

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022494Orig1s000

MEDICAL REVIEW(S)

DIVISION OF MEDICAL IMAGING PRODUCTS

NDA Clinical Review

NDA: 22-494

Sponsor: NCI

Product: F18 Sodium Fluoride Injection

Clinical Reviewer: Ross Filice M.D.

Submission Date: July 26, 2010

Review Date: January 24, 2011

Recommended Regulatory Action

Following the agreement reached with the Sponsor on the package insert, the clinical reviewer recommends approval.

Summary

In this NDA, the Sponsor has relied upon the PET Safety and Effectiveness Notice issued by FDA on March 10, 2000 to support the efficacy of Sodium Fluoride F 18 Injection for defining areas of altered osteogenic activity. Additionally, the Sponsor presented a comprehensive literature review with an organized summary of the articles and proposed the addition of new clinical uses to the drug label.

The FDA clinical reviewer (Michele Fedowitz, M.D.) found these literature data to be supportive of the claim for efficacy in defining areas of altered osteogenic activity. In addition, the literature data provided important new information on dosage of Sodium Fluoride F 18 in current clinical use (8-10 mCi) and on usage in children.

However the clinical reviewer did not agree that the literature provided substantial evidence for any new claims of efficacy in specific disease states (e.g. specific cancers, benign bone diseases).

A number of labeling deficiencies were initially identified, but the Division and the Sponsor have now reached agreement on the package insert. Initial Chemistry, Manufacturing, and Controls as well as Microbiology concerns have also been resolved. Safety updates by the Sponsor and review of the AERS database did not reveal any new safety concerns.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROSS W FILICE
01/25/2011

LIBERO L MARZELLA
01/25/2011

DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS
Clinical Review of NDA Supplement

NDA: 22-494
Serial: 11
Sponsor: NCI
Product: F18 Sodium Fluoride Injection
Clinical Reviewer: Michele Fedowitz
Submission Date: 05/13/2010

EXECUTIVE SUMMARY

The clinical safety update raises no new safety concerns. We will consult the Office of Surveillance and Epidemiology (OSE) to conduct a more detailed search of the safety database for the previous 10 years to confirm the sponsor's claim that there are no safety reports of significance regarding 18F-Na. Regarding the pediatric plan, the Sponsor provides an adequate justification for not performing a pediatric dosimetry study and the reviewer agrees with the plan to extrapolate the radiation absorbed doses in children from published data using phantoms.

From the clinical perspective the only outstanding issue remains the need to revise the package insert (PI). The package insert (PI) contains numerous outstanding deficiencies. The Sponsor needs to address these deficiencies (see below LABEL REVIEW for a list of the deficiencies and for the recommended revised PI).

BACKGROUND

On 06/29/2009 the Agency issued a complete response letter to the sponsor for NDA 22-494, citing chemistry and microbiology deficiencies. On 05/13/2010, the sponsor submitted amendment 9 in response. The following is a review of their Safety Update, Clinical Summary and Update, and Pediatric Plan.

SAFETY UPDATE AND RESOLUTION

The sponsor presents an updated safety summary with this response. No NCI sponsored studies were completed during this time period. The sponsor reports no significant changes or findings in the safety profile. No patients have been enrolled in NCI sponsored studies at this point in time; [REDACTED] (b) (4)

[REDACTED]. There have been no discontinuations. There have been no reported adverse events (including deaths). The sponsor reports there has been no information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data. (Regarding the worldwide experience on the safety of this drug; including an updated estimate of use for drug marketed). The sponsor has been unable to determine the amount of this drug marketed in other countries or in the US because of the decentralized/local nature of its manufacture. It is widely available in many countries as a research product and for clinical use under the practice of pharmacy.

Additionally, the sponsor conducted an updated search of FDA's Adverse Event Reporting System (AERS) database for adverse events associated with use of 18F-NaF (the quarterly files from October 2008 to September 2009). The original search of the AERS database contained no reports which related 18F-Na use to safety. In this update, a search in the four quarterly files since 9/08, 26 events in four patients were identified. Two patients were administered fludeoxyglucose F18. Neither of the remaining two cases could be verified as involving the injectable imaging agent due to empty dosing, route of administration and NDA number fields. It appears, therefore, that there were no verifiable safety reports in the AERS database related to 18F-Na. We will consult the Office of Surveillance and Epidemiology (OSE) to conduct a more detailed search of the safety database for the previous 10 years to confirm the sponsor's claim that there are no safety reports of significance regarding 18F-Na.

Additionally, the sponsor presented an updated literature and provided an organized summary of the articles. This update contains no information on safety. While there is no evidence to contradict the original findings of safety in the Federal Register Notice, the data are likely to be incomplete because the studies were not designed to assess safety. For example, the published studies do not describe the methods for assessment of safety nor do they specifically cite safety findings. *Therefore, the reviewer recommends a more definitive statement of this inadequacy in the label (Adverse Reactions).*

INTEGRATED CLINICAL SUMMARY/UPDATE:

The sponsor presents an updated clinical summary with this response. No NCI sponsored studies were completed during this time period.

In their previous submission (Amendment 4), the sponsor relied upon the PET Safety and Effectiveness Notice issued on March 10, 2000 to support the efficacy for this NDA for Sodium Fluoride F 18 Injection. Additionally, they presented a comprehensive literature review with an organized summary of the articles. Our review found these data to be supportive only of the claim for efficacy in defining areas of altered osteogenic activity. We did not, however, find these articles to provide substantial evidence of any new claims of efficacy in specific disease states (i.e. specific cancers, benign bone diseases).

With this complete response, the sponsor presents an updated literature search with a summary of the articles. These reports were retrieved by a search of Medline through PubMed with the search terms: "Sodium Fluoride / diagnostic use" [MESH]; all permutations of "18F-NaF" as a free text term; and "18F-fluoride" as a free text term. Reviews were not included in this summary. The search obtained 16 articles. Again, our review found these articles to be supportive of the claim for efficacy in defining areas of altered osteogenic activity, but did not provide substantial evidence of any new claims of efficacy in specific disease states (i.e. specific cancers, benign bone diseases)

In the label, 14 Clinical Trials, the sponsor continues to include claims of new diagnostic efficacy in specific benign and malignant disease of bone. Furthermore, 15 References, includes a complete listing of these published articles. *This information will need to be removed as it is neither useful, nor is it supported by adequate and well controlled*

studies. Specifically, the newly submitted data are deficient for one or more of the following reasons:

1. Lack of a reference standard or various reference standards
2. Small study size
3. The endpoints are not clearly appropriate (Evaluation of imaging technique or surgical technique, not an evaluation of efficacy of 18F Fluoride PET)
4. Use of Semiquantitative analysis (SUVmax, SUV analysis, and ROI analysis and automation) which is not well validated and is dependent on technique
5. There is no information regarding the blinding of reads or reading protocol/adjudication of findings
6. Diagnostic performance of the drug relative to a truth standard and to comparative tests is variable

Review of the newly submitted data:

CONTROLLED STUDIES OF METASTASES

1. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, and Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. *J Nucl Med*. 2006 Feb; 47(2):287-97.

Reviewer's Comments:

This is a prospective trial (n=44) to compare the detection of bone metastases by 99mTc-methylene diphosphonate (99mTc-MDP) planar bone scintigraphy (BS), SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT in patients with high-risk prostate cancer. Planar, SPECT, 18F-Fluoride PET, and 18F-Fluoride PET/CT images were interpreted blindly and separately by two readers. The interpretation of 99mTc-MDP BS was made as a consensus reading of 2 nuclear medicine physicians and that of the PET/CT as a consensus reading of a nuclear medicine physician and a radiologist.

Deficiencies:

1. *A composite reference standard that included PET/CT was used,*
2. *Consensus reads (instead of independent reads) were used.*
3. *The primary endpoint and statistical analysis was not predefined, multiple statistical comparisons were performed without conserving the alpha, lesions read as equivocal were categorized as malignant for the purpose of the analyses.*

2. Iagaru A, Mitra E, Yaghoubi SS, Dick DW, Quon A, Goris ML, Gambhir SS. Novel strategy for a cocktail 18F-fluoride and 18F-FDG PET/CT scan for evaluation of malignancy: Results of the pilot-phase study. *J Nucl Med* 2009 Apr; 50(4):501-5.

Reviewer's Comments:

This is a prospective pilot study (November 2007-November 2008) of 14 patients (with cancer) who underwent separate 18F PET/CT and 18F-FDG PET/CT and combined 18F/18F-FDG PET/CT scans for the evaluation of malignancy. The 18F PET/CT, 18F-

FDG PET/CT, and combined 18F/18F-FDG PET/CT scans were interpreted by 2 board-certified nuclear medicine readers unaware of the diagnosis and results of the other imaging studies. In addition to the separate interpretation of the 3 scans for each patient, the CT data from the combined 18F/18F-FDG scan were used to create a bone mask that allowed the display of 18F/18F-FDG in the osseous structures on the PET scan. Each detected lesion was directly compared among the 3 PET/CT scans.

Deficiencies:

- 1. Small study size*
- 2. Evaluation of imaging technique (separate vs combined) not evaluation of efficacy of 18F Fluoride PET*

3. Krüger S, Buck AK, Mottaghy FM, Hasenkamp E, Pauls S, Schumann C, Wibmer T, Merk T, Hombach V, Reske SN. Detection of bone metastases in patients with lung cancer: 99mTc-MDP planar bone scintigraphy, 18F-fluoride PET or 18F-FDG PET/CT. *Eur J Nucl Med Mol Imaging.* 2009; 36:1807-1812.

Reviewer's Comments

This is a retrospective study (n=126) to compare the diagnostic accuracy of 18F-fluorodeoxyglucose (FDG) PET/CT versus standard planar bone scintigraphy (BS) and 18F-labelled NaF (18F) PET for the detection of bone metastases (BM) in non-small cell lung cancer (NSCLC). Two nuclear medicine physicians interpreted BS, 18F PET, and 18F-FDG PET/CT in a blinded and randomized fashion. The results of 18F-FDG PET/CT were made available to an experienced diagnostic radiologist who interpreted CT results. The authors concluded that integrated 18F-FDG PET/CT is superior to BS in the detection of osteolytic BM in NSCLC, and thus possibly obviating the need to perform additional BS or 18F PET in the staging of NSCLC.

Deficiencies:

- 1. Retrospective study*
- 2. Radiologist reads were not blinded to other modalities.*

CONTROLLED STUDIES OF BENIGN BONE DISEASES

Aratake M, Yoshifumi T, Takahashi A, Takeuchi R, Inoue T, Saito T. Evaluation of lesion in a spontaneous osteonecrosis of the knee using 18F-fluoride positron emission tomography. *Knee Surg Sports Traumatol Arthrosc.* 2009 Jan; 17(1):53-9.

Reviewer's comments:

This is a study (n=13) to evaluate using 18F-fluoride PET imaging in spontaneous osteonecrosis of the knee (SONK) lesions. The primary endpoints were to assess whether 18F-fluoride PET imaging can detect lesion in SONK, whether there are significant differences in maximum standardized uptake values (SUVmax) among each stage of this disorder, and if any correlation existed between the maximum SUVmax and size of the SONK lesion measured by radiography and MRI.

Deficiencies:

- 1. Small study size*
- 2. Not clearly blinded*

3. *SUVmax is variable, dependent on technique.*

Dasa V, Abdel-Nabi H, Anders MJ, Mihalko WM. F-18 fluoride positron emission tomography of the hip for osteonecrosis. Clin Orthop Relat Res. 2008 May; 466(5):1081-6. Epub 2008 Mar 24.

Reviewer's Comments:

This is a study (n=11) to evaluate the F-18 fluoride PET imaging modality for use in detection of the bone involved in atraumatic etiologies of osteonecrosis (ON) of the hip. The primary endpoints were evaluation of F-18 fluoride PET scan imaging compared to MRI and SPECT scan imaging. One board-certified nuclear medicine physician evaluated PET scans and bone scans and provided descriptive results. Two attending physicians and one resident in the orthopedic department reviewed all MRI images and staged all hips using the University of Pennsylvania classification system. Results: Nine of 17 hips (8 patients) had acetabular increased uptake when using the F-18 fluoride PET scans that were not seen on MRI, single photon emission computed tomography, or bone scans.

Deficiencies:

1. *Small study size*
2. *There is no information regarding the blinding of reads or reading protocol/adjudication of findings*
3. *MRI read by the orthopedic department*

Laverick S, Bounds G, Wong WL. [18F]-fluoride positron emission tomography for imaging condylar hyperplasia. Br J Oral Maxillofac Surg. 2009 Apr; 47(3):196-9. Epub 2008 Oct 15.

Reviewer's Comments:

This is an assessment of the use of [18F]-fluoride PET for imaging condylar hyperplasia in 5 patients. The scans were reviewed independently of the clinical findings by an observer experienced in PET and unaware of the final outcome. 18F-fluoride PET results were correlated with the operative findings of 5 patients who were suspected of having condylar hyperplasia in order to establish the presence of continued active hyperplastic growth in the affected condyle. Increased [18F]-fluoride uptake correlated with the histological diagnosis of condylar hyperplasia in all patients.

Deficiencies:

1. *Small study size*
2. *There is no information regarding the blinding of reads or reading protocol/adjudication of findings*

Uchida K, Nakajima H, Miyazaki T, Yayama T, Kawahara H, Kobayashi S, Tsuchida T, Okazawa H, Fujibayashi y, and Baba H, Effects of alendronate on bone metabolism in glucocorticoid-induced osteoporosis measured by 18F-Fluoride PET: A prospective study. J Nucl Med. 2009; 50:1808-1814.

Reviewer's Comments

This is a prospective trial (n=24) to evaluate the effects of alendronate treatment on regional bone turnover, measured by 18F-fluoride PET and by global biochemical markers and bone mineral density (BMD), in postmenopausal women with glucocorticoid-induced osteoporosis. Mean standardized uptake value (SUV) was corrected for the injected dose and patient's body weight. SUVs of the lumbar vertebrae and femoral neck were plotted as localized bone metabolism parameters against the values of BMD or biochemical markers.

Deficiencies:

- 1. Small study size*
- 2. 18F-fluoride PET being used to study treatment effect of drug*
- 3. Lack of a reference standard for 18F-fluoride PET performance*
- 4. There is no information regarding the blinding of reads or adjudication of findings*

Wilde F, Steinhoff K, Frerich B, Schulz T, Winter K, Hemprich A, Sabri O, Kluge R. Positron-emission tomography imaging in the diagnosis of bisphosphonate-related osteonecrosis of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2009 Mar; 107(3):412-9. Epub 2009 Jan 4.

Reviewer's Comments

This is a study (n=9) to investigate the sensitivity of 18F-fluoride and 18F FDG PET in the diagnosis of bisphosphonate-related osteonecrosis of the jaw (BRONJ), and to test their suitability for assessing the severity of BRONJ. All patients had biopsy-proven BRONJ. The primary endpoints were to compare the pathologic findings obtained when using 18F fluoride and 18F FDG PET in the diagnosis of BRONJ, and to test the suitability of these methods for assessing the severity of BRONJ.

Deficiencies:

Small study size

- 1. Use of SUV analysis and reference regions is not well validated*
- 2. There is no information regarding the blinding of reads or reading protocol/adjudication of findings*

STUDIES FOLLOWING ORTHOPEDIC PROCEDURES

Nkenke E, Vairaktaris E, Stelzle F, Neukam FW, Stockmann P, Linke R. Osteocutaneous free flap including medial and lateral scapular crests: Technical aspects, viability, and donor site morbidity. *J Reconstr Microsurg.* 2009 Aug 20. Epub ahead of print.

Reviewer's comments

This is a study (n=20) conducted in order to check for metabolism of the bony segments of osteocutaneous free flaps that included lateral as well as medial scapular crests by 18F-fluoride positron emission tomography (PET)/computed tomography (CT) examinations and to assess donor site morbidity. The primary endpoints are evaluation of metabolism of the bony segments of osteocutaneous free flaps that included lateral as well as medial scapular crests by 18F-fluoride PET/ (CT) examinations and donor site morbidity.

Deficiencies:

1. *Small study size*
2. *There is no information regarding the blinding of reads or reading protocol/adjudication of findings*
3. *Lack of a reference standard*
4. *The study uses 18F-fluoride PET to evaluate different surgical techniques*

Sörensen J, Michaelsson K, Strand H, Sundelin S, Rahme H. Long-standing increased bone turnover at the fixation points after anterior cruciate ligament reconstruction: a positron emission tomography (PET) study of 8 patients. *Acta Orthop.* 2006 Dec; 77(6):921-5.

Reviewer's Comments:

This is a cross-sectional pilot study (n=8) to evaluate the healing process with positron emission tomography (PET) scanning in 8 patients with anterior cruciate ligament injury who underwent an anterior cruciate ligament reconstruction. Patients were imaged at varying post-operative time points to approximate bone metabolism differences over time. Primary Endpoints: To investigate changes in bone metabolism at the fixation points in the femur and tibia, using PET scan. SUV in various regions were compared.

Deficiencies:

1. *Small study size*
2. *There is no information regarding the blinding of reads or adjudication of findings*
3. *Use of SUV analysis is not well validated*
4. *Lack of a reference standard*

Temmerman OP, Raijmakers PG, Heyligers IC, Comans EF, Lubberink M, Teule GJ, Lammertsma AA. Bone metabolism after total hip revision surgery with impacted grafting: Evaluation using H₂ 15O and [18F] fluoride PET; a pilot study. *Mol Imaging Biol.* 2008 Sep; 10(5):288-93. Epub 2008 Jun 10.

Reviewer's Comments

This is a prospective pilot study (n=10) to evaluate bone blood flow and bone formation in patients after total hip revision surgery with impacted bone grafting using H₂¹⁵O and [18F] fluoride positron emission tomography (PET) to quantitatively assess the process of bone graft remodeling and new bone formation. The study examined the difference between 2 surgical techniques: hip arthroplasty and revision surgery; both before and after surgery. Primary Endpoints: To evaluate regional bone blood flow and bone metabolism in bone allograft after impaction grafting.

Deficiencies:

1. *Small study size*
2. *The study uses 18F-fluoride PET to examine the difference between two surgical techniques*
3. *There is no information regarding the blinding of reads or adjudication of findings*
4. *Lack of a reference standard*

Ullmark G, Sörensen J, Långström B, Nilsson O. Bone regeneration 6 years after impaction bone grafting: a PET analysis. *Acta Orthop.* 2007 Apr; 78(2):201-5.

Reviewer's Comments:

This study used [18F]-fluoride PET to produce quantitative images of new bone formation in the allograft surrounding the femur stem in 5 patients 6 years after their surgeries. Primary Endpoints: To study bone metabolism and new bone formation in allografts surrounding the femur component in revision THA, 6 years after surgery with the impacted morselized bone allograft technique, and compare the current data with historic data from the same patients during the first year after surgery.

Deficiencies:

- 1. Small study size*
- 2. There is no information regarding the blinding of reads or adjudication of findings*
- 3. Semiquantitative analysis is not validated*
- 4. Lack of a reference standard.*

Ullmark G, Sörensen J, Nilsson O. Bone healing of severe acetabular defects after revision arthroplasty. *Acta Orthop.* 2009 Apr; 80(2):179-83

Reviewer's Comments:

This is a study (n=7) to analyze healing of morselized bone allografts, impacted in large osteolytic acetabular defects at revision arthroplasty. PET imaging with 18F-fluoride was performed 1 week, 4 months, and 1 year after surgery. Standardized uptake values (SUVs) were calculated from ROIs placed at the defect. Primary Endpoints: To produce and analyze quantitative images that correlate with new bone formation.

Deficiencies:

- 1. Small study size*
- 2. There is no information regarding the blinding of reads or adjudication of findings*
- 3. Semiquantitative analysis is not validated*
- 4. Lack of a reference standard.*

WELL CONTROLLED STUDIES OF BONE METABOLISM AND REPAIR

Frost ML, Blake GM, Park-Holohan SJ, Cook GJ, Curran KM, Marsden PK, Fogelman I. Long-term precision of 18F-fluoride PET skeletal kinetic studies in the assessment of bone metabolism. *J Nucl Med.* 2008 May; 49(5):700-7. Epub 2008 Apr 15.

Reviewer's Comments:

The aim of this study (n=16) is to compare the long-term precision of 18F-fluoride PET with that of biochemical markers of bone turnover assessed over 6 months. Primary Endpoints: To evaluate the long-term precision of skeletal kinetic parameters measured at the lumbar spine using of 18F-fluoride PET (Four different methods for analyzing the

18F-fluoride PET data were evaluated) compared with that of conventional biochemical markers of bone turnover assessed over 6 months.

Deficiencies:

- 1. Small study size*
- 2. There is no information regarding the blinding of reads or adjudication of findings*
- 3. Lack of a reference standard*

Frost ML, Blake GM, Cook GJ, Marsden PK, Fogelman I. Differences in regional bone perfusion and turnover between lumbar spine and distal humerus: (18)F-fluoride PET study of treatment-naïve and treated postmenopausal women. *Bone*. 2009 Nov; 45(5):942-8. Epub 2009 Aug 3.

Reviewer's Comments:

This study (n=23) compared regional bone metabolism and perfusion at the lumbar spine and humerus using 18F-fluoride PET in both osteoporosis treatment naïve postmenopausal women (n=11) and those on stable antiresorptive therapy for six months (n=12). This study compares two groups of postmenopausal women for the primary endpoints of evaluation of regional variations in bone metabolism and perfusion between sites of trabecular and cortical bone; and evaluation of observable differences between skeletal sites for variances due to antiresorptive treatment.

Deficiencies:

- 1. Small study size*
- 2. ROI analysis and automation is not well validated*
- 3. There is no information regarding the blinding of reads or adjudication of findings*
- 4. Lack reference standard*

STUDIES IN THE PEDIATRIC POPULATION

Drubach LA, Johnston PR, Newton AW, Perez-Rossello JM, Grant FD, Kleinman PK. Skeletal trauma in child abuse: Detection with 18 F-NaF PET. *Radiology*. 2010 Apr; 255:173-181.

Reviewer's Comments:

This retrospective study (n=22) used 18F-fluoride PET to evaluate skeletal trauma in pediatric patients suspected of having been abused and is compared with high resolution CT.

Deficiencies:

- 1. Small study size*
- 2. There is no information regarding the blinding of reads*
- 3. There is no information regarding the Nuclear Medicine reading protocol or adjudication of these findings*

PEDIATRIC PLAN

Regarding our request for the performance of a dosimetry study among pediatric patients in the post-marketing period, the sponsor reports that initially they considered

determining such a study retrospectively from among approximately 500 patients in the appropriate age groups that have been imaged at Children's Hospital in (b) (4). Unfortunately, those patients all have been imaged only at a single time point, typically 30 or 45 minutes post injection, to minimize both sedation/anesthesia time and radiation dose. Therefore, this database is not useful to determine dosimetry, which requires imaging at multiple time points.

The sponsor reports significant human subject protection issues in the design of a new dosimetry study, particularly:

- minimization of risk [21 CFR 56.111 (a) (1)]
- risk benefit ratio reasonableness [21 CFR 56.111 (a) (2)]
- absence of the prospect of direct benefit, for more than a minimal risk study
- involving children [21 CFR 50.52] [subpart D]
- failure to meet the requirements of subpart D, 50.53; which states: the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition.

The sponsor argues against a new dosimetry study and concludes that it would be more appropriate to accept the published data for pediatric dosimetry based upon the following:

1. There are published data from International Commission on Radiologic Protection, ICRP, reports 53 and 80 that have generally been accepted as reasonable estimates by IRBs, it is difficult to argue that it is of vital importance to obtain more data to refine the estimates.
2. This study would necessitate a significant deviation from the standard of care for these children, and would, we think, skew the risk/benefit ratio and render the study unacceptable in the pediatric population as follows:
 - a. Anesthesia - To perform dosimetry studies in children, the time under anesthesia, and thus anesthesia related risk, would be significantly increased over what is needed for their clinical care, and of no benefit to the specific subject.
 - b. Radiation Exposure - Excessive radiation exposure is an issue if the study is to be performed in a modern PET/CT scanner. Multiple PET scans at different time points to determine empirical dosimetry will require more CT scans, dramatically increasing the radiation exposure in this radiosensitive population.
3. IASOfu (the approved labeling for France) uses the published ICRP data.

Reviewer's Comments:

1. *The retrospective database is inadequate to determine dosimetry because the scans were acquired mainly at the same time point.*
2. *Prolonged anesthesia and repeat CT scans would skew the risk benefit of the study*
3. *This reviewer recommends relying on the published data in ICRP reports 53 and 80*
- 4.

LABEL REVIEW

Full Prescribing Information (FPI):

Reordering of the FPI is recommended to be consistent with the Adreview label (recently approved drug in pharmacologic class). The reviewer recommends more specific information regarding: (2.2) radiation safety / patient preparation (appropriate safety measures before and after administration) and (2.7) Imaging guidelines (optimal imaging parameters).

Dosage and Administration (2.5)

Information regarding the dose (injected activity) in children needs to be included

Radiation Dosimetry (2.6)

The draft label in the 3/2000 guidance contains information (table) and references which are not up to date. The reviewer recommends updating the label and including more concise and current information and references. The updated Radiation Dosimetry information contains new references that will need to be added to the reference list.

Warnings and Precautions (5)

A warning regarding allergic reactions is needed to be consistent with the FDA PET Guidance for Sodium [F18] Injection; a warning is needed regarding the radiation risks of the product consistent with other products in this pharmacologic class.

Adverse Reactions (6)

The reviewer recommends reflecting the lack of complete safety information: “*the completeness of these sources is not known*” and deleting any misleading information.

Physical Characteristics (11.2)

The draft label in the 3/2/2000 guidance cites a publication that needs to be added to the reference list

Clinical Pharmacology (12)

The reviewer recommends updates to the information in the label and exclusion of any promotional (“rapid”, “rapidly”) terms. There are additional, specific diagnostic claims beyond altered osteogenic activity in the Clinical Pharmacology section.

The Clinical Pharmacology (12)/Pharmacodynamics (12.2)

The draft label in the 3/2000 guidance describes clinical uses of Fluorine F18 and cites several publications. The publications are dated (1960s) and the clinical uses are not supported by adequate and well controlled studies. The clinical reviewer recommends that the description of the pharmacodynamics of Fluorine F18 be retained and that the objectionable citations be deleted from the label (see appendix for details).

The Clinical Pharmacology (12)/Pharmacokinetics (12.3)

The draft label in the 3/2000 guidance cites two publications in support of statements about distribution and elimination of Fluorine F18. The reviewer recommends that the two citations be deleted because they contain inadequately supported efficacy claims.

Clinical Studies (14)

The sponsor cites several studies which give additional, specific diagnostic claims beyond altered osteogenic activity. The trials are not adequate or well-controlled and the clinical reviewer recommends that they be deleted from the label.

References (15)

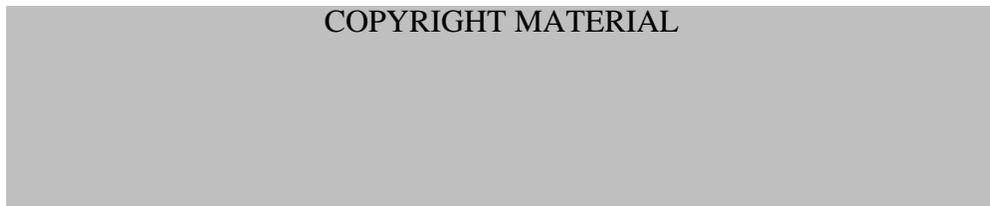
The reviewer recommends excluding much of the Sponsor's submitted information and including only the information pertinent to the product's safe use.

APPENDIX: EXCEPTS FROM THE PACKAGE INSERT IN THE 2000 GUIDANCE

1. *[Page 27. Comment: add this citation to the list]*

Table 1. Principal Emission Data for Fluorine F18

COPYRIGHT MATERIAL



** Produced by positron annihilation
From: Kocher, D.C. "Radioactive Decay Tables" DOE/TIC-I 1026, 89 (1981).

Addendum:

In their search of the AERS Quarterly Data Files (October 2008 to September 2009), the sponsor retrieved 2 unverified adverse event cases possibly involving sodium fluoride F-18 injection. Based upon their conclusions, we performed an internal search of the AERS database. The AERS search was performed on August 16, 2010 for adverse event reports

of sodium fluoride F-18 injection (Fluorine 18, GE Healthcare, NDA 17-042, approved 1972) received since January 1, 2000. The search retrieved 3 cases; we excluded all for mis-coding (correct product was sodium fluoride toothpaste).

It is likely that these 2 cases were mis-coded or did not involve sodium fluoride F-18 injection. The sponsor's conclusions were confirmed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22494	ORIG-1	NATIONAL INSTITUTES HEALTH NATIONAL CANCER INSTITUTE DIV CANCER TREATMENT AND DIAGNOSIS	SODIUM FLUORIDE F 18 INJECTION

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/s/

MICHELE B FEDOWITZ
09/10/2010

LIBERO L MARZELLA
09/10/2010

Summary Review for Regulatory Action

Date	June 24, 2009
From	Dwaine Rieves, MD Director, Division of Medical Imaging and Hematology Products
Subject	Division Director Review
NDA/BLA #	22-494 (a 505b2 application)
Applicant Name	National Cancer Institute (NCI)
Date of Submission	December 30, 2008
PDUFA Goal Date	June 30, 2009
Proprietary Name / Established (USAN) Name	(no proprietary name) Sodium Fluoride F-18 Injection
Dosage Forms / Strength	Multiple dose vial presentations (b) (4) 30 mL (b) (4) (b) (4) 10 to (b) (4) mCi/mL of sodium fluoride in 0.9% saline
Proposed Indication(s)	"indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity."
Action/Recommended Action for NME:	Complete Review

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Project Manager	Thuy Nguyen, M.P.H.
Medical Officer Review	Michele Fedowitz, MD
Statistical Review	Not Applicable (relies solely on prior determination of safety and efficacy for previously approved product)
Pharmacology Toxicology Review	Adebayo Laniyonu, PhD
CMC Review/OBP Review	Milagros Driver, PhD/Eldon Leutzinger, PhD
Microbiology Review	Robert Mello, PhD/Bryan Riley, PhD
Clinical Pharmacology Review	Christy John, PhD
DDMAC	Michelle Safarik, PA-C
DSI	No assignment (not applicable)
CDTL Review	Louis, Marzella, MD, PhD
OSE/DMEPA	Not applicable (505b2)
OSE/DDRE	Not applicable (505b2)
Pediatric and Maternal Health	Not applicable (505b2)

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

TL = Team Leader

1. Introduction:

This 505b2 New Drug Application (NDA) was submitted by the NCI to support the use of Sodium Fluoride F18 Injection for the indication cited above. The applicant's clinical, preclinical, pharmacology and toxicology data predominantly relate to citation to FDA's March 10, 2000 Federal Register notice that stated FDA has approved F18 Sodium Fluoride injection (NDA 17042) in 1972 for use in defining areas of altered osteogenic activity and that the drug was withdrawn from marketing in 1975 for reasons other than safety or efficacy. The applicant did provide 41 published reports pertaining to the use of F18 sodium fluoride injection. Hence, the bulk of the review contents for this application pertained to manufacturing information.

The manufacturing information supplied by the applicant was particularly challenging because the applicant's entire information was contained within referenced Drug Master Files (one held by Siemens Molecular Imaging and the other by (b) (4)). The extent to which the applicant was aware of the quality of the manufacturing information is unclear; this observation is based upon the multiple manufacturing deficiencies detected during the review cycle.

Overall, the major deficiencies during this review cycle pertained to manufacturing information and these deficiencies form the basis for the Complete Review letter. The other review disciplines found the overall risk-benefit profile favorable. Of note, the clinical review team determined that the published data were sufficient to support labeling of the product for use in children. This finding will ultimately be conveyed to the applicant and is notable because the applicant had requested a waiver of pediatric studies.

2. Background:

Positron emission tomography (PET) products have a complicated regulatory history that has involved federal register notices, public workshops and certain user fee agreements. However, F18 sodium fluoride regulatory history is relatively straightforward as follows:

- 1972 FDA approved sodium fluoride F18 injection (Nycomed Amersham) for use as a bone imaging agent to define areas of altered osteogenic activity

- 1975 Marketing of sodium fluoride F18 injection suspended for commercial reasons (not safety concerns)

The NCI notes in the current application that they are relying upon FDA's prior findings of safety and efficacy (the Federal Register notice from 2000) for the previously product. The NCI also notes that they regard approval of their product as important because of periodic shortages of technetium 99m, a major component of the product currently used in bone scans. Hence, approval of sodium flouride F18 injection would, in the applicant's

opinion, help provide an alternate diagnostic modality when conventional bone scans can not be performed due to drug shortages.

3. Chemistry, Manufacturing and Controls:

I concur with the conclusions reached by the chemistry reviewer (Dr. Driver) regarding the unacceptability of the manufacturing of the product. Multiple manufacturing deficiencies were identified and facility inspections also revealed problems. The Office of Compliance had a "with hold approval" recommendation.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. No post-marketing commitments/requirements were requested.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. No outstanding issues were identified and no post-marketing commitments were requested.

6. Clinical Microbiology:

Multiple microbiology deficiencies were evident in the drug master files and I concur with the reviewer (Dr. Mello) regarding the insufficiency of the available information.

7. Clinical/Statistical-Efficacy:

Dr. Michele Fedowitz provided the clinical review for this initial cycle and Dr. Louis Marzella provided the secondary review. I concur with these major findings and recommendations. Importantly, 41 publications were reviewed, including a few that cited use of the product in children. No non-publication data were submitted.

8. Safety:

As noted above, the applicant has relied upon FDA's prior finding of safety and efficacy for F18 sodium fluoride injection (1972 approval). The review of the 41 submitted publications found no information that altered the risk-benefit assessment that supported the 1972 approval.

Post-marketing Requirements (PMR):

The review team envisions the need for one PMR, to obtain dosimetry data in pediatric patients. The available dosimetry data is based upon modeling and the provision of actual, clinically-obtained data will verify the acceptability of the modeling data.

9. Advisory Committee Meeting:

This application was not presented to an Advisory Committee because the product relies upon FDA's prior finding of safety and efficacy for a very similar product. This application is not for a new molecular entity.

10. Pediatrics:

The supplied pediatric plan was a request for waiver of all pediatric studies. However, the review team regards the published data as sufficient to support the use of the product in certain pediatric patients; this topic will be further explored in the subsequent review cycle, following the sponsor's response to the review team's finding.

11. Other Relevant Regulatory Issues:

Overall, the major finding from the review of the application was multiple deficiencies in the manufacturing information. This information is contained within drug master files and the extent to which the applicant is aware of these problems is unclear. Nevertheless, these deficiencies preclude approval and the applicant will be encouraged to work with the holders of the drug master files to resolve the issues. Additionally, we will convey our findings regarding the pediatric data to the applicant in our Complete Review letter.

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/s/

Rafel Rieves
6/24/2009 10:38:30 AM
MEDICAL OFFICER

Cross Discipline Team Leader Review

Date	June 6 , 2009
From	Louis Marzella M.D., Ph.D.
Subject	Cross-discipline Team Leader Review
NDA/BLA #	22-494
Supplement#	Original submission
Applicant	National Cancer Institute/Cancer Imaging Program
Date of Submission	December 31, 2008
PDUFA Goal Date	June 30, 2009
Proprietary Name	- None
Established (USAN) names	- Sodium Fluoride F18 Injection
Dosage form	- Sterile Injection for Intravenous Administration
Strength	- 10- ^{(b) (4)} mCi/ml at end of synthesis (EOS)
Proposed Indication	Positron Emission Tomography (PET) imaging of bone to define areas of altered osteogenic activity
Recommended:	Complete Response Action

1. Introduction

This 505(b)(2) New Drug Application (NDA) relies on the FDA findings of safety and effectiveness of Sodium Fluoride F18 described in the March 10, 2000 Federal Register notice (65 FR 12999-13010). That FR 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 drug was withdrawn from sale in 1975 for reasons other than safety or efficacy.

The NDA applicant (National Cancer Institute, NCI) is not the manufacturer of the sodium fluoride F18 and the NDA references two Drug Master Files (DMFs) for the chemistry, manufacturing, and control (CMC) and microbiology data. The FDA microbiologist determined that there is insufficient information in the DMFs to assess the sterility of the final drug product. The FDA CMC reviewer determined that there is 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 NDA contains no new pharmacology or toxicology data and no new data are needed. The NDA applicant provided a summary of recent publications on the clinical use of sodium fluoride F18.

The primary and secondary clinical reviewers examined the publications for:

- safety signals including lack-of-efficacy reports
 - no safety signals were identified however the completeness of the reports is

- questionable
 - no lack-of-efficacy reports were identified
- clinical experience in various patient populations defined by age and by underlying medical conditions
 - important new information on use and dosage of sodium fluoride F18 in children was identified
- current clinical dosing and administration practices and imaging protocols
 - doses higher than the dose recommended for the reference drug are currently in clinical use
- human dosimetry data
 - need to revise minor (not affecting safety) inaccuracies in numbers cited in the package insert was noted
 - data relevant to children were assessed

Background

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 (lower cost, wider availability) diagnostic alternative to Sodium Fluoride F18 Injection PET imaging is Technetium-99m labeled diphosphonate gamma camera imaging. Tc 99m diphosphonates are indicated for use as bone imaging agents to delineate areas of altered osteogenesis. Alternatively, computed tomography (CT) or magnetic resonance imaging (MRI) 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 (NCI) 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.

The regulatory history of Sodium Fluoride F18 is as follows:

- 1972 - Sodium Fluoride F 18 Injection approved as a bone imaging agent to define areas of altered osteogenic activity (NDA 17042, Nycomed Amersham)

- 1975 - Sodium Fluoride F 18 Injection marketing suspended for commercial reasons
- 2000 - Federal Register Notice of FDA findings of safety and effectiveness of certain PET drugs including Sodium Fluoride F18

The applicant did not request FDA advice before submitting this NDA.

2. CMC

The drug product is a sterile radiopharmaceutical injection for intravenous administration having a potency of 5-200 mCi/ml at EOS (end of synthesis). The drug is contained in a (b) (4) sterile closed vial with an elastomeric stopper and an aluminum crimp seal. Sodium [¹⁸F] Fluoride is the drug substance and the drug product.

The NDA applicant is not the manufacturer of Sodium Fluoride F18 and the NDA makes reference to two DMFs for the CMC and microbiology data. The chemistry and microbiology reviewers identified important deficiencies in the submission and concluded that approval of the NDA is not warranted.

Microbiology review

The FDA microbiologist reviewed DMF (b) (4) titled: “Sodium Fluoride F18 Injection Drug Substance” held by (b) (4). The NDA listed five (b) (4) manufacturing sites. The FDA microbiologist concluded that the information provided in the DMF is not adequate to support approval of NDA 22-494. The deficiencies involve information on: final product container, container closure system, final product vial assembly, (b) (4) process validation, and analytical procedures. Specifically the FDA microbiologist determined that:

- information on the final immediate drug product container (vial size, supplier) needs to be more complete and consistent
- information on container closure system for the drug product is insufficient and there are no data on container closure integrity; this is a concern because of multiple penetrations of the closure system during clinical use; the reviewer concluded that microbiological studies to support the proposed 12-hour storage and use time are needed
- the use of an (b) (4) in final product assembly might compromise the final product vial sterility
- microbiological testing of the (b) (4) environment needs to be performed

- (b) (4) techniques used during manufacturing need to be evaluated by process simulation studies; criteria for operator qualification, microbiological methods and acceptance criteria are necessary
- analytical procedures for bacterial endotoxin testing, for sterility testing, and for (b) (4) integrity need to be adequately described to permit review of the methodology
- specification for start of sterility testing up to (b) (4) EOS requires justification or change (24 hr limit is specified by USP<823>)

The FDA microbiologist also reviewed DMF 21582 titled: “Sodium Fluoride F18 Injection as Manufactured by PETNET Houston LLC...”. Only the specific site listed in the NDA was covered by the review. The FDA microbiologist concluded that the information provided in the DMF is not adequate to support approval of NDA 22-494.

The deficiencies involved information on: final product container, container closure system, (b) (4) process validation, control of drug product, and analytical procedures. The FDA microbiologist determined that:

- packaging for the final dosage form of the product needs important clarifications; no information is provided on the unit-dose syringes for individual patient use, the (b) (4) multiple dose drug product vial does not conform to USP guidance that specifies a 30 ml limit
- information on container closure system for the drug product is insufficient and there are no data on container closure integrity; this is a concern because of multiple penetrations of the closure system during clinical use; microbiological studies to support the 12-hour storage and use time are needed
- microbiological testing of the (b) (4) environment needs to be performed
- (b) (4) techniques used during manufacturing need to be evaluated by process simulation studies; criteria for operator qualification, microbiological methods and acceptance criteria
- testing for endotoxin needs to be completed before release of the drug product
- analytical procedures for bacterial endotoxin testing, for sterility testing, and for (b) (4) integrity need to be adequately described for review of the methodology

CMC review

The FDA CMC reviewer identified the following deficiencies:

- product quality attributes (e.g. strength) and specifications need to be consistent with product labeling and USP requirements
- testing methodology and schedule need to be consistent with CGMP and USP
- acceptance criteria for radiochemical identification, analytical test methods used in the control of product, and stability data for highest radioactivity concentration (b) (4) mCi/ml)
- post approval drug stability protocol
- updated information on single-dose (syringe) and multi-dose vial presentations
- labeling for immediate drug container and shielding and packaging containers
- protocol for the NDA applicant and the DMF holders to communicate changes in the chemistry, manufacturing and controls that could potentially affect the identity, purity, quality, and strength of the drug product

Facilities inspection

The manufacturing facilities were inspected and assessment by the Offices of Compliance and New Drug Quality Assessment is pending.

3. Nonclinical Pharmacology/Toxicology

The NDA submission does not contain new non-clinical pharmacology and toxicology data and no new data are needed.

4. Clinical Pharmacology/Biopharmaceutics

The NDA contains no new clinical pharmacology data and none are required. The pharmacology section of the package insert contains diagnostic claims in benign or malignant diseases of bone that are not supported by adequate and well controlled studies. These claims are not justified. The Clinical Pharmacology section of the label, including the mechanism of action, pharmacodynamics, and pharmacokinetics sections will need to be updated.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical- Efficacy

The NDA applicant did not perform a systematic review and analysis of the published clinical experience with Sodium Fluoride F18. Therefore statistical review of the submission is not needed.

The applicant conducted a non-systematic review of the literature for Sodium Fluoride F18 and other bone imaging agents and provides a descriptive summary of each article selected. The literature provides evidence of clinical use Sodium Fluoride F18 to image bone in various diseases. However as the primary clinical reviewer states, each one of the studies has important flaws in study design and other study protocol aspects, the study reports generally lack important information on study conduct and data analysis procedures (**Table 1**). The study deficiencies include: inconsistent use of reference standards, sample size not based on statistical methods, procedures for minimizing bias not optimal, outcome measure not suitable for regulatory demonstration of clinical benefit, lack of prespecified analysis plan, lack of detailed accounting of missing data. As a result the secondary and primary clinical reviewers agree that the studies are not adequate or well controlled for regulatory purposes and do not provide substantial new evidence of efficacy. As such no new efficacy claims for Sodium Fluoride F18 are warranted including comparative claims vs. other diagnostic agents, claims of specific diagnostic performance, or claims of efficacy in specific clinical conditions.

As the primary clinical reviewer notes (see table 2 of that clinical review) the published studies provide important evidence that the dose in current clinical use differs materially from the dose (0.5-2 mCi) recommended in the reference drug package insert (see guidance: “Pet drug applications-content and format for NDAs and ANDAs”). Doses reported in the publications range from approximately 3 to 20 mCi with average median doses around 8-10 mCi in various benign and malignant disease states. While no data from dose-ranging studies have been presented, the secondary and primary reviewers agree that the reported experience in approximately 1100 patients supports the proposed new recommended dose (8-12 mCi) of Sodium Fluoride F18.

Table 1. Clinical studies of bone imaging agents summarized by the NDA applicant

Authors	Reviewer’s assessment
Submission date: December 30, 2008	
Blau et al 1962	Reference to preliminary clinical experience with 18F NaF (N=18). No data shown.
Blake et al. 2001	Review of bone turnover measurements using 18F NaF and 99mTc-MDP
Hoh et al. 1993	Clinical experience with 18F NaF whole body skeletal imaging in patients (n=19) and healthy volunteers (n=19). <i>Comments: sample size problematic</i>
Schirrmeister et al. 1999	Prospective comparison of diagnostic performance of 18F NaF and 99mTc in patients with breast cancer (N=34; n=6 with known BM). TS: MRI, CT, X-ray, clinical. <i>Comments: sample size is problematic</i>
Petren-Malmin et al. 1998	Descriptive comparison of 18F NaF and CT in patients with breast cancer (N=5)
Schirrmeister et al.	Inpatient descriptive comparison of 18F NaF and 99mTc in patients (N=53) with lung

Authors	Reviewer's assessment
2001	cancer. TS: MRI, other imaging methods and clinical. Primary EP: ROC. Read protocol incomplete, readers of TS had access to investigational scans; n=12 positive for BM. <i>Comments: EP, study power, reading protocol are problematic</i>
Hetzel et al. 2003	Inpatient prospective comparison of 18F NaF and 99mTc in patients (N=103) with lung cancer. TS: MRI, other imaging methods and clinical. EP: ROC. Read protocol incomplete. N=13 positive for BM. <i>Comments: EP, study power, reading protocol are problematic</i>
Schirrmester et al. 1999	Inpatient prospective comparison of 18F NaF and 99mTc in patients (N=44; n=9 with known BM) with prostate, thyroid, or lung cancer. TS: MRI, other imaging methods and clinical (not used consistently) EP: ROC. Read protocol incomplete. n=15 positive for BM. <i>Comments: EP, study power, reading protocol are problematic</i>
Even-Sapir et al. 2006	Inpatient prospective comparison of 18F NaF (using PET/CT) and 99mTc in patients (N=44) with prostate cancer. TS: MRI, other imaging methods and clinical (not used consistently) EP: sens and spec. Read protocol incomplete, consensus reads. n=23 positive for BM. <i>Comments: sens and spect of 18F-PET and 99mTc numerically similar; study power and reading protocol problematic</i>
Grant et al. 2008	Review of 18F NaF clinical studies
Bridges et al. 2008	Review of 18F NaF clinical studies
Frost et al. 2008	Bone metabolism using 18F NaF <i>Comment: unlabeled use</i>
Lim et al. 2007	Prospective experience with 18F NaF in patients (N=94, ages 4-26) with back pain. No TS, no independent blinded reads. <i>Comment: Descriptive data</i>
Ovadia et al. 2007	Experience with 18F NaF (PET-CT) in adolescents (N=15, 9-19 years of age) with back pain. No TS, no independent blinded reads. <i>Comment: Descriptive data</i>
Schiepers et al. 1998	Bone flow using 18F NaF in patients (N=5) with osteonecrosis <i>Comment: Descriptive data</i>
Forrest et al. 2006	Imaging femoral head in patients (N=10) who underwent resurfacing <i>Comment: Descriptive data</i>
Sorensen et al. 2003	Assessment of bone allografts (N=5) <i>Comment: Descriptive data</i>
Piert et al. 1999	Assessment of bone allografts (N=16) <i>Comment: Descriptive data</i>
Dageb et al. 2007	Review of 18F NaF clinical studies
Messa et al. 1993	Comparison of bone metabolism using 18F NaF in patients with renal disease (n=11) and healthy volunteers (n=11) <i>Comment: unlabeled use</i>
Blake et al. 2002	Bone metabolism in postmenopausal women (N=69) <i>Comment: unlabeled use</i>
Installe et al. 2005	Response to bisphosphonates in patients (N=14) with Paget's disease of bone <i>Comment: unlabeled use (response assessment)</i>
Submission date: March 10, 2009	
Beheshti et al. 2008	Prospective inpatient comparison of 18F NaF (PET-CT) and 18F-fluorocholine(PET-CT) in patients (N=38, all positive for BM) with prostate cancer. EP sens and spec. Unblinded consensus reads, contribution of CT to PET-CT diagnosis not assessed. <i>Comment: reading protocol problematic</i>
Berding et al. 1995	Evaluation of bone grafting in patients (N=9) undergoing maxillofacial surgery. <i>Comment: Descriptive data</i>
Bhargava et al. 2008	Single case report
Brunkhorst et al. 2002	Single case report
Brenner et al 2004	Assessment of bone metabolism in patients (N=34) with allogenic bone grafts <i>Comment: unlabeled use</i>
Brenner et al 2004	Comparison of bone metabolism quantitation methods in patients (N=33) after bone resection <i>Comment: unlabeled use</i>
Cook et al. 2002	Assessment of bone metabolism in patients (N=7) with Paget's disease of bone
Cook et al. 1999	Assessment of bone metabolism in postmenopausal women (N=10)
Drubach et al.2008	Single case report
Even-Sapir et al. 2007	Review of clinical studies
Even-Sapir et al. 2004	Prospective inpatient comparison of 18F NaF (PET) and 18F NaF (PET-CT) in patients (N=44, n=26 positive for BM) with various cancers. EP sens and spec. TS: various imaging modalities including 18F-FDG and 99mTc. Blinded consensus reads with 2 day interval between PET and PET-CT reads. <i>Comments: TS, reading protocol problematic</i>
Frost et al. 2007	Assessment of bone turnover in postmenopausal women (N=89) <i>Comment: unlabeled use</i>
Frost et al. 2003	Assessment of bone turnover in postmenopausal women (N=18) treated with bisphosphonates

Authors	Reviewer's assessment
	<i>Comment: unlabeled use</i>
Frost et al. 2004	Assessment of bone turnover in normal, osteopenic and osteoporotic women (N=72) <i>Comment: unlabeled use</i>
Garnie and Maghraby 2008	Assessment of patients (N=67) with back pain.. <i>Comment: No TS, descriptive data</i>
Hawkins et al. 1992	Assessment of 18F NaF turnover (N=13)
Hirata et al. 2005	Assessment of 18F NaF turnover (N=12)
Hoegerle et al. 1998	Randomized parallel group comparison of combined 18F-FDG and 18F NaF and 18FNaF alone in patients (N=60) with various cancers. Blinded reads. EP interobserver agreement. <i>Comments: descriptive statistics, combined bone and soft tissue diagnosis</i>
Langstaer et al. 2006	Review of clinical studies
Laverik et al. 2008	Assessment of condylar hyperplasia (N=8)
Park-Holohan 2001	Assessment of bone turnover in postmenopausal women (N=70) <i>Comment: unlabeled use</i>
Schiepers et al. 1997	Assessment of bone blood flow and 18F NaF uptake
Schiermaster et al. 2001	Retrospective study of patients (N=35) with known thyroid carcinoma metastatic to bone who underwent 18F NaF, 99mTc, 131I, imaging. TS: X-ray, CT, MRI, 18FDG PET, Imaging protocol insufficiently detailed. <i>Comments: Descriptive data</i>
Sterner et al. 2007	Assessment of patients (N=14) post total knee arthroplasty. <i>Comments: Descriptive data</i>
Tayama et al. 2007	Assessment of attenuation correction in patients (N=32) with various conditions
Tse et al. 1994	Single case report
Wade et al. 2006	Single case report

BM bone metastases; EP primary endpoint; ROC receiver operating curve; TS truth standard;

7. Safety

No adverse reactions have been reported for Sodium Fluoride F18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known; the published studies were not specifically designed to capture safety events. The NDA applicant notes that the adverse reactions that would be expected for this drug are those that can occur nonspecifically with any injectable drug, such as infiltration or hematoma at the injection site, vasovagal reactions, or allergic reaction. These reactions have not been reported for Sodium Fluoride F18.

Radiopharmaceuticals are associated with a risk of malignancy due to radiation exposure to the patient. As the primary reviewer states, the maximum effective radiation dose from Sodium Fluoride F18 Injection (12 mSv) is higher than the maximum dose from the other approved bone imaging agents (Tc 99m MDP products, approximately 4 mSv). FDG F18 is an approved PET agent used off-label for bone imaging (dose recommended in label 5-10, dose in clinical use 10-20 mCi). The effective dose for FDG F18 ranges from 3.5 to 14 mSv. Based on the dosimetry data the primary and secondary reviewers agree that the radiation exposure to patients at the proposed new dose is acceptable. For more details the reader is referred to the primary clinical review. The primary and secondary reviewer acknowledge the expert participation by DMIHP's radiation safety team in the review of the published dosimetry data and relevant label revisions.

Given the long latency and high background rate of cancer it is not feasible to quantify the risk associated with the administration of Sodium Fluoride F18. The package insert cites the risk of malignancy as a warning.

The increase in mass dose of Na F associated with the new recommended dose of Sodium Fluoride F18 is clinically unimportant.

8. Advisory Committee Meeting

No advisory committee meeting is needed.

9. Pediatrics

Children are at higher risk of cancer from radiation exposure compared to adults, therefore radiation dosimetry in children requires special attention. Children will receive a weight-based administered activity. The primary reviewer states that the effective dose for children ranges from 3.4 – 3.9 mSv. This dose is lower than the 5 mSv RDRC guidelines for dose limits to pediatric subjects. There are limited clinical data available in children. The currently available weight-based estimations of dose are derived from patient simulators. The primary and secondary reviewers agree that a Post Marketing Requirement to study the radiation dosimetry of the product in a small number of children is needed.

10. Other Relevant Regulatory Issues

 (b) (4)

11. Labeling

The package insert in the submission generally conforms to the insert for Sodium Fluoride F18 recommended by FDA in the March 2000 guidance titled: “Pet drug applications-content and format for NDAs and ANDAs”. The NDA applicant revised the format of that package insert to make it consistent with the current format.

The applicant added to the package insert information and recommendations on clinical use of Sodium Fluoride F18 that are derived from the published clinical experience. The reviewers

agree that the recommended new dose of Sodium Fluoride F18 is uniformly supported by the literature and by published clinical practice recommendations. However the remainder of the clinical information the applicant added to the package insert (e.g. new efficacy claims in specific population subgroups, comparative efficacy claims relative to other imaging agents) is not supported by adequate and well controlled studies and the clinical reviewers recommend that such information be stricken from the label.

In addition the review team recommends updating the Sodium Fluoride F18 label with important clinical information on radiation safety and making the label consistent with recent radiopharmaceutical labels. The reviewers also recommend several formatting changes. The major changes are in the following sections.

- 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.
- 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.

The reader is referred to the revised label recommended by the clinical, CMC, microbiology, and pharmacology reviewers for complete details of label revisions.

12. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

From the clinical perspective the primary and secondary reviewer recommend approval of the NDA pending agreement by the applicant to conduct dosimetry studies of Sodium Fluoride F18 in children and to revise the label as recommended by the NDA review team.

Given the outstanding microbiology and chemistry issues, a complete response action will be taken.

Risk Benefit Assessment

Based on FDA's previous findings of safety and efficacy, the product is indicated for use in PET imaging of altered osteogenic activity in bone. No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature and of FDA's AERS database.

Recommendation for Postmarketing Risk Management Activities

There are limited clinical data available in children. The current weight-based estimations of dose are derived from patient simulators. The NDA applicant needs to study post-marketing the radiation dosimetry of the Sodium Fluoride F18 in two children in each of the following age groups: 1-5, 6-10, and 11-16 years old. The milestones post-approval would be year 0.5: protocol finalized and enrollment open; year 3.5: study completed; year 4: complete study report and proposed revised labeling.

Recommended Comments to Applicant

The chemistry and microbiology deficiencies have been communicated to the NDA applicant. The revised package insert and the requirement for a post-marketing study will be communicated in the planned complete response letter to the applicant.

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MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-494
Priority or Standard	P
Submit Date(s)	30 December 2008
Received Date(s)	31 December 2008
PDUFA Goal Date	30 June 2009
Reviewer Name(s)	Michele Fedowitz, M.D.
Review Completion Date	13 May 2009
Established Name	Sodium Fluoride F18 Injection
(Proposed) Trade Name	Sodium Fluoride F18 Injection
Therapeutic Class	PET Imaging Agent
Applicant	National Cancer Institute (NCI)
Formulation(s)	10- ^{(b) (4)} mCi/mL
Dosing Regimen	single dose 8-12 mCi IV
Indication(s)	PET imaging of bone to define areas of altered osteogenic activity
Intended Population(s)	Patients who are at risk for benign or malignant conditions characterized by alterations in osteogenic activity

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1 Recommendations/Risk Benefit Assessment

Recommendation on Regulatory Action

The clinical reviewer recommends that F18 Sodium Fluoride Injection be approved as a radioactive diagnostic agent for positron emission tomography (PET) indicated for imaging of bone to define areas of altered osteogenic activity. The recommendation for approval of this 505 (b) (2) NDA is based on FDA's findings of safety and effectiveness pursuant to the March 10, 2000 publication of the Federal Register (65 FR 12999-13009); Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications. This notice states that FDA approved F-18 Sodium Fluoride injection (NDA 17-042) in 1972 to define 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 Sponsor's submitted data supports the safety and effectiveness for the product in defining areas of altered osteogenic activity. This reviewer's examination of the recent (1999-2008) literature finds no contradiction to the safety and effectiveness of the product for the proposed use in the intended population.

1.2 Risk Benefit Assessment

This product has an acceptable risk-benefit profile based on FDA's findings of safety and effectiveness in the March 10, 2000 publication of the Federal Register (65 FR 12999-13009). This product has shown clinical utility in PET imaging of osteogenic activity; specifically, imaging of bone metastases, as well as, other benign bone disease. An added benefit of approval would be to have an alternative bone imaging radiopharmaceutical in the event of a 99m-Techetium generator shortage (currently used to prepare 99mTc-labeled diphosphonates). Recently, the aging nuclear reactors worldwide that produce the molybdenum parent required for this generator have been repeatedly shut down for safety reasons; and the shutdowns have sometimes been prolonged. During these shortages, patients, many with life threatening conditions, frequently cannot obtain the studies they need and testing is either cancelled or delayed as a result. Availability of sodium fluoride F 18 for bone imaging meets a critical public health need during the sporadic and prolonged interruptions that have occurred frequently in the supply of 99mTc generators.

No adverse reactions have been reported for Sodium Fluoride F 18 Injection based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known; as the published studies were not specifically designed to capture safety events. The sponsor notes that the primary adverse effects that would be expected for this drug are those that can occur non-specifically with any injectable drug, such as infiltration or hematoma at the injection site, vasovagal reactions, or allergic reaction. These events are theoretical, none have been reported.

Additionally, this product carries a risk of radiation exposure to the patient. Although there is a presumed risk of cancer from any dose of radiation, the risk is small. The International Commission on Radiologic Protection (ICRP) gives a risk coefficient (approximate lifetime risk of death) of 1/2000 for an Effective Dose of 10 mSv (2008). The clinical reviewer recommends including this risk in the label (Warnings and Precautions). This risk would be lower for older adults and higher for pediatric patients. The reviewer recommends including information in the label to reflect these differences (Warnings and Precautions and Use in Specific Populations).

Despite this radiation exposure and presumed risk, the clinical reviewer deems this product to be safe at the suggested administered activities (7 Review of Safety). In fact, there are no radiation dose limits for medically indicated procedures. Nevertheless, the dose to the patient can be estimated based on data from the Nuclear Regulatory Commission¹ and the International Commission on Radiopharmaceutical Protection (ICRP)²; which present phantom-derived dosimetry data of different radiopharmaceuticals (Table 3). For example, the sponsor proposes a maximum administered activity of F18 NaF equal to 592 MBq (12 mCi); therefore, the Effective Dose would be approximately 12 mSv for a 70 kg adult. This maximum effective dose of 12 mSv is reasonable when compared to other important comparators: the dose limits to research subjects for studies under RDRC (Radioactive Drug and Research Committee) is 50 mSv per year [21 CFR 361.1 (b)(3)(i)]; the Nuclear Regulatory Commission's (NRC) dose limits for the occupational exposure of a radiation worker in one year is 50 mSv [10CFR 20.120 1(a)(1)(i)]; and the average background radiation exposure for a United States citizen is approximately 3 mSv.

Since children are at higher risk of cancer (presumably) for an equivalent effective dose, the examination of radiation dosimetry in children with the product requires special attention. In nuclear medicine, children receive a weight-based administered activity. Based on the data from the ICRP (Table 3); the Effective Dose for children ranges from 3.4 – 3.9 mSv, with 3.6 mSv estimated for a 1 year old child. This is below the RDRC guidelines for dose limits to pediatric research subjects (10 % of the maximum adult dose), or 5 mSv. These Effective Dose estimations are derived from phantoms and not actual human data. Therefore, the clinical reviewer recommends that the sponsor comply with a Post Marketing Requirement to study the radiation dosimetry of the product in children. The reviewer also recommends additions to the label (Dosage and Administration, Radiation Dosimetry) to reflect the weight based dosimetry data that are currently available.

1.3 Recommendations for Postmarket Risk Management Activities

See 1.4 Recommendations for Postmarket Studies/Clinical Trials

1.4 Recommendations for Postmarket Studies/Clinical Trials

There is limited clinical data available in children. The currently available weight-based estimations of Dose are derived from phantoms and not actual human data. Therefore, the clinical reviewer recommends that the sponsor agree to a Post Marketing Requirement to study the radiation dosimetry of the product in 6 children in the following, equally represented, cohorts: 1-5 year old, 6-10 year old, and 11-16 year old.

2 Introduction and Regulatory Background

2.1 Product Information

Sodium Fluoride F 18 Injection is a positron emitting radiopharmaceutical. The active ingredient, Sodium Fluoride 18F (18F-NaF), has the molecular formula Na18F, a molecular weight of 40.99, and the following chemical structure: Na+ 18F-. It is cyclotron produced by (b) (4). The half-life of 18F is 109.7 minutes and it decays back to 18O. Each mL of the solution contains 10 (b) (4) mCi no carrier added radioactive fluoride 18F in 0.9% aqueous sodium chloride. The product is provided as a ready-to-use, isotonic, sterile, pyrogen-free, clear and colorless solution, suitable for intravenous administration

The sponsor's proposed indication is as a radioactive diagnostic agent for positron emission tomography (PET) of bone to define areas of altered osteogenic activity. It is intended for use in patients with benign and malignant bone disease. The product has been used in children and will conceivably be used in children for benign or malignant disease. The dosing regimen will be as a single dose intravenous administration between 8-12 mCi for adults.

2.2 Table of Currently Available Treatments for Proposed Indications

The current alternative to Sodium Fluoride F18 Injection PET imaging is gamma camera imaging with the Technetium-99m labeled disphosphonates. Tc 99m disphosphonates are indicated for use as bone imaging agents to delineate areas of altered osteogenesis.

Table 1: Licensed Tc 99m Agents for Imaging Areas of Altered Osteogenic Activity

Trade Name	Chemical Name	NDA	Year of Approval	Manufacturer
MDP-Bracco	Technetium Tc-99m Medronate Kit	18107	1981	BRACCO
Draximage MDP-10	Technetium Tc-99m Medronate Kit	18035	1978	DRAXIMAGE
Draximage MDP-25	Technetium Tc-99m Medronate Kit	18035	1978	DRAXIMAGE

CIS-PYRO	Technetium Tc-99m Pyrophosphate Kit	19039	1987	PHARMALUCENCE
CIS MDP	Technetium Tc-99m Medronate Kit	18124	1979	PHARMALUCENCE
TECHNESCAN	Technetium Tc-99m Oxidronate Kit	18321	1981	MALLINCKRODT
TECHNESCAN PYP KIT	Technetium Tc-99m Pyrophosphate Kit	17538	1974	MALLINCKRODT
TECHNETIUM TC 99M MDP	Technetium Tc-99m Medronate Kit	18141	1979	GE HEALTHCARE

Alternatively, CT or MRI can be used to image bone; however, neither modality is practical for a full body bone survey as is possible with Technetium bone scans.

2.3 Availability of Proposed Active Ingredient in the United States

FDA approved Sodium Fluoride F 18 Injection (NDA 17-042) as a bone imaging agent to define areas of altered osteogenic activity in 1972. The NDA holder, Nycomed Amersham (now GE Healthcare), stopped marketing the drug in 1975. It remains in clinical use for research purposes as a bone imaging agent. In the March 10, 2000 publication of the Federal Register (65 FR 12999-13009); FDA determined that Sodium Fluoride F 18 Injection was not withdrawn from sale for reasons of safety or effectiveness. It is listed in the Orange Book's "Discontinued Drug Products List". The concentration of the reference listed product is 0.5-2 mCi/mL and the proposed manufactured product is a new concentration, 10-^{(b) (4)} mCi/mL.

Sodium Fluoride F 18 is manufactured under the supervision of radiopharmacists following procedures that conform to USP <823> PET compounding standards and the USP monograph for Sodium Fluoride F 18 Injection.

2.4 Important Safety Issues with Consideration to Related Drugs

Radiopharmaceuticals may increase the risk of cancer.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

There has been no presubmission regulatory activity for the NDA. ^{(b) (4)}

2.6 Other Relevant Background Information

The product is approved for marketing in France. The recommended dose is 4 MBq/kg, or 280 MBq (7.6 mCi) for a 70 kg adult.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was presented in electronic form and placed in the FDA EDR site. The narrative sections are appropriate and the sponsor has complied with early requests for a comprehensive and organized presentation of the supportive data needed to justify the proposed dose as well as to update the safety and effectiveness of the product since the FDA's March 2000 findings.

3.2 Compliance with Good Clinical Practices

No new clinical studies were conducted or required in support of this NDA.

3.3 Financial Disclosures

Form FDA 3455 and financial certifications and disclosures are not required since clinical trials were not performed to support the application. The PET Safety and Efficacy notice provided a waiver of the User Fee for application (section IV.E, p13004), provided that the applicant submits with its NDA a statement that it waives any right to market exclusivity to which it might be entitled under the act. The NCI did waive exclusivity.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See review by the FDA chemist for complete listing and discussion of the CMC deficiencies for the application.

The NDA sponsor is not the manufacturer of the drug product; therefore, the NDA holder does not have direct access to manufacturing information. All chemistry, manufacturing and controls (CMC) information and data for the drug product is presented in two Type II Drug Master Files (DMFs) from Siemens Molecular Imaging (DMF # 21582) and (b) (4)

Letters of Authorization from Siemens Molecular Imaging, Inc. allowing FDA to refer to DMF 21582 and from (b) (4) for information are provided. There have been ongoing CMC concerns since filing. Due to this situation, the sponsor, being the NDA holder, needs to identify a mechanism to capture the manufacturing changes (i.e., manufacturing change control protocol) and to inform those in the field of the changes, such as: quality control procedures, container- closure, suppliers of target material or any other change that could potentially affect the identity, purity, quality and strength of the drug product. They need to identify labeling and distribution practices that distinguish between the commercial product and product manufactured and distributed under FDAMA section 121 or for investigational use.

In addition, several deficiencies in the DMF files to support this NDA were identified. Regarding the manufacturing and controls: the product specifications differ from the NDA and USP monograph for Na Fluoride F18 Injection and USP <823> Chapter-Radiopharmaceuticals for PET; there is missing batch information regarding strength of stability lots; there is missing drug product compounding specifications to include test and acceptance criteria for Radiochemical Identity; additional information on process controls, analytical methods and stability protocols is needed.

4.2 Clinical Microbiology

See review by the FDA microbiologist for complete listing and discussion of the Microbiology deficiencies for the application.

Regarding the microbiology processes; it is unclear what methods are actually used and conformance to USP <85> and/or <823>; there are no environmental monitoring action/alert limits; there is no process simulation information (procedures, specifications and actual data); there are no microbial studies data supporting 12 hour storage at room temperature (25 deg C). I.e., the growth potential of the final drug product over that time period; no container/closure integrity data is provided; the bacterial endotoxin testing method needs to be specified as pre-release; there are no DMF letters of authorization (LoAs) submitted to the (b) (4) to support the (b) (4) the Siemens DMF to support the (b) (4) assurance of the sterile 30m (b) (4) vials; (b) (4) unit dose syringe are the final drug product.

4.3 Preclinical Pharmacology/Toxicology

For this NDA for Sodium Fluoride F 18 Injection, information requirements for the Nonclinical Pharmacology and Toxicology section are satisfied by the PET Safety and Effectiveness Notice.

4.4 Clinical Pharmacology

The sponsor presents information from the 2000 Guidance label, which requires updating. In addition, this section of the label contains diagnostic claims in specific benign or malignant diseases of bone which are not supported by adequate and well controlled studies. It also contains promotional claims; such as “rapid” and “rapidly”. This reviewer recommends that these claims be excluded from the label. The Clinical Pharmacology section of the label, including the mechanism of action, pharmacodynamics, and pharmacokinetics sections will need to be updated.

4.4.1 Mechanism of Action

Once bone tracers such as ^{99m}Tc -MDP and F-18 fluoride diffuse through capillaries into bone extracellular fluid (ECF), the evidence strongly suggests they become bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone.

4.4.2 Pharmacodynamics

Uptake of ^{18}F is increased in areas of increased osteogenic activity. In general, the distribution reflects both bone blood flow and osteoblastic activity, with the rate of skeletal mineralization having an important influence on the quantitative uptake of tracer.

4.4.3 Pharmacokinetics

After intravenous administration, ^{18}F -fluoride is cleared from the plasma in a biexponential manner. The first phase has a half-life of 0.4 h, and the second phase has a half-life of 2.6 h. Essentially all the ^{18}F -fluoride that is delivered to bone by the blood is retained in the bone. Tracer retention by the bone is a 2-phase process. In the first phase, the ^{18}F - ion exchanges for an OH^- ion on the surface of the hydroxyapatite matrix of bone. In the second phase, the ^{18}F - ion migrates into the crystalline matrix of bone, where it is retained until the bone is remodeled. One hour after administration of ^{18}F -labeled NaF, only about 10% of the injected dose remains in the blood.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: (Sponsor's) Review of Published Literature on Use of 18 F- Fluoride PET to Define Areas of Altered Osteogenic Activity

Author/Year	Cohort	No. of Subjects	Dose of ¹⁸ F-fluoride	Efficacy Comments	Safety Comments	Reference
<i>Well-Controlled Studies of Bone Metastases</i>						
Beheshti, 2008	Prostate cancer patients	38	10–15 mCi (370–550 MBq)	¹⁸ F-fluoride PET-CT was more sensitive, ¹⁸ F-FCH PET-CT was more specific, for detection of metastatic bone disease.	None	[6]
Petren-Mallmin, 1998	Breast cancer patients	5	5.4–10.8 mCi (185–370 MBq)	Focally increased ¹⁸ F-fluoride uptake was seen in both osteolytic and osteoblastic bone lesions as defined by CT; lesions less than 3 mm on CT were not detected by ¹⁸ F-fluoride PET.	None	[7]
Schirrmeister, 1999	Breast cancer patients	34	10 mCi (370 MBq)	¹⁸ F-fluoride PET was more sensitive than ^{99m} Tc-MDP BS for detection of metastatic bone lesions.	None	[8]
Hetzel, 2003	Lung cancer patients	103	7–20 mCi (261–740 MBq)	¹⁸ F-fluoride PET was more sensitive and more specific than ^{99m} Tc-MDP BS and SPECT for detection of malignant bone lesions; the costs of ¹⁸ F-fluoride PET and SPECT were higher than for ^{99m} Tc-MDP BS.	None	[9]
Schirrmeister, 2001	Lung cancer patients	53	10–15 mCi (370–555 MBq)	¹⁸ F-fluoride PET and SPECT were more sensitive than ^{99m} Tc-MDP BS for detection of metastatic bone lesions.	None	[10]
Schirrmeister, 2001	Thyroid cancer patients	35	10–15 mCi (370–555 MBq)	The sensitivity of ^{99m} Tc-MDP BS combined with WBI was higher than for BS alone, and comparable to ¹⁸ F-fluoride PET and MRI.	None	[11]
Even-Sapir, 2004	Oncology patients	44	8–12 mCi (296–444 MBq)	¹⁸ F-fluoride PET-CT is both sensitive and specific for detection of sclerotic and lytic malignant lesions; offers advantages over ¹⁸ F-fluoride PET and ^{99m} Tc-MDP BS.	None	[12]

Hoegerle, 1998	Oncology patients	60	2.7±0.3 mCi (100±10 MBq)	¹⁸ F-fluoride PET combined with ¹⁸ F-FDG PET was more sensitive and specific than ¹⁸ F-fluoride PET alone, and correlated well with findings from other imaging modalities.	None	[13]
Hoh, 1993	Patients with skeletal disorders and normal volunteers	38 (19/19)	5–10 mCi (185–370 MBq)	No unexpected sites of ¹⁸ F-fluoride uptake were seen in normal volunteers; ¹⁸ F-fluoride PET had improved contrast and localization of benign and malignant bone lesions compared with planar imaging methods.	None	[14]
Schirrmeister, 1999	Oncology patients	44	10 mCi (370 MBq)	¹⁸ F-fluoride PET was more sensitive than ^{99m} Tc-MDP BS for detection of bone lesions, and was independent of anatomical location.	None	[45]
Other Oncology Studies						
Bhargava, 2008	Case report	1	9.8 mCi (363 MBq)	¹⁸ F-fluoride PET was used to locate a lytic lesion in the heel of a 59-year-old male with metastatic renal cancer.	None	[15]
Langsteger, 2006	Patients with malignant tumors or diseases	100+	Not specified	In patients diagnosed by both ¹⁸ F-fluoride and ¹⁸ F-FDG PET-CT (n=20), lesions not detected by ¹⁸ F-fluoride were mostly small osteolytic metastases or located in the bone marrow; lesions not detected by ¹⁸ F-FDG PET-CT were mostly tumors known to have less FDG avidity (e.g., medullary thyroid cancer, renal cell carcinoma).	None	[1]
Author/Year	Cohort	No. of Subjects	Dose of ¹⁸F-fluoride	Efficacy Comments	Safety Comments	Reference
Tse, 1994	Case report	1	Not specified	¹⁸ F-fluoride PET was used to diagnose the nature of pulmonary nodules in a 42-year-old female with fibrous dysplasia, metastatic osteogenic sarcoma, and a breast mass.	None	[16]
Wade, 2006	Case report	1	Not specified	Osseous flare response in a 27-year-old woman with infiltrating ductal carcinoma was compared using ¹⁸ F-fluoride PET, ¹⁸ F-FDG PET-CT, ^{99m} Tc-MDP BS, and MRI	None	[17]
Well-controlled Studies in Benign Bone Disease						
Gamie, 2008	Patients with back pain	67	12–15 mCi (444–555 MBq)	¹⁸ F-fluoride PET was used to identify the cause of back pain in 84% of patients who could not be diagnosed by standard x-ray, CT and/or MRI.	None	[18]
Laverick, 2008	Patients with suspected condylar hyperplasia	5	4 mCi (150 MBq)	Uptake of ¹⁸ F-fluoride correlated with the site of suspected disease identified by clinical examination and plain radiographs; the mandibular condyle that showed increased ¹⁸ F-fluoride correlated with histological diagnosis in all patients.	The radiation burden using ¹⁸ F-fluoride is comparable to that of ^{99m} Tc-MDP BS and better than that of SPECT	[19]
Sterner, 2007	Patients with painful TKA	14	9.4 mCi (350 MBq)	¹⁸ F-fluoride PET was superior to x-ray, showing excellent spatial resolution and differentiation of aseptic loosening from simple synovitis.	None	[20]

<i>Well-controlled Studies of Bone Metabolism and Repair</i>						
Berding, 1995	Patients with pedicle grafts for mandibular reconstruction	9	10 mCi (370 MBq)	Increased blood flow and osteoblastic activity in healing grafts was apparent in ¹⁸ F-fluoride images; there was a lack of influx in areas of potential necrosis.	None	[21]
Brenner, 2004	Bone graft patients	34	0.1 mCi /kg-bw; (3.7 MBq/kg-bw)	¹⁸ F-fluoride PET is useful for assessment of fluoride metabolism and normal healing in bone grafts of the limbs.	None	[22]
Cook, 2002	Patients with Paget's disease	7	4.9 mCi (180 MBq)	A correlation between BSALP and K _{bone} supports the use of K _{bone} as a marker of regional bone formation. Results of influx and flow determination were consistent with the known pathophysiology of Paget's disease.	None	[24]
Forrest, 2006	Patients with osteoarthritis and hip resurfacing	10	6.8 mCi (250 MBq)	SUVs were higher in resurfaced hips than in nonresurfaced hips; the difference was only significant in the lateral aspect of the femoral head.	None	[25]
Frost, 2003	Postmenopausal osteoporotic women	18	2.43 mCi (90 MBq)	¹⁸ F-fluoride PET was useful as a non-invasive method for monitoring changes in bone metabolism during treatment with risedronate	None	[26]
Frost, 2004	Postmenopausal women	72	2.43 mCi (90 MBq)	Differences in bone metabolism kinetics between osteoporotic, osteopenic and normal subjects were evident in ¹⁸ F-fluoride PET scans.	None	[27]
Author/Year	Cohort	No. of Subjects	Dose of ¹⁸ F-fluoride	Efficacy Comments	Safety Comments	Reference
Installe, 2005	Patients with Paget's disease	14	10.75±1.1 mCi (397±41 MBq)	Uptake of ¹⁸ F was higher in pagetic than normal bone; ¹⁸ F-fluoride PET could be used to track changes in bone metabolic with bisphosphonate therapy.	None	[28]
Messa, 1993	Patients with end-stage renal disease	22	10 mCi (370 MBq)	Low-turnover and high-turnover lesions of osteodystrophy could be distinguished using ¹⁸ F-fluoride PET.	None	[29]
Piert, 1999	Patients who had hip revision arthroplasty	16	4.8–10 mCi (160–370 MBq)	¹⁸ F-fluoride PET showed early host bone formation in allogenic bone grafts; allogenic bone graft metabolism decreased over time.	None	[30]
Schiepers, 1998	Subjects with hip trauma and suspected osteonecrosis	5	8.1–10 mCi (300–370 MBq)	The ratio of BBF and influx rate measured using ¹⁸ F-fluoride PET was predictive of treatment outcome (conservative therapy vs. surgery).	None	[31]
Sorensen, 2003	Patients who had undergone THA and impaction bone allografting	5	4.8–10.3 mCi (180–380 MBq)	Angiogenesis and new bone formation visualized using ¹⁸ F-fluoride PET occurred early after impaction of morselized bone allografts around the femoral component in revision THA.	None	[32]
<i>Studies of Bone Pharmacokinetics:</i>						
Blake, 2002	Healthy postmenopausal women	69	0.03 mCi (1 MBq)	Women who were and were not taking HRT could be differentiated using the pharmacokinetic parameter, K _{bone} .	None	[33]

Brenner, 2004	Bone graft patients	33	6.8–10 mCi (250–370 MBq)	Good correlation was obtained between K_{PAT} and K_{NLR} , K_{PAT} and SUV, and K_{NLR} and K_{SUV} ; SUV has limited usefulness in areas of low metabolic activity.	None	[23]
Cook, 1999	Normal postmenopausal women	10	4.86 mCi (180 mBq)	Pharmacokinetic investigation; the non-invasive scaled population input function (IFp) and corrected image-derived input function from the aorta (IFI) correlated well with an arterial input function (IFa) directly measured from a radial artery line.	None	[34]
Frost, 2007	Postmenopausal women	43	2.4 or 4.9 mCi (90 or 180 MBq)	Regional bone turnover at the lumbar spine measured using ^{18}F -fluoride PET and global skeletal bone turnover measured by BSALP and urinary deoxypyridinoline have a similar relationship to changes in BMD.	None	[35]
Hawkins, 1992	Healthy male volunteers, breast cancer patient	12 (11 healthy, 1 breast cancer)	5–10 mCi (185–370 MBq)	Steady-state ratio of ^{18}F -fluoride ion is higher in plasma than in blood, and skeletal kinetics are consistent with three-compartment model.	None	[36]
Hirata, 2005	Patients with osteoporosis, spondylosis deformans, and normal volunteers	12 (5/5/3)	5–8 mCi (185–296 MBq)	A one-point blood sampling method for calculating input function in ^{18}F -fluoride PET was identified.	None	[37]
Author/Year	Cohort	No. of Subjects	Dose of ^{18}F -fluoride	Efficacy Comments	Safety Comments	Reference
Park-Holohan, 2001	Postmenopausal women	70	0.03 mCi (1 MBq)	Pharmacokinetic investigation. Urine flow rates >5 ml/min are necessary to ensure a constant renal clearance of ^{18}F ; 30% of circulating ^{18}F -fluoride is transported in red cells; bone kinetic data for ^{18}F are more accurately reported as whole-blood clearance rather than plasma clearance.	None	[38]
Schiepers, 1997	Subjects with skeletal disorders	9	8.1–10 mCi (300–370 MBq)	Fluoride kinetics measured using ^{18}F -fluoride PET were consistent with pathophysiology of the studied metabolic disorders	None	[39]
<i>Studies in the Pediatric Population:</i>						

Author/Year	Cohort	No. of Subjects	Dose of ¹⁸ F-fluoride	Efficacy Comments	Safety Comments	Reference
Lim, 2007	Young patients with back pain (age range 4–26 years)	94	0.06 mCi /kg-bw; max. 4 mCi (2.1 MBq/kg-bw; max. 148 MBq)	¹⁸ F-fluoride PET was able to locate cause of back pain in 55% of subjects who could not be diagnosed by other methodologies.	Effective dose is similar for ¹⁸ F-NaF and ^{99m} Tc-MDP (3.5 mGy vs. 2.8 mGy); bone surface dose is higher for ^{99m} Tc-MDP (33.4 mGy vs. 6.0 mGy for); bladder wall dose is slightly higher for ¹⁸ F-NaF (32.4 mGy vs. 24.4 mGy).	[40]
Ovadia, 2007	Young patients with back pain (age range 9–19 years)	15	5–10 mCi (185–370 MBq)	Use of ¹⁸ F-fluoride PET-CT lead to diagnosis of cause of back pain in 10 of 15 subjects; in the remaining subjects with no findings on ¹⁸ F-fluoride PET-CT, pain resolved spontaneously.	No issues; suggest using conventional procedures first due to cost and radiation exposure.	[41]
Brunkhorst, 2002	Case study	1	Not provided	¹⁸ F-fluoride PET and ¹⁸ F-FDG PET were used to evaluate extent of metastatic disease in a 15-year-old osteosarcoma patient.	None	[42]
Drubach, 2008	Case report	1	0.5 mCi (18 MBq)	¹⁸ F-fluoride PET was used to locate skeletal injuries in a four-month-old male.	None	[43]
<i>Studies Evaluating Alternative PET Technique Variables</i>						
Tayama, 2007	Various	32	5 mCi (185 MBq)	¹⁸ F-fluoride PET without attenuation correction showed higher mean bone-to-muscle ratios than those with attenuation correction; attenuation correction is not necessary for accurate visual interpretation of ¹⁸ F-fluoride PET images.	None	[44]

5.2 Review Strategy

This medical officer reviewed the organized search and presentation of the current literature provided by the sponsor. They conducted a search of the recent peer-reviewed journal literature to identify original clinical studies and case reports using ¹⁸F-fluoride PET. The initial search of Medline through PubMed included the search terms: “Sodium Fluoride / diagnostic use” [MESH]; all permutations of “¹⁸F-NaF” as a free text term; and “¹⁸F-fluoride” as a free text term limited to humans, clinical trial, randomized controlled trial and case reports. A search was then done in the Embase database on Dialog with the free text term “¹⁸F-fluoride” limited to clinical studies and case studies. Review articles were identified using the same criteria; however, review articles are not included in this summary. The search generated 41 articles of interest. The sponsor also conducted a search of FDA’s Adverse Event Reporting System (AERS) database for adverse events associated with use of ¹⁸F-NaF. All quarterly files currently available on the AERS website were accessed (January 2004–September 2008). Additionally, this medical officer conducted a search of the Medline database using the PubMed search engine and the MeSH database terms, “Sodium Fluoride PET” “NaF PET”. As well, the

radiation dosimetry for the new dose was examined as radiation effects are the main risk carried by this radiotracer (7 Review of Safety)

5.3 Discussion of Individual Studies/Clinical Trials

Not applicable

6 Review of Efficacy

Efficacy Summary

6.1 Indication

Requirements for efficacy for this NDA for Sodium Fluoride F 18 Injection are supported by the PET Safety and Effectiveness Notice, which was issued on March 10, 2000. The Notice states that FDA approved Sodium Fluoride F-18 injection (NDA 17-042) in 1972 as a bone imaging agent to define areas of altered osteogenic activity and further determined that sodium fluoride F 18 injection was not withdrawn from sale for reasons of safety or effectiveness and is still a listed drug. In keeping with the new CDER policy that drug products require Lifecycle Management, its continued use warrants a comprehensive review of the recent literature. This review should include safety (including lack of efficacy reports) and efficacy updates, as well as, an integrated analysis of these findings. The sponsor conducted a comprehensive literature review and provided an organized summary of the articles. The reviewer finds these data to be supportive only of the claim for efficacy in defining areas of altered osteogenic activity. The reviewer does not, however, find these articles to provide substantial evidence of any new claims of efficacy in specific disease states (i.e. specific cancers, benign bone diseases).

In the label, 14 Clinical Trials, the sponsor includes claims of new diagnostic efficacy in specific benign and malignant disease of bone. Furthermore, 15 References, includes a complete listing of these published articles. This information will need to be removed as it is neither useful, nor is it supported by adequate and well controlled studies. Specifically, the submitted data, including the trials labeled as “well-controlled” are deficient for one or more of the following reasons:

1. Small sample size.
2. Various and inconsistent reference standards
3. Data analysis:
 - a. It is not clear the endpoints were pre-specified
 - b. Unsuitable primary endpoint
 - c. Multiple endpoints
 - d. It is not clear the Visual analysis of the images was pre specified
 - e. The reading interpretation was not clearly blinded

4. It is not clear the statistical plan was pre-specified
5. Although there no safety issues identified in any of the studies, they were not designed to capture adverse events, therefore, the adequacy of these findings cannot be ascertained.
6. It was not possible to verify the dose or the quality of the product given.

The following is a review of a selection of the articles deemed “well-controlled” by the sponsor and their deficiencies.

1. Beheshti, M., et al. Detection of bone metastases in patients with prostate cancer by 18F fluorocholine and 18F fluoride PET-CT: a comparative study. *Eur J Nucl Med Mol Imag.* 35:1766–1774, 2008

Reviewer’s Comment: The aim of this prospective trial (N = 38) was to compare the potential value of 18F-fluorocholine (FCH) PET-computerized tomography (CT) and 18F-fluoride PET-CT for the detection of bone metastases in subjects with prostate cancer. Primary endpoint is the comparison of two techniques based on visual interpretation of number, sites, and morphological pattern of bone lesions; radiodensity of lesions; semi-quantitative analysis by means of maximum standardized uptake value (SUVmax); comparison to histopathological and/or follow-up findings.

Deficiencies:

1. *Patients with low risk prostate cancer or history of a second cancer were excluded.*
2. *Data analysis: The reading interpretation was not blinded and was made as a consensus reading of two nuclear medicine physicians and a radiologist who had access to clinical, as well as previous radiological imaging information.*
3. *Small sample size.*
4. *Variable reference standards – histopathology, but also CT and follow up; uses the 18F-sodium fluoride as well.*
5. *Data analysis: It is not clear the endpoints were pre-specified*
6. *Data analysis: It is not clear that the primary endpoint is clinically meaningful. A correlation between modalities is not adequate for determination of efficacy.*
7. *It is not clear the statistical plan is pre-specified*

2. Petren-Mallmin, M., et al. Skeletal metastases from breast cancer: uptake of 18F-fluoride measured with positron emission tomography in correlation with CT. *Skeletal Radiol.* 27(2):72–76, 1998

Reviewer’s Comment: This is an exploratory study evaluating the uptake of 18F Fluoride in 5 breast cancer patients. The primary endpoint is visual correlation of location and diagnosis of lesions observed by CT and PET.

Deficiencies:

1. *Small sample size*

2. *Exploratory study, not prospective*
 3. *The primary endpoint is not suitable. Correlation is not adequate evidence for efficacy.*
 4. *It is not clear that the primary endpoint was pre specified*
 5. *There is no information regarding blinding of imaging reads.*
 6. *The gold standard not well defined*
-
3. Schirrmeister, H., et al. Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. *J Clin Oncol.* 17(8):2381–2389, 1999

Reviewer's Comments: This is a prospective trial (N = 34) to evaluate the sensitivity and specificity of 18F-fluoride PET to detect bone metastases in patients with breast cancer. The endpoints are visual interpretation; extraverterbal lesions detected by PET or BS were confirmed by planar x-ray, MRI or spiral CT. The reading was blinded and independent.

Deficiencies

1. *Various reference standards employed*
 2. *Small sample size*
 3. *Not clear that the endpoints were pre-specified*
 4. *Not clear that the statistical method was pre-specified.*
-
4. Hetzel, M., et al. F-18 NaF PET for detection of bone metastases in lung cancer: accuracy, cost-effectiveness, and impact on patient management. *J Bone Miner Res.* 18(12): 2206–2214, 2003

Reviewer's Comments: This is a prospective study (N = 103) to evaluate the use of 18F-fluoride PET, SPECT and 99mTc-MDP planar bone scan for detection of bone metastases in patients with lung cancer. Multiple endpoints were specificity and sensitivity by visual interpretation, comparison to reference methods, and ROC curve analysis; cost effectiveness.

Deficiencies

1. *Various reference standards*
 2. *It is not clear that the visual analysis is prospectively defined.*
 3. *It is not clear the image analysis was independent.*
 4. *Multiple endpoints*
 5. *It is not clear that the endpoints are suitable; a difference between modalities is not substantial evidence of effectiveness for a particular cancer type.*
 6. *It is not clear that the statistical analysis was prospectively defined*
-
5. Schirrmeister, H., et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18) F-labeled NaF PET in newly diagnosed lung cancer. *J Nucl Med.* 42(12):1800–1804, 2001

Reviewer's Comments:

This is a prospective study (N = 53) designed to compare the sensitivities and specificities of 18F-fluoride PET and BS with and without and SPECT to detect bone metastases in subjects with newly diagnosed SCLC or advanced NSCLC. The primary endpoint was the comparison of sensitivity and selectivity of test methods based on visual interpretation and comparison with reference methods.

Deficiencies

1. *Small sample size*
 2. *Patients with a history of extra pulmonary cancer or known metastatic bone disease were excluded.*
 3. *Various reference standards*
 4. *It is not clear that visual interpretation was pre specified*
 5. *It is not clear that the primary endpoint was pre specified*
 6. *It is not clear that statistical analysis was pre specified.*
6. Schirrmeister, H., et al. Anatomical distribution and sclerotic activity of bone metastases from thyroid cancer assessed with F-18 sodium fluoride positron emission tomography. *Thyroid*. 11(7):677–683, 2001

Reviewer's Comments: A prospective study (N = 35) to evaluate the anatomical distribution and metabolic behavior of bone metastases in subjects with thyroid cancer using a variety of imaging techniques. The primary endpoint was to determine accuracy, sensitivity and specificity of 99mTc-MDP BS with and without WBI on a patient basis.

Deficiencies

1. *The primary efficacy endpoint is unsuitable. It does not evaluate F-18 Sodium Fluoride.*
 2. *Small sample size.*
 3. *In the data analysis, the explanation of the blinding for reading interpretation was not clear.*
7. Even-Sapir, E., et al. Assessment of malignant skeletal disease: Initial experience with 18F-fluoride PET/CT and comparison between 18F-fluoride PET and 18F-fluoride PET-CT. *J Nucl Med*. 45(2):272–278, 2004

Reviewer's Comments:

This prospective study (N = 44) was conducted to evaluate the diagnostic accuracy of 18F-fluoride PET and 18F-fluoride PET-CT in assessing malignant osseous involvement and in differentiating malignant from benign bone lesions in oncologic patients. PET and PET-CT images were interpreted on two separate days in a consensus reading by two individuals. The primary endpoint was lesion-based and patient-based correlation of sensitivity and specificity of PET and PET-CT compared with final diagnoses based on histopathology, contemporaneous imaging, or clinical follow-up.

Deficiencies

1. *Small sample size*
2. *Various reference standards employed*
3. *It is not clear inclusion criteria were prospectively determined*
4. *Reading is not blinded*
5. *It is not clear that visual analysis is pre specified*
6. *It is not clear that statistical analysis is pre specified*
7. *It is not clear that the primary endpoint is suitable: a correlation between PET and PET CT is not does not necessarily provide evidence of diagnostic accuracy.*
8. *It is not clear if the primary endpoint is pre specified*

8. Hoegerle, S., et al. Combined FDG and [F-18] Fluoride whole-body PET: a feasible two-in-one approach to cancer imaging? *Radiology*. 209(1):253–258, 1998

Reviewer's Comments: This is a prospective, controlled trial (N = 60) conducted to determine the feasibility of conducting combined 18F-FDG and 18F-fluoride PET for cancer imaging, and to evaluate the utility of this approach for detecting, localizing, and staging disease. Multiple endpoints are employed: visual interpretation; comparison of findings between methods and agreement between observers for number, status, and topographical localization of total, soft-tissue and skeletal lesions in control and study groups. PET images were interpreted by two experienced, blinded, independent investigators.

Deficiencies

1. *Various reference standards*
2. *It is not clear that visual analysis is pre specified*
3. *It is not clear that statistical analysis is pre specified*
4. *Multiple endpoints*
5. *It is not clear that the endpoints are suitable: Correlation between the two modalities or between readers does not necessarily provide evidence of effectiveness.*
6. *It is not clear if the endpoints are pre specified*

9. Hoh, C.K., et al. Whole body skeletal imaging with [18F] Fluoride ion and PET. *J Comput Assist Tomogr*. 17(1):34–41, 1993

Reviewer's Comments: This is a prospective trial (N = 38) to evaluate the sensitivity and specificity of 18F-fluoride PET to detect areas of altered osteogenic activity in patients with a range of malignant and benign skeletal conditions. The endpoints were visual interpretation, activity ratio, localization potential of projection and tomographic images.

Deficiencies:

1. *Various reference standards*

2. *It is not clear that visual analysis is pre specified*
3. *It is not clear that statistical analysis is pre specified*
4. *Multiple endpoints*
5. *It is not clear that the endpoints are suitable: comparison of projection and tomographic techniques is not necessarily a suitable endpoint to determine efficacy.*
6. *It is not clear if the endpoints are pre specified*

10. Schirrmeister, H., et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus 18F PET. J Nucl Med. 40(10):1623–1629, 1999.

Reviewer's Comments:

A prospective study (n=44) was conducted to evaluate the accuracy of planar radionuclide bone scanning vs. tomographic bone imaging with 18F-NaF PET for detection of osteolytic and osteoblastic bone metastases, as well as to examine dependence on anatomic localization. The endpoints are comparison of sensitivity and specificity of 18F-fluoride PET and 99mTc-MDP BS by visual interpretation (lesion-by-lesion analysis) and differentiation of benign and malignant lesions (ROC curve fitting).

Deficiencies:

1. *Various reference standards were employed*
2. *It is not clear if the readers were blinded. They read independently, however, adjudication of discrepancies was by consensus.*
3. *Multiple endpoints*
4. *It is not clear if the endpoints are pre specified.*
5. *It is not clear that visual analysis is pre specified*
6. *It is not clear that statistical analysis is pre specified*

6.1.7 Subpopulations

In their initial submission, the sponsor did not present a pediatric plan. Furthermore, in their March 10, 2009 amendment, the sponsor requests a pediatric waiver. The reviewer believes that the waiver should not be granted because the recent reported literature provided from the sponsor, documents the product's use in approximately 100 children. The reviewer also notes that Technetium 99m MDP, approved for imaging osteogenic areas of bone, has extensive clinical use in children. Therefore, given the same indication, F18 Sodium Fluoride will most likely be used in the pediatric population. Consistent with 21 CFR 314.55, this new NDA submission requires a pediatric plan.

The sponsor's submitted label contained no information regarding the use of the product in the pediatric population, however, in their submitted data; there is supportive evidence for its use in this population. Based on the reported recent literature, Sodium Fluoride [F18] has been used in approximately 100 children using a weight based dose (2.1 MBq/mCi); with doses ranging from

19 MBq – 148 MBq (0.5 mCi - 4 mCi) in the largest study. The reviewer recommends updates to the label in section 2, Dosage and Administration (2.5 Recommended Dose for Pediatric Patients) and Section 8, Use in Special Populations (8.4 Pediatric Use).

Finally, there is a presumed risk from any dose of radiation (1.2 Risk Benefit Assessment). Although the risk is small, it would be assumed to be higher in children; based on their relatively more radiosensitive biology. Therefore, the reviewer recommends additions to the label (Dosage and Administration, 2.6 Radiation Dosimetry) to reflect the weight based dosimetry data that is currently available. Furthermore, the reviewer recommends that the sponsor comply with a Post Marketing Requirement to study the radiation dosimetry of the product in 6 children in the following, equally represented, cohorts: 1-5 years old, 6-10 years old, and 11-16 years old.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

(See 6.1.7 Subpopulations)

7 Review of Safety

Safety Summary

Requirements for safety for this NDA for Sodium Fluoride F 18 Injection are supported by the PET Safety and Effectiveness Notice, which was issued on March 10, 2000. The Notice states that FDA approved Sodium Fluoride F-18 injection (NDA 17-042) in 1972 as a bone imaging agent to define areas of altered osteogenic activity and further determined that Sodium Fluoride F 18 injection was not withdrawn from sale for reasons of safety or effectiveness and is still a listed drug. In keeping with the new CDER policy that drug products require Lifecycle Management continued use of Sodium Fluoride F 18 Injection warrants a comprehensive review of the recent literature for safety updates, as well as, an integrated analysis of these findings.

The sponsor conducted a comprehensive literature review and provided an organized summary of the articles. Additionally, the sponsor conducted a search of FDA's Adverse Event Reporting System (AERS) database for adverse events associated with use of 18F-NaF. The AERS database contains no reports and the literature contains no information on safety. While there is no evidence to contradict the original findings of safety in the Federal Register Notice, the data are likely to be incomplete because the studies were not designed to assess safety. For example, the published studies do not describe the methods for assessment of safety nor do they specifically cite safety findings. Therefore, the reviewer recommends a more definitive statement of this inadequacy in the label (Adverse Reactions).

Additionally, the sponsor proposes a new dose (8 – 12 mCi) from the reference listed drug (0.5 – 2.0 mCi, maximum not to exceed 4.0 mCi) which requires a review of the literature to support the safety of this new dose. Their search identified 41 articles of interest published since 1992 in which 18F-fluoride PET imaging was used in more than 1100 patients. The majority of these studies used doses of 18F-fluoride substantially higher than the approved dose of the reference listed drug. In nine prospective studies investigating the use of 18F-fluoride PET for detection of

bone metastases in 416 adult cancer patients, doses ranged from 2.7 mCi to 20 mCi (100 MBq to 740 MBq), with an average median dose of 10 mCi (370 MBq) and an average mean dose of 9.2 mCi (340 MBq)¹. Of these patients, 356 received doses higher than 5 mCi. Normal volunteers were included in some of these evaluations. Other publications on the use of 18F-fluoride PET in benign skeletal and metabolic disorders included doses in the studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq). No safety issues were identified; however, the studies were not designed to assess safety. Furthermore, the monograph for Sodium Fluoride F 18 in the USP DI®, Drug Information for the Health Professional (2002 Thomson Micromedex) states that the usual adult and adolescent administered activity for skeletal imaging is 10 mCi (370 MBq) given intravenously. In addition, the recommended dose of IASOfu®, a Sodium Fluoride F18 Injection product that recently received marketing approval in France, is 4 MBq/kg- body weight, or 280 MBq (7.6 mCi) for a 70 kg adult (IASON GmbH). These data are supportive of the safety of the new dose.

The product carries a risk of radiation exposure to the patient. These risks are reasonable based on an analysis of the dosimetry data available for the product. When compared to the current standard imaging agent (Tc 99m MDP products) for osteogenic activity, the Effective Dose from F18 Sodium Fluoride Injection is 2-3 times as high. According to the package insert, the recommended activity is 10-20 mCi (370-740 MBq) for an adult. Based on the dosimetry data from the ICRP³, the Effective Dose for a typical study of Tc99m MDP in an adult would be approximately 2.1 - 4.2 mSv. Of note, the Society of Nuclear Medicine's Procedure Guidelines for bone scintigraphy (06/20/2003); recommend a higher administered activity of 20-30 mCi (740 – 1110 MBq), yielding Effective Doses of 4.2-6.4 mSv.

In fact, the Effective Dose from F18 Sodium Fluoride is similar to other PET agents, for example F18 FDG. In the Package insert for F 18 FDG, the recommended activity is 5-10 mCi for an adult. Based on the dosimetry data from the ICRP³ for F18-FDG (Table 4); the Effective dose would range between 3.5 – 7 mSv. However, the Society of Nuclear Medicine's Procedure Guidelines administered activity is 10-20 mCi (370-740 MBq). Based on the dosimetry data from the ICRP for F18-FDG (Table 4), the maximum Effective Dose would be approximately 14 mSv, slightly higher than the estimated dose from F18 NaF.

The sponsor notes that the primary adverse effects that would be expected for this drug are those that can occur non-specifically with any injectable drug, such as infiltration or hematoma at the injection site, vasovagal reactions, or allergic reaction. These events are theoretical, none have been reported.

Table 3: Estimated Absorbed Radiation Doses (mGy/MBq) after Intravenous administration of Sodium Fluoride F19 Injection

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[1] Data taken from Nuclear Regulatory Commission Report, "Radiation Dose Estimates for Radiopharmaceuticals," NUREG/CR-6345, April 1996.

[2] Data taken from "Radiation dose to patients from radiopharmaceuticals" (ICRP publication 53), Annals of the ICRP, Volume 18, No.1-4, 1987, pages 15, 73-74.

Table 4: 18 F-FDG Radiation Dosimetry for Adults and Children

COPYRIGHT MATERIAL

Data are taken from “Radiation dose to patients from radiopharmaceuticals” (Addendum 2 to ICRP publication 53), (ICRP publication 80) Annals of the ICRP, Volume 28, No.3, 1998, pages 1-123.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The sponsor has provided no dose to dose comparisons to validate the new dose. We find, however, the new dose to be acceptable based on the experience in the recent literature, as well as, radiation dosimetry calculations using ICRP data (7 Review of Safety).

7.2.2 Explorations for Dose Response

None submitted or required

7.2.3 Special Animal and/or In Vitro Testing

None submitted or required

7.2.4 Routine Clinical Testing

None submitted or required

7.2.5 Metabolic, Clearance, and Interaction Workup

None submitted or required

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

None submitted or required

7.3 Major Safety Results

7.3.1 Deaths

None reported

7.3.2 Nonfatal Serious Adverse Events

None reported

7.3.3 Dropouts and/or Discontinuations

Not applicable

7.3.4 Significant Adverse Events

None reported

7.3.5 Submission Specific Primary Safety Concerns

The drug product is injectable. As with any injectable drug product, allergic reactions and anaphylaxis may occur. Additionally, this product carries a risk of radiation exposure to the patient. Although the risk is small, Sodium Fluoride F 18 Injection may increase the risk of cancer. The reviewer recommends that these risks be included in the label, Warnings and Precautions.

7.4 Supportive Safety Results

None submitted or required

7.5 Other Safety Explorations

None submitted or required

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Studies with Sodium Fluoride F 18 Injection have not been performed to evaluate the carcinogenic potential, mutagenic potential, or effects on fertility.

7.6.2 Human Reproduction and Pregnancy Data

Any radiopharmaceutical including Sodium Fluoride F18 injection has a potential to cause fetal harm. Animal reproduction studies have not been conducted with Sodium Fluoride F 18 Injection. It is not known whether Sodium Fluoride F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, Sodium Fluoride F 18 Injection should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable to this single-dose product

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

None

7.7 Additional Submissions

None

8 Postmarket Experience

See 6 Review of Efficacy and 7 Review of Safety

9 Appendices

9.1 Literature Review/References

1. Ad Hoc Health Experts Working Group on Medical Isotopes, *Lessons Learned from the Shutdown of the Chalk River Reactor: A Report Submitted to the Minister of Health*, May 2008
2. Blake, GM, Park-Holohan, SJ, Cook, G, Fogelman, I, Quantitative Studies of Bone with the Use of 18 F-Fluoride and 99mTc-Methylene Disphosphonate, *Semin Nucl Med.* 2001 Jan;31(1):28-49.
3. Perkins A, Hilson A, Hall J. Global shortage of medical isotopes threatens nuclear medicine services. *BMJ.* 2008 Sep 5;337:a1577.

See also footnotes below.

9.2 Labeling Recommendations

The reviewer recommends multiple label updates/changes. In (2) Dosage and Administration, information regarding the new dose (injected activity) in adults and children needs to be included; re-ordering the Full Prescribing Information (FPI) is recommended to be consistent with the Adreview Label (recently approved drug in Pharmacologic class); we recommend more specific information is needed regarding (2.2) radiation safety / patient preparation (appropriate safety measures before and after administration) and (2.7) Imaging guidelines (optimal imaging parameters) . In (5) Warnings and Precautions, a warning regarding allergic reactions is needed to be consistent with the FDA PET Guidance for Sodium [F18] Injection; a warning is needed regarding the radiation risks of the product consistent with other products in this pharmacologic class. In (6) Adverse Reactions, the reviewer recommends reflecting the lack of complete safety information: “*the completeness of these sources is not known.*” (7 Review of Safety) In (8) Use in Specific Populations, the reviewer recommends updating the pediatric section to reflect the increased risk form radiation particular to children “*Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F18 injection*” and adding information regarding its safe use (administered activity) in children. Additionally, the reviewer recommends amending (2.6) Radiation Dosimetry to reflect the known data regarding the age-weight based dosimetry differences.² In (12) Clinical Pharmacology, the reviewer recommends updates to the information in the label and exclusion of any promotional (b) (4) terms. In (14) Clinical Studies and (15) References the reviewer recommends excluding much of the Sponsor’s submitted information and including only the information pertinent to the product’s safe use.

9.1 Literature Review/References

-
- ¹ Stabin, MG, Stubbs, JB and Toohey RE, Radiation Dose Estimates for Radiopharmaceuticals, U.S. Nuclear Regulatory Commission report NUREG/CR-6345, April 1996.
 - ² Radiation Dose to Patients from Radiopharmaceuticals (ICRP publication 53). Ann ICRP, 1987. **18**(1-4): p. 1-377.
 - ³ “Radiation dose to patients from radiopharmaceuticals” (Addendum 2 to ICRP publication 53), (ICRP publication 80) Annals of the ICRP, Volume 28, No.3, 1998, pages 1-123

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Medical Officer Filing Review

NDA 22-494

Sodium Fluoride F18 Injection

Submission Type: 505 (b) (2)

Sponsor: National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD), Cancer Imaging Program (CIP).

Recommendations on Regulatory Action.

Filing

It is this reviewer's recommendation that this 505 (b) (2) NDA application for Sodium Fluoride F18 Injection be filed. The submission format is acceptable and reviewable.

Priority review

Additionally, the product meets an unmet public health need for an alternative bone imaging radiopharmaceutical during the interruptions that have occurred in the supply of ^{99m}Tc generators to prepare the currently used ^{99m}Tc labeled diphosphonates (the only currently approved radiopharmaceutical for bone imaging). While MRI and CT can be used in certain circumstances to image bone, they are not adequate substitutes for a whole body imaging modality, particularly as a metastatic survey. Therefore, it is my recommendation that this NDA be filed as a Priority Review.

Indication:

Indicated for Positron emission tomography (PET) imaging as a bone imaging agent to define areas of altered osteogenic activity. (The same indication as the ^{99m}Tc labeled diphosphonates)

Product:

The active ingredient, sodium fluoride ^{18}F (^{18}F NaF), has a molecular weight of 40.99, and the following chemical structure: $\text{Na}^+ \text{ } ^{18}\text{F}^-$. It is cyclotron produced by (b) (4). The half life of ^{18}F is 109.7 minutes and it decays back to ^{18}O

Sodium Fluoride F 18 Injection is provided as a ready to use, isotonic, sterile, pyrogen free, clear and colorless solution. Each mL of the solution contains 10 -(b) (4) mCi ^{18}F NaF at the end of synthesis reference time in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8.0. The solution does not contain any preservatives. . The drug product prepared by Siemens Molecular Imaging or (b) (4) complies with the USP monograph for Sodium Fluoride F 18 Injection.

Clinical background

- **Intended population:** Patients who are at risk for bony metastases and also for benign conditions characterized by alterations in osteogenic activity.
- **Mechanism of Action:** Fluoride is taken up in bone when Fluoride ions undergo exchange with hydroxyl groups in hydroxyapatite to form fluoroapatite. Uptake is primarily dependent on blood flow to bone and F18 Sodium Fluoride has rapid blood clearance with high bone-to-background activity in a short time. Uptake of ^{18}F is increased in areas of increased osteogenic activity.
- **Clinical use:** F18 Sodium Fluoride is a PET radiopharmaceutical for bone imaging.
- **Other Available Radiopharmaceutical Diagnostic Agents:** ^{99m}Tc diphosphonate compounds In the 1970's, technetium- 99m diphosphonate compounds were developed for bone imaging and rapidly gained market share because of lower cost of the imaging drug and ease of availability of gamma camera ubiquitous in any Nuclear Medicine department for imaging. The use of F18 Sodium Fluoride quickly declined.

- Recently, there have been shortages in the supply of the ^{99m}Tc generators which are used to prepare the ^{99m}Tc labeled diphosphonates; resulting in interruptions in the availability of the product.
- During these shortages, patients frequently cannot obtain bone scans with an approved radiopharmaceutical.
- NCI is seeking NDA approval of F18 Sodium Fluoride to meet that need.

Regulatory History:

- 1972: FDA approved Sodium Fluoride F 18 Injection (NDA 17 042) as a bone imaging agent to define areas of altered osteogenic activity.
- 1975: The NDA holder, Nycomed Amersham (now GE Healthcare), stopped marketing the drug.
- It remains in clinical use for research purposes as a bone imaging agent.
- March 10, 2000 Federal Register Notice : US Department of Health and Human Services, Food and Drug Administration, Positron Emission Tomography Drug Products; Safety and Effectiveness of Certain PET Drugs for Specific Indications: Federal Register 65 (48): 12999 13009.
 - FDA reviewed its records and, under 21 CFR 314.161, determined that Sodium Fluoride F 18 Injection was not withdrawn from sale for reasons of safety or effectiveness. Accordingly, it should be listed in the Orange Book's "Discontinued Drug Products List". It is still a listed drug.
 - Thus, this NDA relies on to the above and on published literature as the basis for approval; no new studies were conducted.
- March 2000 FDA Guidance for Industry, "PET Drug Applications – Content and Format for NDAs and ANDAs"
- October 10, 2008: NCI submitted IND (b) (4)
- December 30, 2008: NCI submits a 505(b) (2) NDA application with reliance on March 10, 2000 Federal Register Notice for safety and efficacy.
 - The manufactured product is a new concentration (10 (b) (4) mCi/mL).
 - Sponsor was granted a waiver of user fee.
 - No pre-submission meeting was held with sponsor.

Product Sourcing: NaF-18 may be studied under IND or RDRC approval; but RDRC approved studies are not to be clinical in nature. The product is supplied by manufacturers that follow procedures that conform to USP<823> PET compounding standards and the USP monograph for Sodium Fluoride F 18 Injection.

Submitted Materials Relevant to Clinical Review:

- Labeling: Package Insert
 - **Format** : new PLR format
 - **Indication** – Indicated for Positron emission tomography (PET) imaging as a bone imaging agent to define areas of altered osteogenic activity. (no change)
 - **Dose** 8 – 12 mCi. (new, higher dose)
 - **Patient subgroups**
 - Pregnancy Category C (no change)
 - Nursing Mothers (new recommendations. See *Appendix D*)
 - Pediatrics (no change, update is needed)
 - **Clinical studies:** Clinical experience in patients who are at risk for bony metastases (cancer patients) and also for benign conditions (trauma, blood flow, spondylolysis, osteoid osteoma, fracture, etc) characterized by alterations in osteogenic activity. (new reports)
 - **References:** (new references are included)

- Reliance on FDA's findings (2000 PET Safety and Effectiveness Notice) for the following:
 - Clinical data section
 - Non-clinical Pharmacology and Toxicology
 - Human Pharmacokinetics and Bioavailability
 - Clinical Microbiology
 - Statistical Section
 - Case Report Tabulation
 - Case Report Forms (no new studies were conducted)
 - Safety Update Report (given the time elapsed since the FDA review, a summary of available experience is needed)
- Patent Information
- Patent Certification
- Debarment Certification
- Field Copy Certification
- User Fee Cover Sheet (Form 3397)
- Reprints of publications

Clinical Review Issues:

In the LABEL:

1. DOSE (2):
 - a. The sponsor proposes a new, higher dose (8 – 12 mCi).
 - b. The previous, labeled dose of Sodium Fluoride F18 Injection was [REDACTED] (b) (4).
 - c. The sponsor provides neither an explanation for this new dose nor an adequate review of the literature to support the safety of this new dose.
 - d. Upon my review of the sponsor's submitted literature, as well as, my own evaluation of the recent literature, the safety of the proposed new dose in the intended population is reasonable. *See Appendix A.*
2. CLINICAL STUDIES (14):
 - a. The sponsor includes a summary of a selected number of publications to illustrate the current clinical uses of the product in malignant and benign conditions.
 - b. This information implies claims of efficacy in specific populations, as well as, claims of superiority over Technetium 99m MDP bone scintigraphy.
 - c. The sponsor has not provided an adequate review to support the inclusion of this material in the label.
3. REFERENCES (15):
 - a. The sponsor includes a bibliography which includes the recent, peer-reviewed literature.
 - b. This information has implied claims as well.
 - c. The sponsor has not provided an adequate review to support the inclusion of this material in the label.
4. USE IN SPECIFIC POPULATIONS, 8.4 Pediatric Use:
 - a. The new label does not propose changes to the current label for use in children.
 - b. However, the sponsor's literature summary presents examples of use in the pediatric population.
 - c. Based on my review of the sponsor's submitted literature, there should be additional information in the label regarding the product's safe use and dosimetry in children. *See Appendix B*

In the SUBMISSION:

1. Clinical Data Section: The submitted literature summary does not include an explanation of the Sponsor's review process.
 - a. The data bases searched
 - b. The search terms employed
 - c. The timelines searched
 - d. The criteria for acceptance or rejection of data
2. Clinical Data Section: In addition, no integrated analyses of updated Safety and Efficacy data are performed.
 - a. The Sponsor relies on the March 2000, PET Safety and Effectiveness Notice for evidence of the safety and effectiveness of the product; in accordance with FDAs Guidance, "PET Drug Applications - Content and Format for NDAs and ANDAs
 - b. The sponsor provides a summary of selected number of publications to illustrate the current clinical uses of the product, "for convenience".
 - c. The product has been in use for 9 years since its evaluation for the Notice (1999 literature review by the agency).
 - d. The Agency has not had access to safety reporting and annual reports, since the product was taken off the market (1975).
 - e. Therefore, in keeping with the new CDER policy that drug products require Lifecycle Management, we conclude that its continued use warrants a comprehensive review of the recent literature for Safety and Efficacy updates, as well as, an integrated analysis of these findings. *See Appendix C.*
3. The sponsor does not submit a Pediatric Plan.

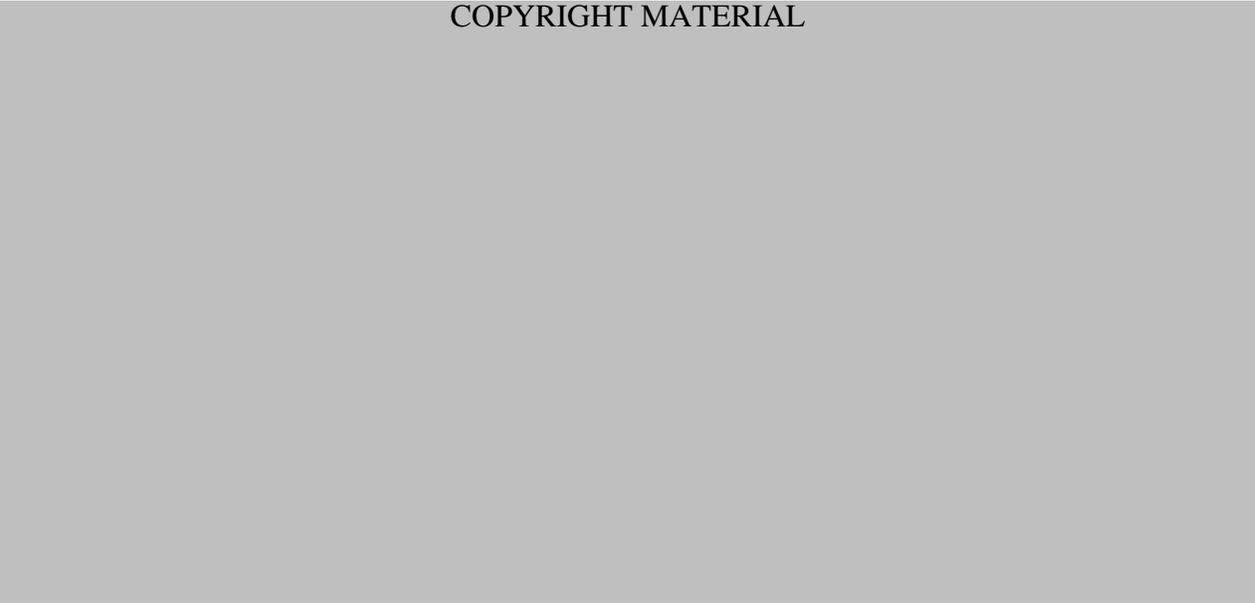
Appendix A

DOSE: While the sponsor does not provide a clear explanation for the safety of their new dose, it is this reviewer's opinion that the radiation safety of this dose can be extrapolated from the following:

1. ICRP International Commission on Radiologic Protection (53 and 80 (Lim 2007). This table provides a comparison of Technetium and F18 Na Fluoride dosimetry. Note, for example, the dose of 4 mCi (148 MBq) F18 NaF would have an effective dose of 4 mSv in a 70 kg adult. A dose of 8 -12 mCi as proposed by the sponsor, would have an effective dose of 8-12 mSv.

ICRP International Commission on Radiologic Protection (53 and 80 (Lim 2007).
Radiation Dosimetry of 99mTc-MDP Scintigraphy vs. 18F-Labeled NaF PET

COPYRIGHT MATERIAL



*Derived from ICRP Report 80. Ann ICRP. 1999;28:75.

yDerived from ICRP Report 53. Ann ICRP. 1987;17:74.

Values in parentheses are doses in mGy (mSv for effective dose) for administered activity listed in table for that patient size.

2. Dose per mCi injected = 0.3 rads to total body and 0.23 rads to bone (Blau, 1962). Therefore, total maximum dose = 3.6 rads to total body and 2.76 rads to bone.
3. The previous dose of 1-4 mCi was based on limits in cost and availability rather than radiation dosimetry (Hoh, 1993).
4. Literature review provided by the sponsor. Most studies had doses in a range similar to the new dose proposed by the sponsor:

Dose mCi	Reference
5-10.	(6, Hoh, 1993)
10	(7, Schirmeister, 1999)
5.4-10.8	(8, Petren-Mallmin, 1998)
10-15.	(9, Schirmeister, 2001)
7-20.	(10, Hetzel, 2003)
10	(11, Schirmeister, 1999)
8-12.	(12, Even-Sapir, 2004)
max 4	(16, Lim, 2007)
5-10.	(17, Ovadia, 2007)
8-10.	(18, Schiepers, 1998)
6.8	(19, Forrest, 2006)
5-10.	(20, Sorensen, 2003)
4-10.	(21, Piert, 1999)

Appendix B: Safety in Children

- The sponsor will need to provide an integrated summary of the recent literature for safety data in pediatric patients.
- Based on this reviewer's examination of the submitted literature, the product may demonstrate safety in children based on the following:
 - The only alternative agent for a metastatic bone survey is Technetium 99m MDP.
 - Based on the calculations from the ICRP International Commission on Radiologic Protection 53 and 80, the dose of F18 NaF Injection does not appear to be orders of magnitude higher than Tc 99m MDP. For example, in a 19 kg child, 2 mSv (for Technetium) versus 3.4 mSv (for F18 Na F).
 - The highest effective dose (3.6 mSv) and the highest organ dose (Bone surfaces = 6 mGy) is in patients < 1 year old (9.8 kg). These are still acceptable dose levels.
 - Even in these patients, the product would likely be used for a metastatic survey (neuroblastoma or leukemia) and the clinical situation would warrant such radiation exposure.
- THE LABEL should potentially include:
 - Information regarding instructions on the safe use of the product in children.
 - Information regarding the dosimetry of the product in children.

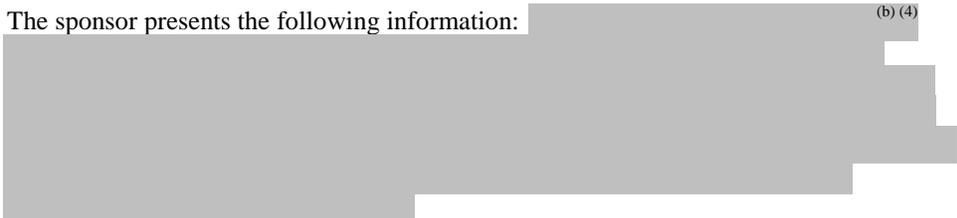
- Post Marketing Requirements should potentially include a small (N=4) dosimetry study in children.

APPENDIX C : INTEGRATED ANALYSIS OF SAFETY AND EFFICACY

- The sponsor presents a summary of the recent literature, which does not include:
 - A clear explanation of their review process, including:
 - The Database(s) searched
 - The search terms employed
 - The timeline searched
 - Their criteria for acceptance or rejection of data / articles
- Despite continued use and use in the pediatric population, the sponsor presents no integrated analysis of recent safety or efficacy findings.
- The sponsor will need to provide a review of the recent literature for safety and efficacy, to include:
 - An integrated summary of these data
 - A comprehensive analysis of these data, including:
 - An evaluation of study design, conduct and outcomes.
 - An evaluation of any new safety information regarding the product use in the intended population.
 - An evaluation of any new safety data in the patient subgroups (particularly pediatric patients).
- This reviewer conducted a literature review:
 - A PubMed Review Search: “Sodium Fluoride PET and safety” returned 0 items
 - In reviewing the sponsor’s submitted literature, while safety was not specifically studied, there appear to be no adverse events or safety issues reported. In particular, 2 studies, Ovadia, 2007 and Schiepers, 1998 had follow up of 20 months and 14-50 months, respectively.
 - Although the literature was not presented in a reviewable format, this reviewer did analyze the submitted literature and found some of the articles to be deficient for lack of one or more of the following items:
 - Clear statement that the study was prospective
 - Clear Standard of Truth
 - Uniform application of the Standard of Truth to all subjects
 - Clearly outlined protocol
 - Clearly outlined endpoints
 - Clearly outlined statistical plan and methodology
 - Clear accounting of patients
 - Clearly defined Imaging Protocol, with attention to:
 - Blinding of Readers
 - Image Handling Methodology
 - Central Reading of Studies
 - In this reviewer’s opinion, the following studies have the most promise to support a supplemental submission supporting efficacy in specific populations:
 - 7, Schirrmeister, 1999
 - 9, Schirrmeister, 2001

- 10, Hetzel, 2003
 - 11, Schirrmeister, 1999
 - 12, Even-Sapir, 2004
 - All of these studies lack a central reading of the imaging data and some lack uniform application of the Standard of Truth to all subjects.
- Additionally, this reviewer conducted a literature review: PubMed Review Search: “Sodium Fluoride PET” returned 19 items. Further search for articles published from 1999 – present revealed, 11 items. Further search for only case reports or clinical trials revealed 8 items.
 - While these articles do not dispute that NaF18 is useful in detecting areas of bone turnover, some suggest that there may be other modalities that are equally adequate, if not better for certain indications. (i.e. FDG PET Brunkhorst, 2002; or I 131 scintigraphy and Tc MDP bone scan Schirrmeister, 2001).
- This reviewer’s assessment of the recent literature concludes that there is no evidence for:
 - lack of efficacy
 - lack of safety
 - at the new dose
 - in the pediatric population
 - comparative claims of efficacy (superiority claims to Technetium 99m MDP)
- This reviewer’s assessment of the recent literature concludes that there may be evidence for:
 - efficacy in various conditions
 - Efficacy in children

- **APPENDIX D - USE IN SPECIFIC POPULATIONS, 8.3 Nursing Mothers:**

- The sponsor presents the following information: (b) (4)

- It is this reviewer’s opinion that, although this statement is more lenient than the previous label, the instructions for breast feeding interruption appear appropriate; especially when compared to other newly -FDA approved Radiopharmaceuticals

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this page is the manifestation of the electronic signature.**

/s/

Michele Fedowitz
2/20/2009 08:26:26 AM
MEDICAL OFFICER

Libero Marzella
2/20/2009 02:30:27 PM
MEDICAL OFFICER

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			x	There are no safety issues with the drugs in the class to which the new drug belongs.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			x	
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			x	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Based on the recent literature, the sponsor will need to provide more information regarding the safe use and dosimetry of the product in children.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			x	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?			x	
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?			x	
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			x	
34.	Are all datasets to support the critical safety analyses available and complete?			x	
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?			x	
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			No clinical trials were conducted to support the application. NCI waives any market exclusivity for the product.
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?			x	

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes _____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

We identify a number of potential deficiencies in information which will be review issues:

1. The sponsor proposes a new, higher dose but does not provide adequate information to support this change. It is this reviewer's opinion that, based on the literature provided; the sponsor could support the safety of this new dose with a comprehensive analysis of the literature.
2. The sponsor provides a summary of peer-reviewed literature in the clinical information section of the label; (b) (4)
3. The Pediatric label is not changed; however, based on the literature submitted by the sponsor, there may be information to support a change in labeling. The pediatric section should be updated to include instructions for clinical use in children, as well as, dosimetry data in children.
4. Section 6, ADVERSE REACTIONS contains no new information. We cannot verify from the submission that no new material safety information has emerged from the current clinical use. The submission does not include an update of the recent literature and a comprehensive analysis of new safety and efficacy data. Despite the March 2000, PET Safety and Efficacy Notice and the FDAs Guidance, "PET Drug Applications - Content and Format for NDAs and ANDAs," the product has been in use for 9 years since its evaluation for the Notice (1999 literature review by the agency) and the Agency has not had access to safety reporting and annual reports, since the product was taken off the market (1975). For these reasons, we conclude that the product's continued use merits a comprehensive review of the recent literature for Safety and Efficacy updates, as well as, an integrated analysis of these findings.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Reviewing Medical Officer

Date

Clinical Team Leader

Date

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Michele Fedowitz
2/20/2009 08:28:14 AM
MEDICAL OFFICER

Libero Marzella
2/20/2009 02:31:12 PM
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