PRODUCT MONOGRAPH

NaF PLus

Sodium Fluoride [^{18}F] Injection, U.S.P.

Parenteral Solution

Diagnostic Radiopharmaceutical

Isologic Innovative Pharmaceuticals Ltd.

1855 32nd Avenue, Lachine, Quebec H8T 3J1

Date of Preparation:

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	*Dosage Form /Strength*	*Clinically Relevant Non-medicinal Ingredients*
Intravenous	Parenteral solution 370 to 7400 MBq/mL	None

DESCRIPTION

Physical Characteristics

Sodium Fluoride [^{18}F] Injection is a sterile solution, suitable for intravenous administration, containing no-carrier-added fluoride [^{18}F] in Sodium Chloride Injection.

Fluoride [^{18}F] is a cyclotron-produced diagnostic radiopharmaceutical. Fluoride [^{18}F] decays to ^{18}O by positron (ß+) emission with a half-life of 110 minutes.

Ninety-seven percent of the decay results in emission of a positron with a maximum energy of 633 keV and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen.

Table 1: Physical Decay Chart for ^{18}F

Time	% remaining	Time	% remaining
1 h	68%	10 h	2.3%
2 h	47%	11 h	1.5%
3 h	32%	12 h	1.1%
4 h	22%	13 h	0.73%
5 h	15%	14 h	0.50%
6 h	10%	15 h	0.34%
7 h	7.1%	16 h	0.23%
8 h	4.8%	17 h	0.16%
9 h	3.3%	18 h	0.11%

The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron.

Table 2: Principal Emission Data for Fluorine [^{18}F]

Radiation/Emission	*Photons per Disintegration*	*Mean Energy*
Positron (β+)	96.73	249.8 keV
Gamma (±)	193.46	511.0 keV

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

External Radiation

The specific gamma-ray constant for fluorine [^{18}F] is 0.3 Gy/hr/kBq at 1cm. The narrow-beam attenuation half value layer is 4.1 mm for lead (and 3.4 cm for concrete). Broad-beam transmission factors at 511 keV for various thicknesses of lead are given in Table 3.

Table 3: Broad-beam transmission factors at 511 keV in lead

mm Pb	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*12*	*14*	*16*	*18*	*20*	*30*
Transmission	0.89	0.79	0.69	0.60	0.52	0.45	0.39	0.34	0.29	0.25	0.18	0.13	0.10	0.07	0.05	0.01

From AAPM Task Group 108: PET and PET/CT shielding requirements. Med Phys 2006[1]

INDICATIONS AND CLINICAL USE

Sodium Fluoride [^{18}F] Injection is indicated as an accessory to positron emission tomography (PET) for the detection of areas of altered osteogenesis associated with bone metastases.

CONTRAINDICATIONS

None known.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Radiopharmaceuticals should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

Sodium Fluoride [^{18}F] Injection should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the foetus.

Where an assessment of the risk-benefit ratio suggests the use of Sodium Fluoride [^{18}F] Injection in nursing woman, breastfeeding should be discontinued for a period of at least 12 hours following the injection.

General

To minimize the radiation-absorbed dose to the bladder, patients should be well hydrated and encouraged to void frequently during the first few hours after administration of Sodium Fluoride [^{18}F] Injection.

The radiopharmaceutical product may be received, used and administered only by authorized persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of local competent official organizations.

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Carcinogenesis and Mutagenesis

Studies with Sodium Fluoride [^{18}F] Injection have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker

Special Populations

Pregnant Women: Sodium Fluoride [^{18}F] Injection should not be administered to pregnant women. The absorbed radiation dose to the foetus has been estimated as follows:

Table 4. Foetal Absorbed Dose Estimate per MBq administered to mother

	Early	3 months	6 months	9 months
Foetal Dose estimate (mGy/MBq)^2	2.2E-02	1.7E-02	7.5E-03	6.8 E-03

Adequate studies have not been performed to determine whether there are adverse effects on the fetus or to characterize the teratogenic potential. Prior to the administration of Sodium Fluoride [^{18}F] Injection to women of childbearing potential, the presence of pregnancy should be assessed. Ideally examinations using radiopharmaceuticals in women of child bearing capability should be performed during the first ten days following the onset of menses. However, such precaution does not exclude the possibility of pregnancy and a pregnancy test may be required if clinically indicated.

Nursing Women: The excretion of Sodium Fluoride [^{18}F] Injection in human milk has not been studied. However naturally occurring stable fluoride [^{19}F] is present in breast milk. Caution should therefore be exercised when Sodium Fluoride [^{18}F] Injection must be administered to a nursing woman. Where an assessment of the risk-benefit ratio suggests the use of Sodium Fluoride [^{18}F] Injection in nursing woman, breastfeeding should be discontinued for a period of at least 12 hours following the injection. Breast milk may be expressed prior to dosing for subsequent use.

Pediatrics: The efficacy and safety of Sodium Fluoride [^{18}F] Injection in the approved indication have not been established in pediatric patients.

Geriatrics: Geriatric patients were included in the studies demonstrating the efficacy and safety of Sodium Fluoride [^{18}F] Injection in the approved indication. There are no known limitations on the clinical use of Sodium Fluoride [^{18}F] Injection in geriatric patients.

ADVERSE REACTIONS

No serious adverse effects have been observed to date.

DRUG INTERACTIONS

Interactions with drugs, food, herbs, and laboratory tests have not been established. Sodium Fluoride [^{18}F] should not be co-administered with any other products.

DOSAGE AND ADMINISTRATION

Dosing considerations

The optimal dose of Sodium Fluoride [^{18}F] Injection has not been systematically investigated. As with all radiopharmaceuticals, only the lowest dose necessary to obtain adequate visualization should be used. Most procedures do not require use of the maximum dose. The dose to be used should be carefully individualized and factors should be considered such as body size and equipment and technique to be employed.

Dosage

The recommended dose of Sodium Fluoride [^{18}F] Injection is 185 to 370 MBq.[3]

Administration

Sodium Fluoride [^{18}F] Injection is administered intravenously.

The individual patient-dose should be withdrawn from the multi-dose vial and the activity measured by a dose calibrator prior to administration. At the product expiry of 18 hours post-end of synthesis, it may not be possible to obtain the activity required to perform a diagnostic test.

Image Acquisition and Interpretation

Whole body PET/CT images are usually acquired at 60 minutes after administration of Sodium Fluoride [^{18}F] Injection.

The rapid localization of ^{18}F in the skeleton and its rapid clearance from the circulation may allow imaging of axial skeleton to begin as early as 30-45 minutes after administration. For quality images of the extremities, image acquisition may need to be delayed until 90-120 minutes after administration.[3]

In general, the degree of ^{18}F uptake does not differentiate benign from malignant processes. Fluoride [^{18}F] accumulates in most areas of increased osteogenesis, including areas of degenerative bone disease. Processes that result in minimal osteoblastic activity, or primarily osteolytic activity, may not be detected. Knowledge of normal accumulation patterns is essential for the accurate interpretation of Fluoride [^{18}F] PET/CT scans. Correlation with skeletal radiographs and other anatomic imaging is essential for diagnosis. The CT component of PET/CT, even when performed primarily for attenuation correction and anatomic registration, also provides diagnostic information.

Instructions for Preparation and Use

No preparation is necessary; the solution is ready to use. It is essential that the user follows the directions carefully and adheres to strict aseptic technique. Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial during the useful life of the radioactive product.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer Sodium Fluoride [^{18}F]

Injection containing particulate matter or discoloration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations

RADIATION DOSIMETRY

ICRP 53 biokinetic data were reanalyzed using OLINDA/EXM V.1.1 [4] with the gender-neutral phantom, and ICRP 103 tissue weighting factors. The effective dose coefficient of Sodium Fluoride [^{18}F] Injection is 1.7E-02 mSv/MBq. The effective dose for the PET scan following a single injected activity of 370 MBq is 6.3 mSv

The critical organ is the urinary bladder (2.0E-01 mSv/MBq), followed by the target organ, osteogenic bone (7.1E-02), and the kidneys (2.0E-03).

Table 4. Radiation Dose Estimates (mSv/MBq)

Organ	*mSv/MBq*
Adrenals	8.6E-03
Brain	7.5E-03
Breasts	4.6E-03
Colon	1.0E-02
Gallbladder	7.0E-03
Gonads	1.1E-02
Heart	6.4E-03
Kidneys	2.0E-02
Liver	6.4E-03
Lungs	6.3E-03
Muscle	7.8E-03
Pancreas	7.4E-03
Red Marrow	1.1E-02
Osteogenic Cells	7.1E-02
Skin	5.6E-03
Small Intestine	8.8E-03
Spleen	6.6E-03
Stomach	6.3E-03
Thymus	5.8E-03
Thyroid	6.7E-03
Urinary Bladder	2.0E-01
Uterus	1.9E-02
Effective Dose Coefficient	1.7E-02

Based on OLINDA/EXM V1.1 analysis of ICRP 53 biokinetic data and ICRP 103 tissue weighting factors

OVERDOSAGE

Cases of overdose are not known to have occurred with Sodium Fluoride [^{18}F] Injection. In case of overdose, the patient should be monitored closely. Effort should be made to increase elimination of the

radiotracer by increasing hydration, frequent voiding, and with forced diuresis at discretion of clinician if clinically indicated

ACTION AND CLINICAL PHARMACOLOGY

Following intravenous administration, about 50% of fluoride [^{18}F] is rapidly taken up by the skeleton where it remains during the time period of its radioactive decay. The remainder of fluoride [^{18}F] is distributed into the extracellular fluid and eliminated by renal excretion within a few hours. Fluoride [^{18}F] is rapidly and biexponentially cleared from the blood by bone deposition and by urinary excretion.

The initial distribution phase has a half-life of 0.40 hours; the elimination half-life is 2.6 hours.[5] Uptake by bone is a function of blood flow and of osteogenic activity.

Fluoride [^{18}F] 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.

Increased fluoride [^{18}F] uptake can occur in areas of increased osteogenic activity, including primary bone malignancy, skeletal metastases, and benign lesions such as trauma, osteomyelitis, arthritis, and metabolic bone disease.

In patients with normal renal function, 20% or more of the fluoride [^{18}F] is cleared from the body in the urine within the first 2 hours after intravenous administration.[6]

Special Populations and Conditions

No data available.

STORAGE AND STABILITY

Sodium fluoride [^{18}F] Injection should be stored upright in a lead shielded container at controlled room temperature. Sodium fluoride [^{18}F] Injection should be used before the residual activity falls below the minimum dose required for a quality diagnostic image, or at most within 18 hours of the end of synthesis, a duration which is based on physicochemical data.

SPECIAL HANDLING INSTRUCTIONS

As in the use of any other radioactive material, care should be taken to minimize radiation exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Radiopharmaceuticals should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radionuclide, and whose experience and training have been approved by the appropriate governmental agency authorised to license the use of radionuclides.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Sodium fluoride [^{18}F] Injection is supplied in a multi-dose, septum-capped, 30 mL glass vial containing 370-7400 MBq/mL of no carrier added Sodium fluoride [^{18}F], at end of synthesis, in approximately 10 to 30 mL.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Sodium fluoride [^{18}F]
Chemical name:	Sodium fluoride [^{18}F]
Molecular formula:	$Na^{18}F$
Molecular mass:	41 Da
Physicochemical properties:	Clear, colorless solution.

Product Characteristics

ISOLOGIC Sodium Fluoride [^{18}F] Injection is a sterile, non-pyrogenic aqueous solution of $Na^{18}F$ in 0.9% sodium chloride with pH of 4.5 to 8.0. Sodium Fluoride [^{18}F] Injection is a positron emitting diagnostic radiopharmaceutical. It is produced in a cyclotron by an $^{18}O(p, n)^{18}F$ nuclear reaction. Fluorine [^{18}F] decays to ^{18}O by positron (ß+) emission with a half-life of 110 minutes. Sodium Fluoride [^{18}F] Injection contains no carrier or stabilizing agent. It contains not less than 90.0 percent and not more than 110.0 percent of the labelled amount of ^{18}F at the time indicated in the labelling.

CLINICAL TRIALS

Two studies were conducted in support of the diagnostic accuracy of Sodium Fluoride (^{18}F) Injection. In addition, a systematic literature review was performed to support its efficacy.

In a prospective study of 23 patients with known or suspected bone metastases, images acquired 45 minutes and 120 minutes after Sodium Fluoride [^{18}F] Injection were assessed for comparative quality and diagnostic accuracy. Both the 45-minute images and the 120-minute images were assessed as "excellent" in 21/23 patients and "very good" in the remaining two patients.

The investigators stated no preference for either imaging time. The SUV ratios at 45 minutes and at 120 minutes were appear to be comparable, with the mean SUV ratio of 3.0 at 45 minutes ($CI_{95\%}$ 2.5 to 3.5) and 2.7 at 120 minutes ($CI_{95\%}$ 2.7 to 3.1) on the transversal view, and 3.3 at 45 minutes ($CI_{95\%}$ 2.7 to 3.9) and 3.2 at 120 minutes ($CI_{95\%}$ 2.6 to 3.8) on the coronal view.

Diagnostic performance was assessed by a single reader blinded to all other imaging and clinical data. The presence of skeletal metastases was determined by clinical follow-up of at least 6 months (median: 484 days, range: 102 to 538 days), other imaging results and biopsy confirmation in one patient. Diagnostic performance was as follows:

Table 5. 23-Patient Prospective Study Blind read

N	TP	FN	TN	FP
23	4	0	17	2

Table 6. 23-Patient Prospective Study

Parameter	Result	$CI_{95\%}$
Sensitivity	100%	40%-98%
Specificity	89%	65%-98%
Accuracy	91%	69%-99%
Positive predictive value	67%	24%-94%
Negative predictive value	100%	77%-99%

The determination of sensitivity and specificity was retrospective and based on a small cohort of patients that were enrolled in a study with the objective of assessing image quality. Hence, the number of patients that were available for the assessment of sensitivity and specificity were very limited, and consequently resulted in wide confidence intervals for the diagnostic parameters.

Images and limited clinical data were collected retrospectively from 100 consecutive patients who had undergone $Na^{18}F$ PET/CT imaging. The final diagnosis (standard of truth) for the presence or absence of skeletal metastases from all available imaging and clinical information and follow-up was malignant in 50 patients (50%), equivocal in 4 patients (4%), and benign in 46 patients (46%). Images were re-read blindly by three nuclear medicine specialists. The four patients who had equivocal truth standards were excluded from analyses. Two additional patients were excluded from analyses due to discordant readings among 3 readers. Sodium Fluoride [^{18}F] PET/CT scintigraphy was found to have the following diagnostic characteristics based on the majority read of three blinded readers:

Table 7. 100-Patient Retrospective Study

Parameter	Result	$CI_{95\%}$
Sensitivity	90%	77%-96%
Specificity	89%	75%-96%
Accuracy	89%	80%-95%
Positive predictive value	90%	77%-96%
Negative predictive value	89%	75%-96%

The systematic literature review included seven published controlled clinical trials supporting the efficacy of Sodium Fluoride [^{18}F] Injection in the diagnosis of bone metastases.[7-13] All studies included patients with known primary tumours and with known or suspected bone metastases. The studies included an acceptable standard of truth based on other imaging modalities and clinical follow-up. Sodium Fluoride [^{18}F]-PET scans were read by two blinded readers in all studies. In addition, in two studies, images were presented and interpreted both as PET alone and as the fused PET/CT image.

Table 8. Systematic Literature Review - ^{18}F-PET

STUDY	N	Sensitivity	Specificity
Schirrmeister 1999a	34	100% (77%-99%)	94% (69%-100%)
Schirrmeister 1999b	44	100% (75%-99%)	100% (85%-100%)
Schirrmeister 2001	53	92% (60%-100%)	100% (89%-100%)
Hetzel 2003	103	91% (75%-98%)	97% (89%-100%)
Even-Sapir 2004	44	88% (69%-97%)	56% (31%-78%)
Even-Sapir 2006	25	100% (68%-99%)	93% (64%-100%)
Krüger 2009	68	94% (71%-100%)	100% (91%-100%)
Pooled	371	94% (88%-97%)	95% (91%-97%)

Table 9. Systematic Literature Review - ^{18}F-PET/CT

STUDY	N	Sensitivity	Specificity
Even-Sapir 2004	44	100% (84%-100%)	89% (64%-98%)
Even-Sapir 2006	41	100% (80%-100%)	100% (81%-100%)
Pooled	85	100% (90%-100%)	95% (81%-99%)

Sensitivity and specificity were generally excellent across studies. In the two studies in which images were read both as PET only and as PET/CT, CT improved specificity and resulted in fewer equivocal interpretations (equivocal interpretations were excluded from the analyses).

DETAILED PHARMACOLOGY

At the picogram mass dose administered, fluoride [^{18}F] has no pharmacodynamic effects. Fluoride [^{18}F] is extracted by bone in an identical manner to the naturally occurring stable fluoride [^{19}F] isotope. It is known that increased fluoride ^{18}F ion deposition in bone can occur in areas of increased osteogenic activity. See “ACTION AND CLINICAL PHARMACOLOGY” above.

TOXICOLOGY

No toxicology studies have been conducted with Sodium Fluoride [^{18}F] Injection. The toxicology of the ^{18}F isotope would not be expected to be different from that of the naturally occurring stable ^{19}F isotope.

Stable fluorine [^{19}F] is a natural trace element. Wide variations in daily human intake exist depending on the concentration of fluorine in local drinking water, the primary source of fluorine. The inhabitants of most countries in the western world have a daily intake of approximately 1 mg. The Federal-Provincial-Territorial Committee on Drinking Water has recommended an optimal fluorine concentration of 0.8 to 1.0 mg/L. The maximum acceptable concentration of fluorine in drinking water is 1.5 mg/L, a level at which Health Canada believes there is no undue health risks.[14] The mass dose of fluorine in Sodium Fluoride [^{18}F] Injection is in the order of picograms (10^{-12} g), a negligible amount compared to the daily intake.

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PART III: CONSUMER INFORMATION

Sodium Fluoride [^{18}F] Injection

This leaflet is part III of a three-part "Product Monograph" published when Sodium Fluoride [^{18}F] Injection was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Sodium Fluoride [^{18}F] Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Sodium Fluoride [^{18}F] Injection is used to do a bone scan, which is a nuclear medicine test that can help your doctor see if cancer has spread to your bones.

What it does:

Sodium Fluoride [^{18}F] Injection contains a radioactive form of the same fluorine, ^{19}F, found in drinking water and toothpaste. Just like the natural fluorine, the radioactive fluorine is absorbed by bones. Bones are living tissue that constantly break down and build up. If any areas of your bones are breaking down or building abnormally, the radioactive fluoride will be absorbed differently in that part of the bone. When a picture is taken with a special camera called PET/CT scanner, the specialist will be able to see the activity of fluoride [^{18}F] in these unusual areas.

When it should not be used:

Sodium Fluoride [^{18}F] Injection is a radioactive product and should not be used if you are pregnant.

What the medicinal ingredient is:

The medicinal ingredient, fluorine [^{18}F], is a radioactive form of the fluorine that is already in your bones and teeth. Fluorine is mostly found in your water. The amount of radioactive fluorine in Sodium Fluoride [^{18}F] Injection is millions of times less than what is in a glass of water.

What the important non-medicinal ingredients are:

There are no important non-medicinal ingredients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Sodium Fluoride [^{18}F] Injection should not be administered to pregnant women.

BEFORE you receive Sodium Fluoride [^{18}F] Injection talk to your doctor or pharmacist if you think you might be pregnant.

If you are breast-feeding, do not give your baby any breast milk in the 12 hours after you receive Sodium Fluoride [^{18}F] Injection.

The radioactivity that is not absorbed into your bones is eliminated in your urine. Unless your doctor tells you otherwise, you should drink 500 ml or more of water within 1 hour before the examination, and another 500 ml after. You should empty your bladder frequently in the first few hours after the injection to reduce the amount of radioactivity in your body.

INTERACTIONS WITH THIS MEDICATION

Drug-drug interactions with Sodium Fluoride [^{18}F] Injection have not been evaluated.

PROPER USE OF THIS MEDICATION

This product will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

There have been no reported side effects for this product to date. Sodium Fluoride [^{18}F] Injection is called a 'tracer' meaning that it is given in very small doses and at such low doses, has no anticipated effect of its own.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

No serious side effects have been reported for Sodium Fluoride [^{18}F] Injection. If you experience any unusual effects after receiving the product, you should contact medical staff at the facility where you receive the injection.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Isologic Innovative Pharmaceuticals Ltd., 1855 32nd Avenue, Lachine, Quebec H8T 3J1.

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