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PACKAGE INSERT

SODIUM FLUORIDE F18 INJECTION 10-200mCi/ml
For Intravenous Use

INDICATION AND USAGE

Sodium Fluoride F18 Injection 10-200mCi/ml is indicated for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity.

DOSAGE AND ADMINISTRATION

A) **Radiation Safety – Drug Handling**

- Wear waterproof gloves and effective shielding when handling Sodium Fluoride F18 Injection 10-200mCi/ml. Use appropriate safety measures, including shielding, consistent with proper patient management to avoid unnecessary radiation exposure to the patient, occupational workers, clinical personnel, and other persons.
- 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 radionuclide, and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclide.
- Use aseptic technique to maintain sterility during all operations involved in the manipulation and administration of Sodium Fluoride F18 Injection 10-200mCi/ml.
- The dose of Sodium Fluoride F18 Injection 10-200mCi/ml should be minimized consistent with the objectives of the procedure, and nature of the radiation detection devices employed.
- The final dose for the patient should be calculated using proper decay factors from the time of End of Synthesis (EOS), and measured by a suitable radioactivity calibration system before administration. [See Description-Physical characteristics]

B) **Radiation Safety – Patient Preparation**

- To minimize the radiation-absorbed dose to the bladder, encourager adequate hydration. Encourage the patient to ingest at least 500ml of fluid immediately prior and subsequent to the administration of Sodium Fluoride F18 Injection 10-200mCi/ml.
- Encourage the patient to void one-half hour after administration of Sodium Fluoride F18 Injection 10-200mCi/ml and as frequent thereafter as possible for the next 12 hours.

C) **Drug Preparation and Administration**

- Calculate the necessary volume to administer based on calibration time and dose.

- Inspect Sodium Fluoride F18 Injection 10-200mCi/ml visually for particulate matters and discolouration before administration, whenever solution and container permit.
- Do not administer Sodium Fluoride F18 Injection 10-200mCi/ml containing particulate matters or discolouration; dispose of these unacceptable or unused preparations in a safe manner, in compliance with applicable regulations.
- Aseptically withdraw Sodium Fluoride F18 Injection 10-200mCi/ml from its container.

D) **Recommended Dose for Adults**

Administer 300-450 MBq (8-12 mCi) as an intravenous injection.

E) **Recommended Dose for Paediatric Patients**

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq – 148 MBq (0.5 mCi-4 mCi) were used.

F) **Radiation Dosimetry**

The age/weight-based estimated absorbed radiation doses (mGy/ MBq) from intravenous injection of Sodium Fluoride F18 Injection are shown in Table 1. These estimates were calculated based on human data and using the data published by the Nuclear Regulatory Commission [1] and the International commission on radiological Protection for Sodium Fluoride F18 Injection [2]. The bone, bone marrow and urinary bladder are considered target and critical organs.

Table 1: Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection

Organ		Estimated Radiation Dose mGy/MBq				
		Adult 70 kg [1]	15 year 56.8 kg [2]	10 year 33.2 kg [2]	5 year 19.8 kg [2]	1 year 9.7 kg [2]
Adrenals		0.0062	0.012	0.018	0.028	0.052
Brain		0.0056	N/A	N/A	N/A	N/A
Bone surfaces		0.060	0.050	0.079	0.13	0.30
Breasts		0.0028	0.0061	0.0097	0.015	0.030
GI	Gallbladder wall	0.0044	N/A	N/A	N/A	N/A
	Stomach wall	0.0038	0.008	0.013	0.019	0.036
	Small intestine	0.0066	0.012	0.018	0.028	0.052
	Upper large intestine wall	0.0058	0.010	0.016	0.026	0.046

Lower large intestine wall	0.012	0.016	0.025	0.037	0.063
Heart wall	0.0039	N/A	N/A	N/A	N/A
Kidneys	0.019	0.025	0.036	0.053	0.097
Liver	0.0040	0.0084	0.013	0.021	0.039
Lungs	0.0041	0.0084	0.013	0.020	0.039
Muscle	0.0060	N/A	N/A	N/A	N/A
Ovaries	0.011	0.016	0.023	0.036	0.063
Pancreas	0.0048	0.0096	0.015	0.023	0.044
Red marrow	0.028	0.053	0.088	0.18	0.38
Skin	0.0040	N/A	N/A	N/A	N/A
Spleen	0.0042	0.0088	0.014	0.021	0.041
Testes	0.0078	0.013	0.021	0.033	0.062
Thymus	0.0035	N/A	N/A	N/A	N/A
Thyroid	0.0044	0.0084	0.013	0.020	0.036
Urinary bladder wall	0.25	0.27	0.4	0.61	1.1
Uterus	0.019	0.023	0.037	0.057	0.099
Other tissue	N/A	0.010	0.015	0.024	0.044
Effective Dose Equivalent mSv/MBq	**0.027**	**0.034**	**0.052**	**0.086**	**0.17**

[1] Data from Nuclear Regulatory Commission Report, *Radiation Dose Estimates for Radiopharmaceuticals,* NUREG/CR-6345, page 10, 1996.
[2] Data from ICRP publication 53, *Radiation Dose to Patients from*

G) **Imaging Guidelines**

- Imaging of Sodium Fluoride F18 Injection 10-200mCi/ml can begin 1-2 hours after administration; optimally at 1 hour post administration.
- Encourage the patient to void immediately prior to imaging the fluoride F18 radioactivity in the lumbar spine or bony pelvis.

DOSAGE FORMS AND STRENGHTS

Multiple-dose vial containing 370-7400 MBq/ml (10-200 mCi/ml) at EOS reference time of no-carrier-added sodium fluoride F18 in aqueous 0.9% sodium chloride solution.
Sodium Fluoride F18 Injection 10-200mCi/ml is a clear, colourless, sterile, pyrogen-free and preservative-free solution for intravenous administration.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

A) **Allergic Reactions**

As with any injectable drug product, allergic reactions and anaphylaxis may occur. Emergency resuscitation equipment and personnel should be immediately available.

B) **Radiation Risks**

Sodium Fluoride F18 Injection 10-200mCi/ml may increase the risk of cancer. Carcinogenic and mutagenic studies with Sodium Fluoride F18 Injection 10-200mCi/ml have not been performed. Use the smallest dose necessary for imaging and ensure safe handling to protect the patient and health care worker [see Dosage and Administration-A].

ADVERSE REACTIONS

No adverse reactions have been reported for Sodium Fluoride F 18 Injection 10-200mCi/ml based on a review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems. However, the completeness of these sources is not known.

DRUG INTERACTIONS

The possibility of interactions of Sodium Fluoride F 18 Injection 10-200mCi/ml with other drugs taken by patients undergoing PET imaging has not been studied.

USE IN SPECIFIC POPULATIONS

A) **Pregnancy - Pregnancy Category C**

Any radiopharmaceutical including Sodium Fluoride F 18 Injection 10-200mCi/ml has a potential to cause fetal harm. The likelihood of fetal harm depends on the stage of fetal development, and the radionuclide dose. Animals reproductive and development toxicity studies have not been conducted with Sodium Fluoride F 18 Injection 10-200mCi/ml. Prior to the administration of Sodium Fluoride F 18 Injection 10-200mCi/ml to women of childbearing potential, assess for presence of pregnancy. Sodium Fluoride F 18 Injection 10-200mCi/ml should be given to a pregnant woman only if clearly needed.

B) **Nursing Mothers**

It is not known whether Sodium Fluoride F 18 Injection 10-200mCi/ml is excreted into human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to interrupt nursing after administration of Sodium Fluoride F 18 Injection 10-200mCi/ml or not to administer, taking into account the importance of drug to the mother. The body of scientific information related to radioactivity decay, drug tissue distribution and drug elimination shows that less than 0.01% of radioactivity administered remains in the body

after 24 hours (10 half-lives). To minimize the risks to a nursing infant, interrupt nursing for at least 24 hours.

C) **Pediatric Use**

In reported clinical experience in approximately 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq-148 MBq (0.5mCi – 4 mCi) were used. Sodium Fluoride F 18 was shown to localize to areas of bone turnover including rapidly growing epiphyses in developing long bones. Children are more sensitive to radiation and may be at higher risk of cancer from Sodium Fluoride F 18 Injection 10-200mCi/ml.

DESCRIPTION

A) **Chemical Characteristics**

Sodium Fluoride F 18 Injection 10-200mCi/ml is a positron emitting radiopharmaceutical, containing no-carrier-added, radioactive fluoride F18 that is used for diagnostic purposes in conjunction with PET imaging. It is administered by intravenous injection. The active ingredient, sodium fluoride F18, has the molecular formula Na[18F] with a molecular weight of 40.99, and has the following chemical structure: Na^{+} $^{18}F^{-}$

Sodium Fluoride F 18 Injection 10-200mCi/ml is provided as a ready-to-use, isotonic, sterile, pyrogen-free, preservative-free, clear and colorless solution. Each ml of the solution contains between 370 MBq to 7400 MBq (10 mCi to 200 mCi) sodium fluoride F18, at the EOS reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 4.5 and 8. The solution is presented in 10 ml multiple- dose glass vials with variable total volume and total radioactivity in each vial.

B) **Physical Characteristics**

Fluoride F18 decays by positron (β+) emission and has a half-life of 109.7 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 2). Fluorine F18 atom decays to stable ^{18}O-oxygen.

Table 2: Principal Emission Data for Fluoride F18

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

* Produced by positron annihilation

[3] Kocher, D.C. Radioactive Decay Data Tables DOE/TIC-11026, 69, 1981.

The specific gamma ray constant for fluoride F18 is 5.7 R/hr/mCi (1.35×10^{-6} Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of various thickness of

Pb. The range of attenuation coefficients for this radionuclide is shown in table 3. For example, the interposition of an 8 mm thickness of Pb with a coefficient of attenuation of 0.25 will decrease the external radiation by 75%.

Table 3:Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0	0.00
4	0.50
8	0.25
13	0.10
26	0.01
39	0.001
52	0.0001

Table 4 lists the fraction of radioactivity remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 4: Physical Decay Chart for Fluoride F18

Time Since Calibration	Fraction Remaining
0*	1.00
15 minutes	0.909
30 minutes	0.826
60 minutes	0.683
110 minutes	0.500
220 minutes	0.250
440 minutes	0.060
12 hours	0.011
24 hours	0.0001

* Calibration time

CLINICAL PHARMACOLOGY

A) Mechanism of Action

Fluoride F18 ion 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.

B) Pharmacodynamics

Increased fluoride F18 ion deposition in bone can occur in areas of increased osteogenic activity during growth, infection, malignancy (primary or metastatic) following trauma, or inflammation of bone.

C) Pharmacokinetics

After intravenous administration, fluoride F18 ion is rapidly cleared from the plasma in a biexponential manner. The first phase has a half-life of 0.4 hour, and the second phase has a half-life of 2.6 hour. Essentially all the fluoride F18 that is delivered to bone by the blood is retained in the bone. One hour after administration of fluoride F18 only about 10% of the injected dose remains in the blood. Fluoride F18 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.

Deposition of fluoride F18 in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluoride F18. Fluoride F18 does not appear to be bound to serum proteins.

In patients with normal renal function, 20% or more of the fluorine ion is cleared from the body in the urine within the first 2 hours after intravenous administration.

NONCLINICAL TOXICOLOGY

A) **Carcinogenesis, Mutagenesis, Impairment of Fertility**

Studies to assess reproductive toxicity, mutagenesis and carcinogenesis potential of Sodium Fluoride F 18 Injection 10-200mCi/ml have not been performed.

CLINICAL STUDIES

A) **Metastatic Bone Disease**

The doses used in reported studies 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). In PET imaging of bone metastases with Sodium Fluoride F 18 Injection 10-200mCi/ml , focally increased tracer uptake is seen in both osteolytic and osteoblastic bone lesions. Negative PET imaging results with Sodium Fluoride F 18 Injection 10-200mCi/ml do not preclude the diagnosis of bone metastases. Also, as benign bone lesions are also detected by Sodium Fluoride F 18 Injection 10-200mCi/ml, positive PET imaging results cannot replace biopsy to confirm a diagnosis of cancer.

B) **Other Bone Disorders**

The doses used in reported studies ranged from 2.43 mCi to 15 mCi (90 MBq to 555 MBq), with an average median dose of 8.0 mCi (300 MBq) and an average mean dose of 7.6 mCi (280 MBq).

REFERENCES

1. Stabin, M.G., Stubbs, J.B. and Toohey R.E., *Radiation Dose Estimates for Radiopharmaceuticals,* U.S. Nuclear Regulatory Commission report NUREG/CR-6345, page 10, 1996.
2. *Radiation Dose to Patients from Radiopharmaceuticals,* ICRP publication 53, Ann ICRP, 18 pages 15 and 74, 1987.

3. Kocher, D.C., "Radioactive Decay Data Tables: A Handbook of decay data for application to radiation dosimetry and radiological assessments" DOE/TIC-11026, page 69, 1981.

HOW SUPPLIED

Sodium Fluoride F 18 Injection 10-200mCi/ml is supplied in a multiple-dose glass vial with elastomeric stopper and aluminum crimp seal containing between 370 and 7400 MBq/ml (10-200 mCi) of no carrier-added sodium fluoride F 18, at the EOS reference time, in aqueous 0.9% sodium chloride solution. The total volume and total radioactivity per vial are variable. Each vial is enclosed in a shielding container of appropriate thickness.

The product is available in a 10 ml vial configuration with a variable fill volume.

STORAGE

For strict intravenous injection. Multi-dose vial. Store in a shielded container at 30°C or below. Radioactive medication. Disposal of radioactive waste must comply with CRPNS, NEA guidelines. Use the solution within 8 hours of the EOS reference time.

HANDLING

Receipt, transfer, handling, possession, or use of this product is subject to the regulations and licensing requirements of Radiation Protection Act of National Environment Agency, Singapore, or its equivalent of an Agreement States or Licensing States as appropriate.

PATIENT COUNSELLING INFORMATION

A) **Pre-study Hydration**

Encourage patients to drink at least 500ml of water prior to drug administration.

B) **Post-study Voiding**

To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible, use a toilet and flush several times after each use; wash hands thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, wash the clothing separately.

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