

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022494Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

*Office of Clinical Pharmacology and Biopharmaceutics*  
*New Drug Application Filing and Review Form*

**General Information About the Submission**

	Information		Information
NDA Number	22-494	Brand Name	Sodium fluoride-18
OCBP Division (I, II, III, IV, V)	V	Generic Name	
Medical Division	Medical Imaging and Hematology Products	Drug Class	Imaging
OCBP Reviewer	Christy S. John, Ph.D.	Indication(s)	For PET imaging of bone osteogenic activity
OCBP Team Leader	Young Moon Choi, Ph.D	Dosage Form	2 mCi/mL
		Dosing Regimen	8-12 mCi
Date of Submission	12/18/2008	Route of Administration	Intravenous Injection
Estimated Due Date of OCPB Review	5/28/2009	Sponsor	NCI, NIH
PDUFA Due Date	6/18/2009	Priority Classification	YES
Division Due Date	6/9/2009		

**Clin. Pharm. and Biopharm. Information**

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
<b>Mass balance:</b>				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:				
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD:</b>				
Phase 2:				
Phase 3:				
<b>PK/PD:</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				

solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>Dissolution:</b>				
<b>(IVIVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies:</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>	25 References			
<b>Total Number of Studies</b>	There are no clinical studies conducted. This application is based on published literature.			
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
<b>Application fileable ?</b>		YES		
<b>Comments sent to firm ?</b>		NONE		
<b>QBR questions (key issues to be considered)</b>				

<p><b>Other comments or information not included above</b></p>	<p>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. FDA reviewed its records and determined that Sodium Fluoride F 18 Injection was not withdrawn from sale for reasons of safety or effectiveness, and that it should be listed in the Orange Book's "Discontinued Drug Products List". Since the strength of the product manufactured by the original DMF holders (10 400 mCi/mL) differs from that of the reference listed drug (2 mCi/mL), the sponsor is not submitting an abbreviated NDA (ANDA) as described in section 505(j) of Federal Food, Drug and Cosmetic Act. The current application is being voluntarily submitted according to the Guidance for Industry: PET Drug Applications—Content and Format for NDAs and ANDAs (3, U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER)) and FDA's PET Safety and Effectiveness Notice (1, U.S. Department of Health and Human Services. Food and Drug Administration). Thus, this NDA relies on reference to the latter and on published literature as the basis for approval; no new studies were conducted.</p>
<p><b>Primary reviewer Signature and Date</b></p>	<p><b>Christy S. John, Ph.D</b></p>
<p><b>Secondary reviewer Signature and Date</b></p>	<p><b>Young Moon Choi, Ph.D.</b></p>

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Christy John  
3/19/2009 10:15:02 AM  
BIOPHARMACEUTICS

<b>NDA</b>	22-494	<b>Submission Date</b>	December 30, 2008
<b>Brand Name</b>	Sodium Fluoride [F-18]		
<b>Generic Name</b>	Sodium Fluoride [F-18]		
<b>Reviewer</b>	Christy S. John, Ph.D		
<b>Team Leader</b>	Young Moon Choi, Ph.D.		
<b>OCP Division</b>	V		
<b>ORM Division</b>	Division of Medical Imaging and Hematology Drug Products		
<b>Sponsor</b>	National Cancer Institute, NIH		
<b>Relevant IND(s)</b>	None		
<b>Submission Type; Code</b>	P	1	
<b>Formulation; Strength(s)</b>	Single-dose syringe containing 370–(b) (4) MBq/mL (10–(b) (4) mCi) of no-carrier-added sodium [ F ] fluoride at the end of synthesis (EOS) reference time in aqueous 0.9% sodium chloride solution.		
<b>Indication</b>	Sodium Fluoride F-18 Injection is a radioactive diagnostic agent for positron emission tomography (PET) indicated for diagnostic PET imaging of bone to define areas of altered osteogenic activity.		
<b>Proposed Dose</b>	Administer 300–450 MBq (8.0 –12.0 mCi) as an intravenous injection. It is recommended that imaging with Sodium Fluoride F 18 Injection can begin 1 hour after administration.		

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## 1 Executive Summary

The applicant (NCI, NIH) has submitted this 505(b)(2) application for the approval of NDA 22-494 for sodium fluoride F-18 or [<sup>18</sup>F] as a bone imaging agent to define altered osteogenic activity of bone. This NDA relies on 41 published literature references since 1992 in which <sup>18</sup>F-fluoride PET imaging was used to identify bone metastases and benign skeletal disorders in adults. No new clinical or clinical pharmacology studies were conducted in support of this NDA. This review has focused on these publications to glean the clinical pharmacology information, such as proposed dose, pharmacokinetics, and radiation dosimetry.

The present submission was granted a priority review based on a medical need.

### 1.1.1 Recommendations:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed NDA 22-494. The application was found to be acceptable from a clinical pharmacology perspective provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert.

### 1.2 Phase IV Commitments: None

### 1.3 Summary of Clinical Pharmacology Findings:

The proposed radioactivity dose is 8-12 mCi to be injected intravenously, and the bone scan is recommended to start at one to two hours after injection of <sup>18</sup>F-fluoride. This is based on the clinical experience and the doses reported in the published literature. No clinical dose finding studies were performed for this NDA. In nine prospective studies investigating the use of <sup>18</sup>F-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).

It appeared that a dose range of 8-12 mCi produced a high tumor detection rate, high sensitivity and good resolution on PET images. Therefore, the dose is acceptable from an efficacy perspective (See Pages 7-8 of this review). The radiation exposure to the organs after administration of the proposed dose are acceptable from radiation safety perspective (See Dosimetry Pages 11-13 of this review).

#### **Pharmacokinetics:**

This information has been taken from a review article (G. Blake et al. Sem. Nucl. Med. 31, 28-49, 2001) and references cited therein.

**Distribution:** After intravenous administration, approximately 30% of the injected dose of <sup>18</sup>F-fluoride is sequestered within circulating red blood cells. Then <sup>18</sup>F-fluoride is freely diffusible from the red cells into bone extra cellular fluid, where it becomes bound by chemisorption at the surface of bone crystals. All the <sup>18</sup>F-fluoride that is delivered to bone by the blood is retained in the bone. In general, this 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. There is minimal binding of  $^{18}\text{F}$ -fluoride by serum proteins.

**Elimination:**  $^{18}\text{F}$ -fluoride is cleared from the plasma in 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. One hour after administration of  $^{18}\text{F}$ -labeled NaF, only about 10% of the injected dose remains in the blood. Therefore imaging is recommended at one to two hours after administration of  $^{18}\text{F}$ -labeled NaF.

Fluoride ions are freely filtered by the glomerulus. Reabsorption of fluoride in the nephron is mediated by hydrogen fluoride, and consequently,  $^{18}\text{F}$  renal clearance varies with pH renal clearance of fluoride is also modified by diet. However, the effect of urine flow rate is the most important for nuclear medicine studies that use  $^{18}\text{F}$ . At high urine flows (>5 mL/min]), fluoride renal clearance averages 60% to 90% of GFR. However, for flows < 1 mL/min, renal clearance may be as low as 5% of GFR. Therefore, establishing good hydration of the patient and maintaining urine flow rates in the range of 5 to 10 mL/min are important for the conduct of imaging using  $^{18}\text{F}$  labeled NaF.

**Radiation absorbed dose:** The radiation absorbed doses to various organs and the effective dose equivalents for a 70 kg, 19 kg and 9.8 kg patients are listed in Table I. The critical organs (organs receiving highest absorbed doses) are bone surface, red marrow and urinary bladder. The pediatric patients have higher radiation exposure. The effective dose equivalent to 70, 19, and 9.8 kg patient is 0.027, 0.086 and 0.17 mSv/MBq, respectively.

For a maximum proposed dose of 12 mCi (444 MBq) a total effective dose appeared 11.988 mSv or 1198 mrem. The absorbed radiation dose allowed for occupational radiation workers is 5000 mrem. Thus radiation absorbed dose by injecting the proposed maximum dose of 12 mCi is below the allowed radiation absorbed doses and is acceptable.

Table I. The radiation absorbed doses to various critical organs and the effective dose equivalent (mSv/MBq) based on weights (International Society of Radiation Protection Report 53 Ann. 1987, 17, 74).

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## Question Based Review

### 2.1. General Attributes of the drug

#### 2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Sodium Fluoride F-18 ( $\text{Na}^{18}\text{F}$ ) was initially introduced in 1962 as an imaging agent for bone lesions. The agent was approved for clinical use by FDA in 1972 to define areas of altered osteogenic activity (NDA 17 042).  $^{18}\text{F}$ -Fluoride has favorable tracer kinetics as a radiopharmaceutical for bone imaging: it accumulates in bone rapidly to a high concentration and clears quickly from the circulation, allowing a high bone to background uptake ratio within a short time. As a result, exposure of patients to radiation is low and imaging can be obtained within an hour after intravenous administration of  $^{18}\text{F}$  fluoride.  $^{18}\text{F}$  Fluoride was replaced by  $^{99\text{m}}\text{Tc}$  labeled diphosphonates in 1970s as the standard imaging agents for bone scintigraphy because of the convenience in producing  $^{99\text{m}}\text{Tc}$  on site from  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generators. Gamma cameras also are optimally designed for detecting 140 keV photons from  $^{99\text{m}}\text{Tc}$  rather than higher energy 511 keV photons from  $^{18}\text{F}$ . Therefore, the decline in use of  $^{18}\text{F}$  fluoride in bone scintigraphy was due to technical and logistic issues, as opposed to limitations of fluoride ion as a radiotracer. The applicant has submitted this 505(b)(2) application for the approval of NDA 22-494 for sodium fluoride [F-18] as a bone imaging agent to define altered osteogenic activity of bone. This NDA relies on published literature references as a basis of its approval. No new clinical or clinical pharmacology studies were conducted in support of this NDA. No IND was filed for the drug.

Recently, there have been problems with  $^{99\text{m}}\text{Tc}/\text{Mo-99}$  generators with respect to Mo-99 breakthrough. If this problem persists, the availability of Tc-99m/Mo-99 generators could become an issue. F-18 bone scanning provides an alternative to Tc-99m based bone imaging agents. For this reason a priority review was granted by Agency for the review of this NDA.

#### 2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology of the drug?

The active ingredient, sodium fluoride  $^{18}\text{F}$  ( $^{18}\text{F}$  NaF), has the molecular formula  $\text{Na}^{18}\text{F}$ , a molecular weight of 40.99, and the following chemical structure:  $\text{Na}^+ \text{ } ^{18}\text{F}^-$ . It is produced by particle acceleration in a  $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$  nuclear reaction from  $\text{H}_2^{18}\text{O}$ . Radiopharmaceuticals administered for PET procedures typically incorporate radionuclides with very short physical half lives ( $t_{1/2}$ ). The half life of  $^{18}\text{F}$  is 109.7 minutes and it decays back to  $^{18}\text{O}$ . Sodium Fluoride F-18 [ $^{18}\text{F}$ ] Injection is provided as a ready to use, isotonic, sterile, pyrogen free, clear and colorless solution. Each mL of the solution contains  $10\text{--}(b)(4)$  mCi  $^{18}\text{F}$  NaF at the end of synthesis (EOS) 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 only known source of non-radioactive fluoride ion present are trace quantities found in the distilled water and saline solutions used in preparing the product. The drug product prepared by Siemens Molecular Imaging or  $(b)(4)$  complies with the USP monograph for Sodium Fluoride F-18 Injection.

#### 2.1.3 What are the proposed mechanism(s) of action and therapeutic indication?

$^{18}\text{F}$  fluoride diffuses through capillaries into bone ECF, where it becomes bound by chemisorption at the surface of bone crystals. In general, this 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.

#### **2.1.4. What are the proposed dosage(s) and route(s) of administration for adults?**

The proposed dosage is 8-12 mCi to be injected intravenously. The dose is based on the literature reports. No clinical dose finding studies were performed for this NDA. In nine prospective studies investigating the use of <sup>18</sup>F-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).

A dose of 8-12 mCi produced higher tumor detection rates and more accurate differentiation between benign and malignant lesions with 18F. Compared with F-18 PET and reference standard method, Radionuclide bone scanning (RNB) had a sensitivity of 82.3 % in detecting malignant tumors.

#### **2.1.5. What is the dose used for pediatric patients?**

The sponsor did not propose a dose for pediatric patients. In clinical experience in approximately 94 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq – 148 MBq (0.5 mCi - 4 mCi) were used (Ruth Lim et al. J. Pediatric Orthopedics. 2007, 27, 277-282).

### **2.2 General Clinical Pharmacology**

As reported earlier, there was no clinical pharmacology or clinical studies conducted by the sponsor for this submission. Only literature data was submitted to support the application. Stable fluoride is a natural trace element and at least 99% of whole body fluoride is thought to be present in skeleton as fluoroapatite. After intravenous administration, <sup>18</sup>F-fluoride is rapidly 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. All the <sup>18</sup>F-fluoride that is delivered to bone by the blood is retained in the bone. Tracer retention by the bone is a two-phase process. In the first phase, the <sup>18</sup>F- ion exchanges for an OH- ion on the surface of the hydroxyapatite matrix of bone. In the second phase, the <sup>18</sup>F- ion migrates into the crystalline matrix of bone, where it is retained until the bone is remodeled. One hour after administration of <sup>18</sup>F-labeled NaF, only about 10% of the injected dose remains in the blood.

#### **2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

There are no studies conducted. All clinical pharmacology data is taken from published literature. The dosing claims are based on the efficacy results of different published reports. According to several reports higher tumor detection rates and more accurate differentiation between benign and malignant lesions with <sup>18</sup>F was observed as compared to Tc-99m-MDP bone scan. Compared with F-18 PET and reference standard methods ( (b) (4) ), Tc-99m-MDP bone scan had a sensitivity of 82.3 % in detecting malignant tumors.

#### **2.2.2 What is the basis for selecting the response endpoints, i.e, clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?**

Deposition of <sup>18</sup>F-fluoride in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the <sup>18</sup>F-fluoride from the blood perfusing the bone. There were no pharmacodynamic factors determined or reported in the literature. The clinical endpoints were the quality of images, higher sensitivity of 18F PET and reference standard methods ( (b) (4) ) as compared to radionuclide bone scan (RNB). According to a clinical study (J. Nucl. Med. 1999, 49, 1623-1629) with <sup>18</sup>F PET twofold more lesions were detected than with RNB. The detection rates of bone metastases were 100% with PET both in patients with osteoblastic metastases associated with cancer of prostate and in patients with osteolytic

metastases associated with cancer of the thyroid and lung. In contrast, with RNB only 49.3% of osteoblastic metastases and 44.8% of osteolytic metastases were detected.

## 2.2.4 Exposure-response Evaluation

### 2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No exposure response studies were conducted or studies reported in literature. Although different doses of the radiopharmaceutical were administered in different literature reports, however, there does not appear to be much effect of dose in determining the efficacy outcome. As stated above, the clinical endpoints were the quality of images, higher sensitivity of 18F PET and reference standard methods as compared to RNB.

### 2.2.4.2 Does this drug prolong the QT or QTc interval?

Single-dose of Sodium [<sup>18</sup>F] fluoride contains “No- carrier -added” sodium [18F] fluoride. There is no stable fluoride present in the present in the dose. The effect of QT or QTc has not been studied. It is acceptable as 18F does not have any appreciable mass and the drug is administered once in a hospital setting.

### 2.2.4.3. Is [<sup>18</sup>F] fluoride PET imaging efficacious in detecting bone metastasis?

Bone scan (BS) using Tc-99m-MDP (planar scintigraphic imaging) is the most widely used method for detecting skeletal metastases. Several studies are reported in literature showed that <sup>18</sup>F PET is more sensitive and accurate in detecting osteolytic and osteoblastic metastasis. In this study 44 patients with known prostate, lung or thyroid carcinoma were examined with both planar imaging and <sup>18</sup>F PET. A panel of reference methods including MRI of the spine, I-131 scintigraphy, conventional radiography and spiral CT was used as the gold standard. BS and <sup>18</sup>F PET were compared by a lesion-by-lesion analysis using a five-point receiver operating characteristic (ROC) curve analysis. <sup>18</sup>F PET showed 96 metastases (67 of prostate carcinoma and 29 of lung and thyroid cancer), on the other hand BS showed only 46 metastases (33 of prostate cancer and 13 of lung or thyroid cancer). All lesions detected by BS were also detected by <sup>18</sup>F PET. Compared with <sup>18</sup>F PET and the gold standard, BS had a sensitivity of 82.8% in detecting malignant and benign bone lesion. The area under ROC curve was 0.99 for <sup>18</sup>F PET and 0.64 for BS. (**J. Nucl Med. 1999, 40, 1623-1629**). Table II shows the total number of benign or malignant lesion detected by bone scanning and <sup>18</sup>F PET. Table III shows the number of patients with metastases, benign lesions or normal findings on <sup>18</sup>F PET imaging or radionuclide bone scanning (RNB). Table IV. Osseous lesions detected at different sites by <sup>18</sup>F PET imaging or radionuclide bone scanning (RNB)

Table II. Benign and malignant lesion detected by bone scan (RNB and 18 F PET)

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Reference: J. Nucl Med. 1999, 40, 1623-1629

Table III. Patients with metastases, benign lesions or normal findings on  $^{18}\text{F}$  PET imaging or radionuclide bone scanning (RNB)

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Reference: J. Nucl Med. 1999, 40, 1623-1629

Table IV. Osseous lesions detected at different sites by  $^{18}\text{F}$  PET imaging or radionuclide bone scanning (RNB)

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Values in parenthesis indicate percentage of lesions detected by  $^{18}\text{F}$  PET  
Reference: J. Nucl Med. 1999, 40, 1623-1629

Similarly, several other literature reports have reported a high sensitivity and accuracy. M. Hetzel et al. (Journal of Bone and Mineral Research, 2003, 18, 2206-2214) reported a study in 103 patients with lung cancer undergoing bone scan. This study used 7-20 mCi of F-18 Fluoride. Receiver Operating Characteristic (ROC) curve was used for determination of diagnostic accuracy. The area under the ROC curve for planar bone scanning was 0.77, 0.875 for SPECT and 0.989 for F-18 PET.

Even-Sapir, E. et al (J. Nuclear Medicine, 2006, 47, 287-297) compared the detection of bone metastases by Tc-99m-MDP using planar imaging (BS), SPECT and F-18-Fluoride PET, and 18-Fluoride PET/CT in patients with high risk prostate cancer in a prospective study. The study used a dose of 8-12 mCi of F-18 fluoride. In patient-based analysis, 23 patients had skeletal metastatic spread (52%) and 21 did not. Categorizing equivocal and malignant interpretation as suggestive for malignancy, the sensitivity, specificity, positive predictive value, and negative predictive value of planar BS were 70%, 57%, 64%, and 55% respectively, of SPECT were 92%, 82%, 86%, and 90%, of F-18 Fluoride PET were 100%, 62%, 74%, and 100%, and of F-18 fluoride were 100%, for all parameters. Based on these and several other literature reports 8-12 mCi dose of F-18 Fluoride for PET imaging is adequate from an efficacy perspective.

## 2.2.5 Pharmacokinetic Characteristics

### 2.2.5.1 What are the PK characteristics of the drug and its major metabolites?

Stable fluoride is a natural trace element and at least 99% of whole body fluoride is thought to be present in skeleton as fluoroapatite.  $^{18}\text{F}$ -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. All the  $^{18}\text{F}$ -fluoride that is delivered to bone by the blood is retained in the bone. Tracer retention by the bone is a two-phase process. In the first phase, the  $^{18}\text{F}$ -ion exchanges for an  $\text{OH}^-$  ion on the surface of the hydroxyapatite matrix of bone. In the second phase, the  $^{18}\text{F}$ -ion migrates into the crystalline matrix of bone, where it is retained until the bone is remodeled. One hour after administration of  $^{18}\text{F}$ -labeled  $\text{NaF}$ , only about 10% of the injected dose remains in the blood.

Approximately 30% of the injected dose of  $^{18}\text{F}$ -fluoride is sequestered within circulating red blood cells. However,  $^{18}\text{F}$ -fluoride is freely diffusible from the red cells to the bone surface; moreover, red blood cell uptake does not appear to interfere with uptake of the tracer by bone. The total uptake of  $^{18}\text{F}$ -fluoride by the bone is similar to that of  $^{99\text{m}}\text{Tc}$ -MDP (another bone scanning agent used in nuclear medicine clinics routinely), at approximately 50% of the injected dose.

There is minimal binding of  $^{18}\text{F}$ -fluoride by serum proteins. This is an important difference between  $^{18}\text{F}$ -fluoride and  $^{99\text{m}}\text{Tc}$ -MDP and other  $^{99\text{m}}\text{Tc}$ -diphosphonate bone agents, all of which show significant protein binding. Approximately 30% of  $^{99\text{m}}\text{Tc}$ -MDP is protein-bound immediately after injection; this fraction increases to approximately 70% by 24 h after injection. The non-protein-bound fraction of  $^{99\text{m}}\text{Tc}$ -MDP is rapidly cleared from the blood with a half-life similar to that of  $^{18}\text{F}$ -fluoride, but the protein-bound fraction is cleared much more slowly. Hence, it is necessary to wait 2–3 h after injection of  $^{99\text{m}}\text{Tc}$ -MDP before imaging. By comparison, imaging can be performed less than 1 h after  $^{18}\text{F}$ -labeled  $\text{NaF}$  administration.

#### 2.2.5.1. How does the dosimetry of $\text{Na}^{18}\text{F}$ compare to $\text{Tc-}^{99\text{m}}\text{MDP}$ ?

Several factors affect the radiation dose of  $^{18}\text{F}$  relative to that of single-photon emitters (such as  $^{99\text{m}}\text{Tc}$ ). With a positron emitter such as  $^{18}\text{F}$ , energy is delivered by the positron itself (mean energy, 250 keV) and by the two 511-keV annihilation photons, whereas  $^{99\text{m}}\text{Tc}$  emits a single 140-keV ray, as well as conversion electrons in low abundance. These differences affect the relative internal dosimetry of  $^{18}\text{F}$  and  $^{99\text{m}}\text{Tc}$ . The  $^{18}\text{F}$  positron will deposit essentially all its kinetic energy in the source organ, whereas the different energies of 511-keV and 140-keV photons result in different patterns of internal radiation dose. The soft-tissue half-value layers for the 511- and 140-keV photons are 7.3 and 4.6 cm, respectively, so that 511 keV photons can deliver their energy to organs distant from the source organ, whereas the 140-keV photons will deliver more of their energy to organs near the source organ. On the other hand, the half-life for  $^{18}\text{F}$  is 110 min, compared with 6 h for  $^{99\text{m}}\text{Tc}$ , leading to a shorter exposure period and, in turn, to a reduced radiation dose for  $^{18}\text{F}$ . Considering these factors, the dosimetry of both  $\text{Na}^{18}\text{F}$  and  $\text{Tc-}^{99\text{m}}\text{MDP}$  was calculated using the reports 53 and 80 of International Commission on Radiological Protection (ICRP) (Table V).

Table V. Weight based radiation absorbed doses for  $^{99m}\text{Tc}$ -MDP and  $^{18}\text{F}$

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The weight based organ absorbed radiation dose for intravenous injection of  $^{18}\text{F}$  in mGy/mBq are given in Table V. These estimates are based on human data and published by the International Commission on Radiation Protection (ICRP) for  $^{18}\text{F}$  intravenous injection.

The effective dose is a quantity developed by the International Commission on Radiological Protection (1991) for purposes of radiation protection. The effective dose is assumed to be related to the risk of a radiation-induced cancer or a severe hereditary effect. It takes into account the absorbed doses that will be delivered to the separate organs or tissues of the body during the lifetime of an individual due to intakes of radioactive materials, the absorbed doses due to irradiation by external sources, the relative effectiveness of different radiation types in inducing cancers or severe hereditary effects, the susceptibility of individual organs to develop a radiation-related cancer or severe hereditary effect, considerations of the relative importance of fatal and nonfatal effects, and the average years of life lost from a fatal health effect. The sievert (Sv) is the special name for the international (SI) unit of effective dose. US regulatory agencies continue to use traditional units in regulation, this position statement also gives the effective dose in rem, which is the special name for the traditional unit. The millisievert (mSv) and millirem (mrem) are one one-thousandth of a sievert and rem, respectively (100 mrem = 1 mSv).

The effective dose equivalent to a 70 kg patient is 0.027 mSv/MBq. For a maximum dose of 12 mCi (444 MBq) a total effective dose of 11.988 mSv or 1198 mrem (Table VI). The absorbed radiation dose allowed for occupational radiation workers is 5000 mrem. Thus radiation absorbed dose by a maximum dose of 12 mCi is below the allowed radiation absorbed doses and is acceptable.

Table VI. Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection (International Society of Radiation Protection Report 53 Ann. 1987, 17, 74).

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#### **2.2.5.2 What is radiation absorbed doses for different pediatric age groups?**

The radiation absorbed dose to different pediatric age groups is higher than adults, as expected. The effective dose equivalent (mSv/MBq) for kids ages 10, 5 and 1 year old was about 2-fold, 3-fold, and 6-fold higher as compared to 70 kg adult, respectively. Because of high radiation absorbed dose for the pediatric subjects, a weight based dose (2.1 MBq/kg) is recommended for pediatric subjects. Based upon effective dose equivalent mSv/MBq the following are radiation

exposure for various pediatric age groups based on 2.1 MBq/kg is given in Table VII. The justification for this dose is based upon the literature report (Ruth Lim et al. J. Pediatric Orthopedics. 2007, 27, 277-282) on the use of F-18 PET imaging in 94 pediatric subjects (ages 4-26, mean age 15 years). This study used a dose of 2.1 MBq/Kg and it appeared clinically useful for making accurate diagnosis and radiation exposure to kids was acceptable.

**Table VII. Radiation absorbed doses for various pediatric age groups**

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### **2.3 Intrinsic factors**

**2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?**

The effect of Na<sup>18</sup>F on age, gender, race, weight, height, organ dysfunction has not been studied. This is acceptable as these factors will not substantially affect the efficacy of <sup>18</sup>F PET imaging.

### **2.4 Extrinsic Factors**

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?**

The effect of Na<sup>18</sup>F on drugs, diet, smoking, alcohol use has not been studied. This is acceptable as these factors do not affect substantially the efficacy of <sup>18</sup>F PET imaging.

### **2.4.3 Drug-Drug Interactions**

No drug-drug interaction studies were conducted. Na<sup>18</sup>F is a no- carrier added molecule (microdosing), therefore drug interaction studies are not necessary.

### **2.4 General Biopharmaceutics:**

Not applicable

**3. Detailed labeling Recommendations:**

**The clinical pharmacology section of the label has been modified to read as follows:**

Sponsor's proposed Label	Agency's recommendation
<p style="text-align: right;">(b) (4)</p>	<p>2.6 Recommended dose for pediatric patients Administer 2.1 MBq/kg as an intravenous injection.</p>
<p><b>12 CLINICAL PHARMACOLOGY</b></p> <p><b>12.1 Mechanism of Action</b> <sup>18</sup>F-Fluoride normally accumulates in the skeleton in an even fashion, with greater deposition in the axial skeleton (e.g., vertebrae and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.</p> <p>12.2 Pharmacodynamics</p> <p style="text-align: right;">(b) (4)</p> <p>12.3 Pharmacokinetics</p> <p style="text-align: right;">(b) (4)</p>	<p><b>12 CLINICAL PHARMACOLOGY</b></p> <p><b>12.1 Mechanism of Action</b> <sup>18</sup>F-Fluoride normally accumulates in the skeleton in an even fashion, with greater deposition in the axial skeleton (e.g., vertebrae and pelvis) than in the appendicular skeleton and greater deposition in the bones around joints than in the shafts of long bones.</p> <p>12.2 Pharmacodynamics</p> <p>Increased <sup>18</sup>F-fluoride deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.</p> <p>12.3 Pharmacokinetics</p> <p>After intravenous administration, <sup>18</sup>F-fluoride is rapidly 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 <sup>18</sup>F-fluoride that is delivered to bone by the blood is retained in the bone. One hour after administration of <sup>18</sup>F-labeled NaF, only about 10% of the injected dose remains in the blood. F-18 fluoride diffuses through capillaries into bone extracellular fluid space, where it becomes bound by chemisorption at the surface of bone crystals, preferentially at sites of newly mineralizing bone.</p> <p>Deposition of <sup>18</sup>F-fluoride in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the <sup>18</sup>F-fluoride. <sup>18</sup>F-Fluoride does not appear to be bound to serum proteins.</p>

#### **4. Appendices**

**N/A**

##### **4.1 Proposed Package Insert**

10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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