SODIUM FLUORIDE F 18 INJECTION
INVESTIGATOR'S BROCHURE

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LIST OF ABBREVIATIONS

^{18}F-NaF	Sodium fluoride F 18
CT	Computerized axial tomography
EOS	End of synthesis
FDA	Food and Drug Administration
keV	Kiloelectron volt
MBq	Megabecquerel
mCi	Millicurie
MDP	Methylene diphosphonate
mGy	Milligray
MRI	Magnetic resonance imaging
mSv	Millisievert
NaF	Sodium fluoride
NCA	No carrier added
NDA	New Drug Application
PET	Positron emission tomography
rem/mCi	Estimated absorbed radiation
US	United States
USP	United States Pharmacopeia

2 SUMMARY

Sodium Fluoride F 18 Injection, a positron-emitting radiopharmaceutical containing no carrier-added (NCA) radioactive fluoride ^{18}F, is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. Sodium Fluoride F 18 Injection is indicated as a bone imaging agent to define areas of altered osteogenic activity. The tendency for fluoride ^{18}F to accumulate in the vicinity of primary and metastatic malignancy in bone has proven clinically useful in detection of such lesions [*i.e.*, Schirrmeister, 1999, 2001; Hetzel, 2003; Even-Sapir, 2004].

3 INTRODUCTION

PET is a medical imaging modality that uses a unique type of radiopharmaceutical drug. PET drugs contain an atom that disintegrates principally by emission of a positron, which provides dual photons that are used for imaging, primarily for diagnostic purposes. Most PET drugs are produced using cyclotrons at locations (PET centers) in close proximity to the patients to whom the drugs are administered. Each PET drug is ordinarily injected into the patient within a few minutes or hours of production.

Sodium Fluoride F 18 Injection is provided as a ready-to-use, isotonic, sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains 10–400 mCi fluoride ^{18}F at the end of synthesis (EOS) reference time in 0.9% aqueous sodium chloride. Fluoride ^{18}F ions decay by positron emission with a half-life of 109.7 minutes. The drug product complies with the United States Pharmacopeia (USP) monograph for Sodium Fluoride F 18 Injection, and is manufactured following procedures that conform to the radiopharmaceuticals for PET compounding standards (USP <823>).

A New Drug Application (NDA) for use of Sodium Fluoride F 18 Injection as a bone imaging agent to define areas of altered osteogenic activity was approved by FDA in 1972 (NDA 17-042). The recommended dose of Sodium Fluoride F 18 Injection for this indication was 0.5 to 2.0 mCi (16.5 to 74.0 MBq), with a maximum recommended dose of 4.0 mCi as an intravenous injection. The current Sodium Fluoride F 18 Injection NDA-holder stopped marketing the drug in 1975, around the time that ^{99}Tc-labeled diphosphonate compounds were introduced. Recent advances in PET technology have led to renewed interest in the use of this compound to detect bone metastases in cancer patients. Studies have shown sodium fluoride F 18 (^{18}F-NaF) PET and ^{18}F-NaF PET/computerized axial tomography (CT) to be superior to conventional methods, such as whole-body magnetic resonance imaging (MRI) and ^{99m}Tc-methylene diphosphonate (MDP) bone scans, for accurate and sensitive detection of bone metastases [Schirrmeister, 1999, 2001; Hetzel, 2003; Even-Sapir, 2004]. Evaluations in this setting have used ^{18}F-NaF doses ranging from 7 to 20 mCi. Additional studies directly comparing accuracy, sensitivity, and cost-effectiveness of available bone imaging technologies are needed in order to establish the appropriate standard of care for cancer patients at risk for bone involvement.

4 PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION

4.1 Description

Sodium Fluoride F 18 Injection is provided as a ready-to-use, isotonic, sterile, pyrogen-free, clear and colorless solution for intravenous injection. It is produced by particle acceleration in a ^{18}~~^{20}~~~~Ne~~O (~~d~~p,~~α~~n) ^{18}F nuclear reaction from $H_2{}^{18}O$. Each mL of the solution contains between 370 to 14,800 MBq (10–400 mCi) of carrier-free fluoride ^{18}F, at the 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 nonradioactive fluoride ion present is that found in the distilled water and saline solutions used in preparing the product. The drug complies with the USP monograph for Sodium Fluoride F 18 Injection.

The active ingredient, ^{18}F-NaF, has the molecular formula of Na^{18}F with a molecular weight of 40.99, and has the following chemical structure: Na^+ $18F^-$.

4.2 Physical Properties

Fluoride ^{18}F decays by positron (β+) emission and has a half-life of 109.7 minutes. The principal photons used for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron. For use in correcting the physical decay of this radionuclide, fractions remaining at selected intervals after calibration are shown in Table 1.

Table 1. Physical Decay Chart for Fluoride ^{18}F

Time Since Calibration	Fraction Remaining
0 minutes	1.00
15 minutes	0.909
30 minutes	0.827
60 minutes	0.684
110 minutes	0.500
220 minutes	0.250
440 minutes	0.060
12 hours	0.011
24 hours	0.0001

4.3 Storage

Sodium Fluoride F 18 Injection should be stored upright in a lead-shielded container at controlled room temperature. Expiration date and time are provided on the container label. Storage and disposal of Sodium Fluoride F 18 Injection should be in accordance with the regulations and general license, or its equivalent, of an Agreement State or a Licensing State.

5 NONCLINICAL STUDIES

Studies with Sodium Fluoride F 18 Injection have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility. Animal reproduction studies have not been conducted with Sodium Fluoride F 18 Injection. In contrast, the toxicology of the non-radioactive compound is well established due to extensive use in municipal water fluoridation systems, various dental products, and in a variety of industrial applications [Subcommittee on Health Effects of Ingested Fluoride, 1993; NTP, 1990]. Approximately 75–90% of the fluoride ingested each day is absorbed from the alimentary tract [Subcommittee on Health Effects of Ingested Fluoride, 1993]. The *in vitro* data indicate that the genotoxicity of fluoride is limited primarily to doses much higher than those to which humans are exposed on a daily basis. In addition, genotoxic effects are not always observed, even at high doses, and the preponderance of the genotoxic effects that have been reported are of the types that probably are of no or negligible genetic significance [Subcommittee on Health Effects of Ingested Fluoride, 1993]. Adverse effects on reproductive performance associated with high concentrations of fluoride intake have been reported in nonclinical studies; the water or food threshold fluoride concentration associated with these effects is approximately 100 mg/L (100 mg/kg) [Subcommittee on Health Effects of Ingested Fluoride, 1993]. Two-year dosed water studies found equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats, based on the occurrence of a small number of osteosarcomas in dosed animals [NTP, 1990]. There was no evidence of carcinogenic activity in female F344/N rats or in male or female B6C3F1 mice receiving sodium fluoride at concentrations of 25, 100 or 175 ppm for two years [NTP, 1990]. The large number of epidemiological studies in humans showing a lack of correlation of cancer risk with drinking fluoridated water suggests that if any link exists, it must be very weak [Subcommittee on Health Effects of Ingested Fluoride, 1993].

The toxicology of Sodium Fluoride F 18 Injection will be the same as that of the non-radioactive compound, except for the radiation exposure. However, the amount of fluoride ions in Sodium Fluoride F 18 Injection at the indicated dose is very low, and provides assurance that toxic effects will not be observed.

6 PREVIOUS HUMAN EXPERIENCE

6.1 Clinical Pharmacology

Fluoride ^{18}F ions usually accumulate 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 deposition of fluoride ^{18}F around joints can occur in arthritis or following trauma. Increased deposition has also been documented in bone around fracture sites, in osteomyelitis, fibrous dysplasia, spondylitis tuberculosa, Paget's disease, hyperstosis frontalis interna, myositis ossificans, and in rapidly growing epiphyses. The tendency for fluoride ^{18}F to accumulate in the vicinity of primary and metastatic malignancy in bone has proven clinically useful in detection of such lesions [FDA, 2000].

6.2 Pharmacokinetics and Metabolism

Following intravenous administration, Sodium Fluoride F 18 Injection provides fluoride ^{18}F ions that rapidly equilibrate, primarily with the extracellular fluid space. The fluoride ^{18}F ions are then rapidly cleared by bone deposition and by excretion into the urine [FDA, 2000]. Deposition of fluoride ^{18}F in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluoride ions from the blood perfusing the bone [Vandyke, 1965]. Fluoride ^{18}F ions do not appear to be bound to serum proteins [FDA, 2000]. The clearance of fluoride ^{18}F from blood is rapid [Weber, 1969]. Fluoride ^{18}F is rapidly eliminated via the renal system. In patients with normal renal function, 20% or more of the fluoride ^{18}F is cleared from the body in urine within the first two hours after intravenous administration [Harmer, 1969]. Subsequently, small amounts of fluoride ions continue to be excreted in urine, further diminishing radioactivity of fluoride ions in soft tissues of the body.

6.3 Integrated Summaries of Drug Safety and Therapeutic Efficacy

An NDA for use of Sodium Fluoride F 18 Injection as a bone imaging agent to define areas of altered osteogenic activity was approved by FDA in 1972 (NDA 17-042). The recommended dose of Sodium Fluoride F 18 Injection for this indication was 0.5 to 2.0 mCi (16.5 to 74.0 MBq), with a maximum recommended dose of 4.0 mCi as an intravenous injection. According to the PET Safety and Effectiveness Notice, the agency's findings regarding the already approved NDA for Sodium Fluoride F 18 Injection are the basis for approval of this agent for bone imaging [FDA, 2000].

Fluoride is a normal body constituent. The amount of fluoride ions in Sodium Fluoride F 18 Injection at the indicated dose is expected to have minimal effect on normal human physiology. When Sodium Fluoride F 18 Injection was approved for marketing in 1972, no adverse reactions were noted in over 400 patient studies reported in the medical literature [FDA, 2000]. In a 1999 review of the published literature, publicly available reference sources and adverse drug reaction reporting systems indicated that no adverse reactions have been reported for Sodium Fluoride F 18 Injection [FDA, 2000].

The estimated absorbed radiation doses to a human adult (70 kg) from intravenous administration of Sodium Fluoride F 18 Injection are provided in Table 2. Bone and bone marrow are considered the target and critical organs. To minimize the radiation-absorbed dose to the bladder, adequate hydration should be encouraged to stimulate frequent voiding during the first few hours after intravenous administration

Table 2. Estimated Absorbed Radiation Doses after Intravenous Administration of Sodium Fluoride F 18 Injection in Adult Humans (70 kg) [FDA, 2000]

Organ	Estimated Radiation Dose	
	mGy/MBq	rad/mCi
Adrenals	0.0062	0.023
Brain	0.0056	0.021
Breasts	0.0028	0.010
Gallbladder wall	0.0044	0.016
Lower large intestine wall	0.012	0.043
Small intestine	0.0066	0.025
Stomach	0.0038	0.014
Upper large intestine wall	0.0058	0.021
Heart wall	0.0039	0.015
Kidneys	0.019	0.071
Liver	0.0040	0.015
Lungs	0.0041	0.015
Muscle	0.0060	0.022
Ovaries	0.011	0.039
Pancreas	0.0048	0.018
Red marrow	0.028	0.010
Bone surfaces	0.060	0.22
Skin	0.004	0.015
Spleen	0.0042	0.015
Testes	0.0078	0.029
Thymus	0.0035	0.013
Thyroid	0.0044	0.016
Urinary bladder wall	0.25	0.91
Uterus	0.019	0.070
Effective dose equivalent	0.027 mSv/MBq	0.10 rem/mCi

7 OVERALL DISCUSSION OF DATA AND GUIDE FOR THE INVESTIGATOR

Sodium Fluoride F 18 Injection is a radiopharmaceutical, and should be handled in accordance with all applicable regulations. Radiopharmaceuticals should be used only by personnel (*e.g.*, physicians or radiopharmacists) who are qualified by specific training in the safe use and handling of radioactive drugs and materials. In the use of any radiopharmaceutical, care should be taken to ensure minimum radiation exposure to the patient and all personnel involved in the procedure.

It is not known whether Sodium Fluoride F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Therefore, Sodium Fluoride F 18 Injection should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus. The effects of Sodium Fluoride F 18 Injection on human breast milk are unknown. Because many drugs are excreted in human milk, caution should be exercised when Sodium Fluoride F 18 Injection is administered to a nursing woman. The safety and effectiveness of Sodium Fluoride F 18 Injection has not been established in pediatric patients, and prudence suggests limiting exposure in growing children; carefully selected pediatric use has been reported [Lim 2007]. Like other bone imaging agents, Sodium Fluoride F 18 Injection is known to localize in rapidly growing epiphyses in developing long bones.

Sodium Fluoride F 18 Injection preparations containing particulate matter or discoloration should not be administered. To maintain sterility, aseptic technique must be used during all operations involved in the manipulation and administration of Sodium Fluoride F 18 Injection. The final dose to the patient should be calculated using proper decay factors from the time of EOS, and measured by a suitable radioactivity calibration system before administration. (See decay factors in Table 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. The patient should void one-half hour after the administration of Sodium Fluoride F 18 Injection and as frequently thereafter as possible. The patient should be instructed to void immediately prior to imaging the lumbar spine or bony pelvis to reduce background radioactivity.

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

8 REFERENCES

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