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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Date	January 24, 2011
From	Louis Marzella M.D., Ph.D.
Subject	Cross-discipline Team Leader Review
NDA/BLA #	22-494
Supplement#	Class 2 resubmission
Applicant	National Cancer Institute (NCI), Division of Cancer Imaging and Diagnosis, Cancer Imaging Program
Date of Submission	July 26, 2010
PDUFA Goal Date	January 28, 2011
Proprietary Name	None
Established (USAN) names	Sodium Fluoride F18 Injection
Dosage form	Sterile Injection for Intravenous Administration
Strength	10-200 mCi/ml at end of synthesis (EOS)
Proposed Indication	Positron Emission Tomography (PET) imaging of bone to define areas of altered osteogenic activity
Recommended:	Approval

Recommended Regulatory Action

The present July 26, 2010 class 2 resubmission by NCI is in response to FDA's June 29, 2009 complete response letter to the original 505(b)(2) new drug application (NDA) for Sodium Fluoride F18 injection. The resubmission (supporting document 016) and subsequent amendments in response to FDA information requests is intended to address outstanding chemistry, manufacturing and controls (CMC), microbiology, and labeling issues.

The CDTL agrees with the assessments by the NDA review team that the resubmission addresses the outstanding deficiencies. The CDTL agrees with the recommendation that the application be approved.

With respect to outstanding product Quality issues, the FDA Quality reviewer (Milagros Salazar Ph.D.) and Microbiology reviewer (Robert Mello Ph.D.) have determined that the application is approvable with respect to the CMC and microbiology data. In addition Dr. Salazar has determined that the shielding and container labels are acceptable. Finally Dr. Salazar notes that the Applicant will not manufacture or distribute Sodium Fluoride F18 Injection. The approved manufacturing site and sole supplier of the drug product under this NDA will be Siemens Molecular Imaging-PETNET Solutions, (SMI-PETNET Solutions, Inc.) in Durham, NC.

With respect to other outstanding labeling issues, the FDA clinical reviewer (Ross Filice M.D.) notes that the FDA and the Applicant have reached agreement on the content and format of the package insert through informal negotiations. The clinical reviewer finds the package insert to be adequate and recommends approval of the application.

Introduction

Sodium Fluoride F18 is a radiopharmaceutical proposed for use as a diagnostic agent for positron emission tomography (PET) of bone to define areas of altered osteogenic activity. Bone imaging is made possible by the uptake of fluoride in bone where fluoride ions undergo exchange with hydroxyl groups in hydroxyapatite to form fluoroapatite. Fluoride uptake is dependent on rates of blood flow to bone and Sodium Fluoride F18 has rapid blood clearance with high bone-to-background activity shortly after administration. Uptake of fluoride is higher in areas of bone undergoing increased osteogenic activity.

The intended population for Sodium Fluoride F18 bone imaging is patients with cancers who are at risk for bony metastases and patients with non-cancer conditions also characterized by alterations in osteogenic activity of bone. A commonly used diagnostic alternative to Sodium Fluoride F18 Injection PET imaging is Technetium-99m labeled diphosphonate gamma camera imaging. Alternatively, computed tomography or magnetic resonance imaging can be used to image bone. Recurrent world-wide shortages in the supply of the 99mTc generators decrease the availability of 99mTc-labeled diphosphonates bone scanning for cancer patients. The NDA Applicant seeks approval of Sodium Fluoride F18 to make an alternative bone scanning agent available whenever 99mTc shortages occur. The Division granted NCI's request for NDA priority review.

Original NDA Submission

FDA received the submission on December 31, 2008 and issued a complete response letter on June 29, 2009 because of CMC, microbiology, and labeling deficiencies.

Chemistry manufacturing and controls

Sodium [¹⁸F] Fluoride is the drug substance and the drug product. The drug product is a sterile radiopharmaceutical injection for intravenous administration having a potency of 10-200 mCi/ml at EOS (end of synthesis).

The NDA Applicant is not the manufacturer of the product and the NDA references two Drug Master Files (DMFs, Type II) for the CMC and microbiology data. The first DMF (21582) is held by Siemens Molecular Imaging-PETNET Solutions Inc. The second DMF (b) (4). The FDA CMC reviewer identified important DMF deficiencies in the following areas: product quality attributes (e.g. strength) and specifications; testing methodology and schedule; acceptance criteria for radiochemical identification, analytical test methods used in the control of product, and stability data for highest radioactivity concentration; post approval drug stability protocol; information on single-dose (syringe) and multi-dose vial presentations; labeling for immediate drug container and shielding and packaging containers. The FDA Quality reviewer also determined that there was insufficient evidence to verify compliance by the DMF holders with current good manufacturing practices (CGMP) for PET products. The reviewer requested that a mechanism be established for DMF holders to communicate to the NDA applicant any changes in the CMC that might affect the identity, purity, quality, or strength of the drug product.

The FDA microbiologist determined that there was insufficient information in the DMFs to assess the sterility of the final drug product. The deficiencies involved information on final product container, container closure system, final product vial assembly, (b) (4) process validation, and analytical procedures.

FDA issued the first DMF deficiency letter to SMI-PETNET on June 17, 2009 and to (b) (4) on June 23, 2009.

Pharmacology and toxicology

The NDA contains no new pharmacology or toxicology data and no new data are needed.

Clinical

The NDA applicant provided a summary of recent publications on the clinical use of Sodium Fluoride F18. The FDA clinical reviewer (Michel Fedowitz M.D., see clinical review dated May 13, 2009) examined the publications for safety signals including lack-of-efficacy reports and no safety signals were identified. Reports of clinical experience in various patient populations defined by age and by underlying medical conditions showed important new information on use and dosage of Sodium Fluoride F18. Specifically doses higher than the dose recommended for the reference drug are currently in clinical use for adults. Clinical experience in children has also been reported.

The FDA clinical reviewer recommended approval of the original application based on FDA's findings of safety and efficacy communicated in the March 10, 2000 Federal Register notice (65 FR 12999-13009). This notice states that FDA approved F 18 Sodium Fluoride injection (NDA 17 042) in 1972 for use in defining areas of altered osteogenic activity and that the NDA holder, Nycomed Amersham (now GE Healthcare), stopped marketing the drug in 1975. The product was not withdrawn from sale for reasons of safety or effectiveness. The clinical reviewer determined that the Applicant's submitted data supports the safety and effectiveness for the product in defining areas of altered osteogenic activity. The clinical reviewer's examination of the available literature found no contradiction to the safety and effectiveness of the product for the proposed use in the intended population.

Dr. Fedowitz found material deficiencies in the proposed package insert. The applicant cited several clinical studies and added new diagnostic claims beyond altered osteogenic activity. However the studies are not adequate or well-controlled and the clinical reviewer also recommended that this information not be added to the label. The reviewer recommended updating the information in the label pertinent to the product's safe and effective use as follows:

- Dosage and Administration: change recommended dose in adults, add recommendation for dosing in children, and dosimetry in relation to age; streamline the presentation of the radiation safety/patient preparation sections.
- Warnings and Precautions: add allergic reactions warning, precautions for increased cancer risk in children and information for safe use by nursing mothers.

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- Adverse Reactions: add the caution that the completeness and reliability of the available reports is questionable.
- Product Description: revise numbers for specific gamma ray constant.
- Clinical Pharmacology: remove implied claims of diagnostic performance.
- Clinical Studies: retain only information relevant to dosing recommendations in adults and children.
- References: retain only references to dosimetry studies.

NDA Resubmission

FDA received a complete resubmission on July 26, 2010.

Chemistry manufacturing and controls

The resubmission referenced DMF 21582 held by Siemens Molecular Imaging-PETNET Solutions Inc. FDA issued the first DMF deficiency letter on June 17, 2009 and received a response on March 25, 2010. FDA issued a second deficiency letter on September 10, 2010 and received a response on January 6, 2011. The FDA Quality reviewer found the responses to be acceptable.

The Quality reviewer had asked the Applicant to provide a standard operating procedure for post-marketing controls and surveillance. The Applicant provided an acceptable comprehensive protocol (SOP 22-494-001) titled: "Post-approval coordination between NCI and Drug Master File holders who supply Sodium Fluoride F18 Injection for NCA NDA 22-494."

The FDA office of Compliance found the SMI-PETNET manufacturing facility in Durham NC to be acceptable and to conform with USP <823> for PET compounding and with the USP monograph for Sodium Fluoride F18 Injection.

The resubmission also referenced a second DMF (b) (4) FDA issued a total of two deficiency letters for this DMF. On December 27, 2010, the Applicant withdrew (b) (4) as a supplier of drug product because the DMF holder would not be able to address the outstanding deficiencies before the PDUFA date for the NDA resubmission.

The Microbiology reviewer found that the resubmission had fully addressed the outstanding microbiology issues and recommended approval.

Clinical

The Applicant removed new efficacy claims for Sodium Fluoride F18 and made other changes in format and content of the package insert (see label appended to approval letter for details). The sponsor provided an acceptable justification for relying on published dosimetry data based on phantoms for estimation of radiation exposure in children. No postmarketing commitments are needed.

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/s/

LIBERO L MARZELLA
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