primary endpoints and secondary endpoints. The clinical and statistical staff verified that the applicant supplied sufficient evidence of Lymphoseek clinical safety and efficacy. Lymphoseek was shown in clinical studies to successfully localize to lymph nodes in a manner that facilitated surgical identification of the nodes.

Lymphoseek is to be supplied as a kit which contains five "powder" vials and five "diluent" vials. A kit contains sufficient drug to nominally expose (b) (4) patients and, because the diluent contains a preservative, one reconstituted vial may supply doses for up to (b) (4) patients. Lymphoseek is relatively complicated to reconstitute because the mass dose, reconstitution vial volume and the ultimate volume to be injected into a patient with a syringe(s) need to be considered during the drug's preparation.

Considerable review effort was expended in refining the prescribing information to clearly describe the reconstitution directions.

2. Background:

The localization of lymph nodes has assumed an important role in the surgical care of patients with melanoma and breast cancer because removal of lymph nodes can help assess the extent of metastatic disease. Importantly, the sponsor's proposed indication related to the relatively non-specific localization of lymph nodes; not the more specific indication for "sentinel lymph node detection." The Lymphoseek application signaled the important difference between the non-specific structural-type indication the company was seeking (all lymph node localization) in contrast to the more specific indication of sentinel lymph detection. Both indications are clinically important but have different clinical implications.

- The non-specific lymph node localization indication (also known as "lymph node mapping") sought by Navidea is in line with use of the drug by surgeons who are attempting to ensure they have identified all lymph nodes draining a melanoma or breast cancer. Subsequent lymph node pathology information may alter the management of the patient's cancer therapy and/or further diagnostic evaluation.

- The more specific sentinel lymph node detection indication (which the sponsor was not seeking) relates to the identification of the "first" lymph node(s) draining a primary cancer such that the absence of cancer within this "first" lymph node may negate the need for excision of other lymph nodes.

These are important indication/usage distinctions and the sponsor's proposed labeling makes no claims relevant to the use of the drug in sentinel lymph node detection. Currently, two drugs are approved for use in lymph node mapping: isosulfan blue and sulfur colloid. Isosulfan blue is also sometimes referred to as a "vital blue dye" or "blue dye."

The applicant's clinical development program was typical for lymph node mapping agents in that two phase 3 clinical studies examined the extent to which Lymphoseek and another tracer ("blue dye") were detected within lymph nodes excised from patients who were undergoing surgical procedures aimed at complete lymph node excision (based on palpation, visual examination or detection of the tracer within nodes).

A pre-NDA meeting was held in which the applicant described the success of the phase 3 clinical studies and their plan to seek a lymph node mapping indication. The applicant currently has an on-going phase 3 study (b) (4)

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal who reviewed the applicant's supplied manufacturing information as well as the information contained within several referenced drug master files. Based upon information supplied in this second cycle submission, Dr. Kasliwal confirms that all manufacturing issues have been resolved. Facility inspectional issues have also been resolved. Dr. Kasliwal has not identified a need for post-marketing studies.

I concur with Dr. Kasliwal's observations and conclusion.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Olayinka Dina who found the supplied nonclinical pharmacology/toxicology data supportive of the drug's approval. In vitro binding assays showed the drug product bound specifically to mannose binding receptors on the surface of human macrophages. Safety pharmacology studies in beagle dogs showed that intravenous doses of the drug caused no toxicity even at doses substantially in excess of those proposed for clinical use (564-fold higher). Pharmacokinetic studies of subcutaneous dosing in dogs, rabbits and rats showed rapid systemic absorption of the drug (into the blood within 4 minutes of injection) from the injection site with predominant excretion of the drug via urine. Lymph node localization of the drug was identified in the popliteal node ipsilateral to a subcutaneous injection site; localization was not detected in the contralateral popliteal node.

Single dose toxicology studies in rats, rabbits and dogs as well as repeat dose toxicology studies in rats and dogs all showed no toxicity (with the no adverse effect level cited as the maximum administered dose). Genetic toxicology studies were negative in the in vitro bacterial reverse mutation, in vitro mouse lymphoma and in vivo bone marrow micronucleus assays. Carcinogenicity studies were not performed and the sponsor submitted a waiver for reproductive and developmental toxicology studies. The waiver was granted, as shown in Dr. Paul Brown's supervisory memorandum.

Local irritation studies in rabbits showed the drug produced no injection site histopathology; no specific toxicology studies were performed for impurities due to the known tolerability nature of the impurities (b) (4) and their low concentrations.

5. Clinical Pharmacology/Biopharmaceutics:

I have read the review performed by Dr. Christy John and I concur with his recommendations to approve the "same day" surgery dose of Lymphoseek (b) (4)

Dr. John described the proposed Lymphoseek dose as a "micro-dose" with low systemic exposure. He noted that immunogenicity tests were not performed but he did not regard immunogenicity as a concern (Lymphatic mapping is likely to be rarely, if ever, performed more than one time in a patient).

Dr. John further noted that 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% injected dose in each tissue.

6. Clinical Microbiology:

Dr. John Metcalfe completed the review of the applicant's microbiology-related information; he detected no deficiencies and I concur with his findings. No post-marketing studies were proposed.

7. Clinical/Statistical-Efficacy:

Dr. Brenda Ye performed the primary clinical review and Dr. Alex Gorovets performed the Cross Discipline Team Leader review. Dr. Satish Misra performed the statistical review. I have read the reviews and concur with the findings.

The applicant performed two phase 3 clinical studies that succeeded upon their study objectives and verified the ability of Lymphoseek to provide clinically useful information. In both phase 3 studies, patients with breast cancer or melanoma had injection of Lymphoseek and blue dye ("tracers"). Subsequently, surgeons performed intraoperative lymph node resection, removing all visible, palpable or tracer-identified lymph nodes. Both phase 3 studies achieved the primary endpoints of showing "concordance" with blue dye.

Perhaps the most notable finding from Dr. Misra and Ye's review was that the clinical data were (b) (4)

The following comments are an excerpt from the proposed labeling that succinctly summarizes the ability of Lymphoseek to tag lymph nodes and allows a comparison to the blue dye tracer.

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) 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 handheld 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 sent for histopathology evaluation.

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. (b) (4)

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

Study	T	Nodes n	BD Present n (%); 95% CI	LS Present n (%); 95% CI	Only BD Present, n (%); 95% CI	Only LS Present, n (%); 95% CI	Neither BD nor LS Present, n (%); 95% CI
One	M	155	99 (64%) (56 - 71%)	145 (94%) (89 - 97%)	1 (1%) (0 - 4%)	47 (30%) (23 - 38%)	9 (6%) (3 - 11%)
	B	154	108 (70%) (62 - 77 %)	146 (95%) (90 - 98%)	7 (5%) (2 – 9%)	45 (29%) (22 - 37%)	1 (1%) (0 - 4%)
Two	M	196	115 (59%) (51 - 66%)	196 (100%) (98 - 100%)	0 (0 - 2%)	81 (41%) (34 - 49%)	0 (0 - 2%)
	B	180	112 (62%) (55 - 69%)	180 100%) (98 - 100%)	0 (0 - .2%)	68 (38%) (31- 45%)	0 (0 - 2%)

T = tumor; 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.

8. Safety:

Based upon the exposure of 531 patients to Lymphoseek, the most notable safety findings pertain to the radiation risks implicit for radiopharmaceuticals as well as the *potential* for a hypersensitivity reaction (especially considering the dextran-nature of the Lymphoseek active moiety. Clinical studies identified only mild injection site pain/discomfort (in less than 1% of patients) as adverse reactions. No hypersensitivity reactions were detected.

Post-marketing Requirements (PMR): none
Post-marketing Commitments (PMC): none

9. Advisory Committee Meeting:

This application was not reviewed at an Advisory Committee because the clinical data presented no unique concerns and the nature of the proposed indication is similar to currently approved products. External advisory consultation was not necessary due to the lack of any unsettled clinical or statistical matters. The main issues during the review pertained to manufacturing and facility information.

10. Pediatrics:

Based upon the proposed indication, Ms. Jeanine Best documented that the applicant has been granted a full waiver for pediatric studies under the PREA expectation because melanoma and breast cancer are considered "adult indications" such that clinical studies would be impossible or impracticable in the pediatric population.

11. Other Relevant Regulatory Issues:

Dr. Lee's review documents no notable deficiencies from inspection of the clinical data obtained from clinical sites involved in the phase 3 studies. Five good clinical practice inspections were performed; four clinical sites and the sponsor site.

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/s/

RAFEL D RIEVES
03/05/2013