

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022494Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 22-494	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Sodium Fluoride, F18 Established/Proper Name: NAF Dosage Form: Injection Strengths: 10-200mCi		
Applicant: National Cancer Institute (NCI)		
Date of Receipt: December 30, 2008		
PDUFA Goal Date: January 26, 2011	Action Goal Date (if different): January 26, 2011	
Proposed Indication: Sodium Fluoride is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Published Literature, Sodium Fluoride, F18	Federal Register Notice (65 FR 12999-13009)

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)
Literature and FDA Guidance

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
*If “NO,” proceed to question #5.
If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Sodium Fluoride Injection	17-042	Yes

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing: Sodium Fluoride

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

Change in concentration, Original product 2mCi, this product 10-200mCi

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)? No

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.

If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent? YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.
If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)? YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.
If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information UNLESS the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

JAMES W MOORE
02/23/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology

Application Number: NDA 22-494

Name of Drug: Sodium Fluoride (F-18) Injection

Applicant: National Cancer Institute (NCI)

Date: January 25, 2011

Material Reviewed:

Submission Date: October 29, 2011, December 27, 2010

Receipt Date: October 29, 2010, December 27, 2010

Submission Date of Structure Product Labeling (SPL): December 27, 2010

Type of Labeling Reviewed: Word/SPL

Background and Summary

A CR letter was issued for this application on June 29, 2009. The National Cancer Institute resubmitted their application on May 13, 2010. All deficiencies were addressed in the resubmitted application except changes to Siemens' DMF. The DMF was resubmitted on July 26, 2010 and found to be acceptable. On October 14, 2010, the Division requested changes to the package insert submitted by the National Cancer Institute in their May 13, 2010 submission. The National Cancer Institute resubmitted the labeling on October 29, 2010. The Division found this labeling to be acceptable. Additional labeling changes were requested in the November 29, 2010 correspondence sent to the National Cancer Institute. NCI's response to FDA's November 30, 2011 was also acceptable. A review of the carton and container label by DMEPA on January 25, 2011 recommended that the statement "Use within 12 hrs of EOS" should be placed on the immediate container and shield label by the Division. After review by the chemistry team, it was decided that this statement would be added to the carton and shield label. The revised carton and shield labels were sent to the National Cancer Institute for their concurrence with the change.

Review

FDA's package insert of October 13, 2010 was compared to the package insert submitted by NCI on October 29, 2010. FDA's label of November 29, 2010 was compared to NCI's label of December 27, 2010 and found to be acceptable. The statement recommended by DMEPA and accepted by chemistry was sent to the National Cancer Institute. NCI agreed with the change recommended by FDA.

Recommendations

The changes to the package insert requested by FDA from the National Cancer Institute have all been implemented and found to be acceptable. The carton and shield labels were acceptable to NCI and FDA. Therefore, I recommend that FDA issue an approval letter for this application.

James Moore, PharmD., M A.
Regulatory Project Manager, DMIP

Supervisory Concurrence

Kyong Kang, PharmD.
Chief, Project Management Staff
January 26, 2011

CSO LABELING REVIEW

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/s/

JAMES W MOORE
01/26/2011

KYONG A KANG
01/26/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 2, 2010

TO: Michele Fedowitz, MD, Medical Officer, Division of Medical Imaging Products

THROUGH : Jo Wyeth, PharmD, Team Leader, Division of Pharmacovigilance II

FROM: Sara Camilli, PharmD, Safety Evaluator, Division of Pharmacovigilance II (DPV II)

SUBJECT: Consult Request RCM 2010-1771, AERS Search for All Adverse Events

APPLICATION/DRUG: NDA 22-494/Sodium Fluoride F-18 Injection

The following information was transmitted via email on August 19, 2010 in response to a consult request from the Division of Medical Imaging Products.

We searched FDA's Adverse Event Reporting System (AERS) on August 16, 2010 for adverse event reports associated with 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 (the correct product was sodium fluoride toothpaste).

NCI, the sponsor for NDA 22-494, retrieved 2 unverified adverse event cases possibly involving sodium fluoride F-18 injection in search of the AERS Quarterly Data Files (October 2008 to September 2009). NCI could not confirm association to the product sodium fluoride F-18 injection due to missing data fields. It is likely that these 2 cases were mis-coded or did not involve sodium fluoride F-18 injection.

Of note, FDA initially received 2 of the cases (ISR 6133308 and ISR 6314258) during the period October 2008 to September 2009.

DPV II will continue to monitor AERS for adverse event reports associated with sodium fluoride F-18 injection.

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/

SARA L CAMILLI
09/02/2010

JO H WYETH
09/03/2010

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: March 2, 2009

To: Thuy Nguyen – Regulatory Project Manager
Division of Medical Imaging and Hematology Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

Subject: NDA 22-494
DDMAC labeling comments for Sodium Fluoride F 18 Injection

DDMAC has reviewed the proposed PI and container labeling for Sodium Fluoride F 18 Injection (sodium fluoride) dated February 3, 2009, and submitted for consult on February 24, 2009. We offer the following comments.

Highlights

Indications and Usage

1. Because the safety and effectiveness of sodium fluoride have not been established in pediatric patients, we recommend including a limitation to the indication that the drug is only for use in adults.

Dosage and Administration

1.  (b) (4)

We recommend providing a time limit to when the drug should be administered; as proposed, the text above  (b) (4). For instance, the How Supplied section of the proposed PI states that the solution should be used within 12 hours of the end of synthesis (EOS) calibration. Including a time limit to use would be consistent with the labeling for technetium Tc 99m agents.

Adverse Reactions

1. As proposed, the text in this section minimizes the risks of sodium fluoride. For consistency with the Adverse Reactions section of the proposed Full Prescribing Information, we recommend including the statement, “However, the completeness of these sources is not known.”

Full Prescribing Information

Indications and Usage

1. Please see comment under “Highlights – Indications and Usage.”

Dosage and Administration

Imaging

1. Please see comments under “Highlights – Dosage and Administration.”

Patient Preparation

1. “The patient should be instructed to ingest copious amounts of fluid immediately prior and subsequent to the administration of Sodium Fluoride F 18 Injection.”

According to the Patient Counseling Information section of the proposed PI, patients should drink at least (b) (4) of water prior to drug administration. This reviewer does not consider (b) (4) to be a “copious” amount of liquid. Therefore, we recommend specifying how many ounces of water patients should consume for context.

2. “The patient should void one-half hour after administration of Sodium Fluoride F 18 Injection and as frequently thereafter as possible.”

For consistency with the labeling for technetium Tc 99m agents, we recommend specifying for how many hours after drug administration patients should void as frequently as possible (e.g., 4 to 6 hours).

Drug Handling

1. “As with other injectable drug products, allergic reactions and anaphylaxis may occur.” (emphasis added)

This phrase is promotional in tone and minimizes the risks of sodium fluoride administration. Therefore, we recommend deleting.

Adverse Reactions

1. [REDACTED] (b) (4)

Are these statements accurate?

Use in Specific Populations

Pediatric Use

1. [REDACTED] (b) (4) Sodium Fluoride F 18 Injection [REDACTED] (b) (4) to localize [REDACTED] (b) (4) rapidly growing epiphyses in developing long bones.”

Because safety and effectiveness have not been established in pediatric patients, we recommend deleting mention [REDACTED] (b) (4) in this patient population.

Clinical Pharmacology

Pharmacokinetics

1. This section of the proposed PI contains multiple mentions of the words [REDACTED] (b) (4) which are promotional in tone. Therefore, we recommend providing context for these words.

Clinical Studies

Metastatic Disease

1. This section of the proposed PI contains numerous claims of sodium fluoride superiority over other imaging agents and modalities. Were these studies adequately designed to serve as substantial evidence to support such comparative claims? If not, we recommend deleting.

Even if these claims are supported by substantial evidence, we recommend the sponsor present only the factual results of the studies and not characterize/qualify them. For example, the Breast Cancer subsection states the following:

[REDACTED] (b) (4)

Patient Counseling Information

1. For consistency with the Dosage and Administration section of the proposed PI, we recommend including language in this section that instructs patients to void [REDACTED] (b) (4) after drug administration and as frequently as possible for however many hours thereafter.

Container Labeling

We have reviewed the proposed container labeling and have no comments at this time.

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/s/

Michelle Safarik
3/2/2009 12:01:30 PM
DDMAC PROFESSIONAL REVIEWER