PRODUCT MONOGRAPH

Osteovision®

[F-18]-Sodium Fluoride (NaF) Injection, USP

≤ 11.1 GBq/mL (≤ 300 mCi/mL) at End of Synthesis

Diagnostic Radiopharmaceutical

Centre for Probe Development and Commercialization (CPDC)
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Osteovision®

[F-18]-Sodium Fluoride (NaF) Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Parental solution ≤ 11.1 GBq/mL (≤ 300 mCi/mL) at End of Synthesis	*None*

DESCRIPTION

Physical Characteristics

Osteovision® ([F-18]-Sodium Fluoride (NaF) Injection, USP) is a sterile, non-pyrogenic aqueous solution, suitable for intravenous administration, containing no-carrier-added F-18 in Sodium Chloride Injection.

F-18 is a radioisotope of fluoride produced in a cyclotron. F-18 decays to O-18 by positron (β+) emission with a half-life of 109.8 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.

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 1: Radioactive decay rate of F-18

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1	7	0.071
1	0.685	8	0.048
2	0.469	9	0.033
3	0.321	10	0.023
4	0.220	11	0.016
5	0.151	12	0.011
6	0.103	-	-

Table 2: Principal Emission Data for F-18[1]

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

External Radiation

The specific gamma-ray constant for F-18 is 0.3 Gy/h/kBq at 1 cm. The narrow-beam half value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb) and 3.4 cm for concrete. Refer to Table 3 for broad-beam transmission factors.[2]

Table 3: Transmission Factors of Broad Beam 511 keV Photons in Lead[2]

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

INDICATIONS AND CLINICAL USE

Osteovision® ([F-18]-Sodium Fluoride (NaF) 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.

Osteovision® 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 Osteovision® in nursing woman, breastfeeding should be discontinued for a period of at least 12 hours following the injection.[3]

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 Osteovision®.

Osteovision® 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 licences 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 Osteovision® 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.

Contamination

The following measures should be taken for up to 6 hours after receiving Osteovision®: Toilet should be used instead of urinal. Toilet should be flushed several times after use. Universal precautions normally used for handling blood and urine are adequate to cope with radiation risk. Special precautions such as bladder catheterisation should be taken following administration to incontinent patients to minimise the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Special Populations

Pregnant Women: Osteovision® 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

Foetal Dose estimate (mGy/MBq)[4]	**Early**	**3 months**	**6 months**	**9 months**
	2.2E-02	1.7E-02	7.5E-03	6.8E-03

Adequate studies have not been performed to determine whether there are adverse effects on the foetus or to characterize the teratogenic potential. Prior to the administration of Osteovision® to women of child-bearing 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 [F-18]-NaF Injection in human milk has not been studied. However, naturally occurring stable fluoride, F-19, is present in breast milk. Caution should therefore be exercised when Osteovision® must be administered to a nursing woman. Where an assessment of the risk-benefit ratio suggests the use of Osteovision® in a 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.

Paediatrics: The efficacy and safety of Osteovision® in the approved indication have not been established in paediatric patients.

Geriatrics (> 65 years of age): Geriatric patients were included in the studies demonstrating the efficacy and safety of Osteovision® in the approved indication. There are no known limitations on the clinical use of Osteovision® 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. Osteovision® should not be co-administered with any other products.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The optimal dose of Osteovision® 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 Osteovision® is 185 - 370 MBq.[5,6]

Administration

Osteovision® 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 12 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 Osteovision®.

The rapid localization of [F-18]-fluoride 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.[6]

In general, the degree of [F-18]-fluoride uptake does not differentiate benign from malignant processes. [F-18]-fluoride 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 Osteovision® 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. The maximum injection volume is 10 mL. It is essential that the user follows these 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 discolouration prior to administration whenever solution and container permit. Do not administer Osteovision® containing particulate matter or discolouration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.

Directions for Quality Control

A certificate of analysis to document all quality control release testing results for Osteovision® should be obtained from the manufacturer prior to patient administration.

RADIATION DOSIMETRY

ICRP 53 biokinetic data were reanalyzed using OLINDA/EXM V.1.1 with the gender-neutral phantom and ICRP 103 tissue weighting factors (Table 5).[7] The effective dose coefficient of [F-18]-NaF is 1.7E-02 mSv/MBq. The effective dose 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 mSv/MBq), and the kidneys (2.0E-02 mSv/MBq).

Table 5: [F-18]-NaF Injection 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**

OVERDOSAGE

Cases of overdose are not known to have occurred with Osteovision®. 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 the discretion of the clinician if clinically indicated.

ACTION AND CLINICAL PHARMACOLOGY

Following intravenous administration, about 50% of [F-18]-fluoride is rapidly taken up by the skeleton where it remains during the time period of its radioactive decay. The remainder is distributed into the extracellular fluid and eliminated by renal excretion within a few hours. [F-18]-fluoride 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.[8] Uptake by bone is a function of blood flow and osteogenic activity.

[F-18]-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.

Increased [F-18]-fluoride 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 [F-18]-fluoride is cleared from the body in the urine within the first 2 hours after intravenous administration.[9]

Special Populations and Conditions

No data available.

STORAGE AND STABILITY

Osteovision® should be stored upright in a lead shielded container at room temperature (15 - 30 °C). It should be used before the residual activity falls below the minimum dose required for a quality diagnostic image, or at most within 12 hours after the end of synthesis.

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 radionuclides, 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

Osteovision® ([F-18]- NaF Injection) is supplied in a multi-dose, septum-capped, 10 or 30 mL glass vial containing ≤ 11.1 GBq/mL (≤ 300 mCi/mL) of no-carrier-added [F-18]-NaF at end of synthesis.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

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

Product Characteristics

Osteovision® ([F-18]-Sodium Fluoride (NaF) Injection) is a sterile, non-pyrogenic aqueous solution of [F-18]-NaF in 0.9% sodium chloride (saline) with a pH of 4.5 - 8.0. Osteovision® is a positron-emitting diagnostic radiopharmaceutical. The [F-18]-fluoride component is produced in a cyclotron by the $^{18}O(p, n)^{18}F$ nuclear reaction.

F-18 decays to O-18 by positron (β+) emission with a half-life of 109.8 minutes. Osteovision® contains no carrier or stabilizing agent. It contains, at the time of calibration, the radioactive amount of [F-18]-NaF (± 10%) stated on the label.

CLINICAL TRIALS

Osteovision® was authorized in an Abbreviated New Drug Submission (ANDS).

The focus of the ANDS was a physicochemical-based comparison; no clinical trial data was generated and submitted for this product. The Canadian Reference Product (CRP) cited in the ANDS was "NaF Plus" (Sodium Fluoride [^{18}F] Injection, U.S.P., Isologic Innovative Radiopharmaceuticals Ltd.); refer to that product's Product Monograph for a summary of clinical trial data for the CRP.[5]

DETAILED PHARMACOLOGY

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

TOXICOLOGY

No toxicology studies have been conducted with Osteovision®. The toxicology of the [F-18]-fluoride isotope would not be expected to be different from that of the naturally occurring stable [F-19]-fluoride isotope.

Stable [F-19]-fluoride is a natural trace element. Wide variations in daily human intake exist depending on the concentration of [F-19]-fluoride in local drinking water, the primary source of [F-19]-fluoride. 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 [F-19]-fluoride concentration of 0.8 - 1.0 mg/L. The maximum acceptable concentration of [F-19]-fluoride in drinking water is 1.5 mg/L, a level at which Health Canada believes there are no undue health risks.[10] The mass dose of [F-19]-fluoride in Osteovision® is at the picogram level (10^{-12} g), a negligible amount compared to the daily intake.

REFERENCES

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(3) Guideline on core SmPC and package leaflet for sodium fluoride (^{18}F). European Medicines Agency. EMA/CHMP/465616/2014. October 2014.

(4) Russell JR, Stabin MG, Sparks RB, Watson E. Radiation absorbed dose to the embryo/fetus from radiopharmaceuticals. *Health Phys*. 1997; 73(5):756-69

(5) NaF Plus (Sodium Fluoride [^{18}F] Injection U.S.P., Canadian Product Monograph (Manufacturer: Isologic Innovative Radiopharmaceuticals Ltd).

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(10) Guidelines for Canadian Drinking Water Quality Summary Table Prepared by the Federal-Provincial-Territorial Committee on Drinking Water of the Federal-Provincial-Territorial Committee on Health and the Environment August 2012. Available at http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/2012-sum_guide-res_recom/index-eng.php

PART III: CONSUMER INFORMATION

Osteovision®

([F-18]-Sodium Fluoride (NaF) Injection, USP)

This leaflet is part III of a three-part "Product Monograph" published when Osteovision® was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about Osteovision®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Osteovision® 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:

Osteovision® contains ^{18}F, a radioactive form of the same fluoride, ^{19}F, found in drinking water and toothpaste. Just like natural fluoride, the radioactive fluoride 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 a PET/CT scanner, the specialist will be able to see the activity of ^{18}F-fluoride in these unusual areas.

When it should not be used:

Osteovision® is a radioactive product and should not be used if you are pregnant.

What the medicinal ingredient is:

The medicinal ingredient, ^{18}F-fluoride, is a radioactive form of the fluoride that is already in your bones and teeth. The amount of radioactive fluoride in Osteovision® 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

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

Osteovision® should not be administered to pregnant women. BEFORE you receive Osteovision® 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 Osteovision®.

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 Osteovision® have not been evaluated.

PROPER USE OF THIS MEDICATION

The maximum injection volume is 10 mL.
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. Osteovision® is called a 'tracer' meaning that it is given in such low doses that it 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 Osteovision®. If you experience any unusual effects after receiving the product, you should contact medical staff at the facility where you received 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 0701E
    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: Centre for Probe Development and Commercialization (CPDC)
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