Attachment II

Sample Formats — Labeling for

Ammonia N 13 Injection
Fludeoxyglucose F 18 Injection [^{18}F] FDG
and
Sodium Fluoride F 18 Injection

This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the content and format of NDAs and ANDAs for certain positron emission tomography (PET) drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

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Diagnostic - For Intravenous Administration

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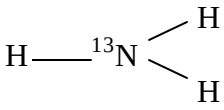
Ammonia N 13 Injection
Diagnostic - For Intravenous Administration

DESCRIPTION

Ammonia N 13 Injection is a positron emitting radiopharmaceutical, containing radioactive [^{13}N] ammonia, that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. It is administered by intravenous injection.

The active ingredient, [^{13}N] ammonia, has the molecular formula of $^{13}NH_3$ with a molecular weight of 16.02, and has the following chemical structure:



Ammonia N 13 Injection is provided as a ready to use sterile, pyrogen-free, clear and colorless solution. Each mL of the solution contains between _____MBq to _____MBq * (___mCi to ___mCi) * of [^{13}N] ammonia, at the end of synthesis (EOS) reference time, in 0.9% aqueous sodium chloride. The specific activity of [^{13}N]ammonia is not less than ____ Ci/mmol,* and the pH of the solution is between ___ to ___.[*,2]

Physical Characteristics

Nitrogen N 13 decays by emitting positron to Carbon C 13 (stable) and has a physical half-life of 9.96 minutes. The principal photons useful for imaging are the dual 511 keV gamma photons that are produced and emitted simultaneously in opposite direction when the positron interacts with an electron (Table 1).

Table 1. Principal Radiation Emission Data for Nitrogen N 13

Radiation/Emission	% Per Disintegration	Energy
Positron (β+)	100	1190 keV (Max.)
Gamma (±)**	200	511 keV

** Produced by positron annihilation

[*] All missing information should be filled in by the applicant.

[2] Current USP standards state the specific activity should be "not less than 37 x 10 [4] MBq (10 Ci) per mmol, and the pH <791> should be "between 4.5 and 8.5." The current USP standards for Ammonia N 13 Injection are being revised.

The specific gamma ray constant for nitrogen N 13 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1 cm. The half-value layer (HVL) of lead (Pb) for 511 keV photons is 4.1 mm. Selected coefficients of attenuation are listed in Table 2 as a function of lead shield thickness. For example, the use of 52.8 mm thickness of lead will attenuate the external radiation by a factor of about 1000.

Table 2. Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
4.1	0.5
8.3	0.25
13.2	0.1
26.4	0.01
52.8	0.001

Table 3 lists fractions remaining at selected time intervals from the calibration time. This information may be used to correct for physical decay of the radionuclide.

Table 3. Physical Decay Chart for Nitrogen N 13

Minutes	Fraction Remaining
0*	1.000
5	0.706
10	0.499
15	0.352
20	0.249
25	0.176
30	0.124

* Calibration time

CLINICAL PHARMACOLOGY

General

Ammonia N 13 Injection is a radiolabeled analog of ammonia that is rapidly distributed to all organs of the body after intravenous administration. Optimal PET imaging of the myocardium is generally achieved between 15 to 20 minutes after administration.

Pharmacodynamics

Following intravenous injection, ammonia N 13 enters the myocardium through the coronary arteries. It is extracted from the blood in the coronary capillaries into the myocardial cells where it is rapidly metabolized to glutamine N 13 and retained in the

cells. The presence of ammonia N 13 and glutamine N 13 in the myocardium allows for PET imaging of the myocardium. The PET technique measures myocardial blood flow based on the assumption of a three-compartmental disposition of intravenous ammonia N 13 in the myocardium. In this model, the value of the rate constant, which represents the delivery of blood to myocardium, and the fraction of ammonia N 13 extracted into the myocardial cells is a measure of myocardial blood flow. PET imaging for myocardial blood flow assessment usually begins at the time of administration of Ammonia N 13 Injection and continues for about 10 minutes.

Pharmacokinetics

Following intravenous injection, Ammonia N 13 Injection is cleared rapidly from the blood with a biologic half-life of about 2.84 minutes (effective half-life of about 2.21 minutes). In the myocardium, its biologic half-life has been estimated to be less than 2 minutes (effective half-life less than 1.67 minutes). In the brain its biologic half-life is less than 3 seconds.

This mass dose of Ammonia N 13 Injection is very small as compared to the normal range of ammonia in the blood (0.72 – 3.30 mg) in a 70 kg healthy adult man. (See Dosage and Administration section.)

Distribution

Based on the reviewed literature information, plasma protein binding of ammonia N 13 or its N 13 metabolites has not been studied.

Metabolism

Ammonia N 13 undergoes a five-enzyme step metabolism in the liver to yield urea N 13 (the main circulating metabolite). It is also metabolized to glutamine N 13 (the main metabolite in tissues) by glutamine synthase in the skeletal muscles, liver, brain, myocardium, and other organs. Other metabolites of ammonia N 13 include small amounts of N 13 amino acid anions (acidic amino acids) in the forms of glutamate N 13 or aspartate N 13.

Elimination

Ammonia N 13 is eliminated from the body by urinary excretion mainly as urea N 13.

Pharmacokinetics in Special Populations

Renally Impaired Patients: Based on the reviewed literature, the effects of renal impairment on the kinetics of Ammonia N 13 Injection have not been studied.

Hepatically Impaired Patients: Based on the reviewed literature, the effects of hepatic impairment on the kinetics of Ammonia N 13 Injection have not been studied.

Pediatric Patients: Based on the reviewed literature, the kinetics of Ammonia N 13 Injection in pediatric patients has not been studied.

Drug-Drug Interactions

Based on the reviewed literature, the possibility of interactions of Ammonia N 13 Injection with other drugs taken by patients undergoing PET imaging has not been studied.

CLINICAL TRIALS

The efficacy data for Ammonia N 13 Injection in PET was derived from the evaluation of 14 independent literature reports that assessed a total of approximately 739 patients. In a key, prospective, blinded image interpretation study,[3] the sensitivity and specificity of PET imaging using Ammonia N 13 Injection in identifying myocardial perfusion abnormalities in patients presenting for coronary angiography is derived and shown in Table 4.

Table 4: Comparison of Identified Coronary Artery Disease in Patients Imaged with Ammonia PET and Coronary Angiography

Coronary Angiography	PET Perfusion Defects [a,b,c]	
	None or Possible (N=68)	Probable to Severe (N=106)
None to Mild Stenosis	66	12
Significant Stenosis	2	94

a PET sensitivity 98% (95% confidence interval: 92.1 – 99.7%)
b PET specificity 85% (95% confidence interval: 74.7 – 91.7%)
c PET images are the pooled result of 111 patient image sets obtained with ammonia N 13 and 82 patient image sets obtained with Rubidium-82.

In this calculation, there were 12 false negatives and 2 false positives. Thus, further clinical work-up for patients involving angiography or other tests may be indicated.

Thirteen other reviewed literature reports were supportive of the above trial's results. None of the reviewed studies evaluated the use of ammonia in a screening assessment to detect early coronary artery disease in a healthy, asymptomatic population. The effectiveness and safety as well as the effect on cardiovascular morbidity and mortality of Ammonia N 13 Injection in the screening setting is unknown.

[3] Demer, L. L, K. L. Gould, R. A. Goldstein, R. L. Kirkeeide, N. A. Mullani, R. W. Smalling, A. Nishikawa, and M.E. Merhige. Assessment of coronary artery disease severity by PET: Comparison with quantitative arteriography in 193 patients. *Circulation* 1989; 79:825-35.

INDICATIONS AND USAGE

Ammonia N 13 Injection is indicated for PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary artery disease.

CONTRAINDICATIONS

None known.

WARNINGS

None known.

PRECAUTIONS

General

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 radionuclides. (See Drug Handling section.) 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 by using the smallest dose of radioactivity consistent with safety and relative value of diagnostic information.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with Ammonia N 13 Injection have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been performed with Ammonia N 13 Injection. It is not known whether Ammonia N 13 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ammonia N 13 Injection should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

The effects of Ammonia N 13 Injection on human breast milk are unknown. Caution should be exercised when Ammonia N 13 Injection is administered to a nursing woman. Wherever possible, infant formula should be substituted for breast milk up to 4 to 6 hours after administration.

Pediatric Use

The safety and effectiveness of Ammonia N 13 Injection have been established in pediatric patients on the basis of clinical studies in adults, known metabolism of ammonia, and radiation dosimetry in the pediatric population. (See Radiation Dosimetry section.)

ADVERSE REACTIONS

Ammonia is a normal body constituent. The amount of ammonia in Ammonia N 13 Injection at the indicated dose has minimal effect on normal human physiology.

A 1999 review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems indicated that adverse reactions have not been reported for Ammonia N 13 Injection. However, patients should be appropriately monitored for adverse drug reactions, and such reactions should be reported to FDA, if they occur.

OVERDOSAGE

Overdoses of Ammonia N 13 Injection have not been reported. (See Radiation Dosimetry section for related information.)

DOSAGE AND ADMINISTRATION

The recommended dosages of Ammonia N 13 Injection, as an intravenous injection, are:

1. Rest Imaging Studies

    a. A dose of 10-20[4] mCi is injected through a catheter inserted into a large vein.

    b. After 3 minutes from the initial injection, resting data are acquired for 15-20 minutes.

[4] The highest recommended dose of radioactivity (20 mCi) is associated with a mass dose of 0.05 - 0.1 μmol (0.801 - 1.602 μg) of ammonia N 13.

2. Stress Imaging Studies

    a. After 40 minutes from the initial injection (to allow for isotope decay), a pharmacologic stress-inducing drug may be administered in accordance with its approved labeling.

    b. After 8 minutes from the injection of the pharmacologic stress inducing drug, a second dose of Ammonia N 13 Injection 10-20 mCi may be injected. Images should be acquired for 15-20 minutes.

Patient Preparation

To minimize radiation dose to the bladder, the patient should be hydrated and encouraged to void when the examination is completed and thereafter as often as possible.

Drug Handling

Ammonia N 13 Injection, like other parenteral drug products, should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit. Ammonia N 13 Injection preparations containing particulate matter or discoloration should not be administered. They should be disposed of in a safe manner, in compliance with applicable regulations.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves and effective shielding should be worn when handling the product.

The contents of each vial are sterile and non-pyrogenic. To maintain sterility, aseptic technique must be used during all operations involved in the manipulation and administration of Ammonia N 13 Injection.

As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other persons.

Ammonia N 13 Injection, like other radioactive drugs, must be handled with care and appropriate safety measure should be used to minimize radiation exposure to clinical personnel. Care should be taken to minimize exposure to the patient consistent with proper patient management. 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 authorized to license the use of radionuclides.

Radiation Dosimetry

The converted radiation absorbed doses in rem/mCi are shown in Table 5. Based on these data, the absorbed doses per unit of activity in selected organs are higher in pediatric patients under 10 years of age. These organs are the heart, bladder wall, red marrow, testes, and ovaries. Specifically, the absorbed radiation doses per unit activity of

Ammonia N 13 Injection for adults and pediatric patients 15 years old or older (5 years old or older for the brain) are similar. However, for pediatric patients under 10 years of age (under 1 year old for the brain), the absorbed radiation doses per unit activity appear to be higher than adult values. These data also indicate that for each of the age groups evaluated (i.e., pediatric patients from 1, 5, 10, and 15 year(s) old as well as adults), the organ with the highest radiation exposure is the urinary bladder wall.

Table 5: N 13: Absorbed Radiation Dose Per Unit Activity (rem/mCi) for Adults and Pediatric Groups 1, 5, 10, and 15 Years Old

Organ	Adult	15 year old	10 year old	5 year old	1 year old
Adrenals	0.0085	0.0096	0.016	0.025	0.048
Bladder wall	0.030	0.037	0.056	0.089	0.17
Bone surfaces	0.0059	0.0070	0.011	0.019	0.037
Brain	0.016	0.016	0.017	0.019	0.027
Breast	0.0067	0.0067	0.010	0.017	0.033
Stomach wall	0.0063	0.0078	0.012	0.019	0.037
Small intestine	0.0067	0.0081	0.013	0.021	0.041
*ULI	0.0067	0.0078	0.013	0.021	0.037
**LLI	0.0070	0.0078	0.013	0.020	0.037
Heart	0.0078	0.0096	0.015	0.023	0.041
Kidneys	0.017	0.021	0.031	0.048	0.089
Liver	0.015	0.018	0.029	0.044	0.085
Lungs	0.0093	0.011	0.018	0.029	0.056
Ovaries	0.0063	0.0085	0.014	0.021	0.041
Pancreas	0.0070	0.0085	0.014	0.021	0.041
Red marrow	0.0063	0.0078	0.012	0.020	0.037
Spleen	0.0093	0.011	0.019	0.030	0.056
Testes	0.0067	0.0070	0.011	0.018	0.035
Thyroid	0.0063	0.0081	0.013	0.021	0.041
Uterus	0.0070	0.0089	0.014	0.023	0.041
Other tissues	0.0059	0.0070	0.011	0.018	0.035

*Upper large intestine, **Lower large intestine

HOW SUPPLIED

Ammonia N 13 Injection is packaged in ___mL [*] single dose/multiple dose glass vial containing between ___MBq to ___MBq * (___mCi to ___mCi) * of [^{13}N]ammonia, at the end of synthesis (EOS) reference time, in approximately ___mL * volume.

[*] All missing information should be filled in by the applicant.

Storage

Store at _____ *

Use the solution within ____ minutes * of the End of Synthesis (EOS) calibration time.

Expiration Date and Time

The expiration date and time are provided on the container label.

Caution: Rx ONLY

Manufactured by: *
Distributed by: *

Facility Name *
Complete Address
City, State and Zip Code *

* All missing information should be filled in by the applicant.

LABELING
IMMEDIATE CONTAINER
VIAL/LEAD PIG

Ammonia N 13 Injection
Diagnostic-For Intravenous Administration

Lot#_____ ExpirationDate/Time:_____/_____ *
(___ minutes after EOS)

Calibration: Date_____ * Time_____ * (EOS)

Activity Concentration:_____mCi* in_____mL*@ EOS

Each mL contains _____ - _____MBq * (____ - ___ mCi) * of [^{13}N] ammonia @ EOS and 9 mg of sodium chloride. Store upright in a shielded container at controlled room temperature. Do not use if cloudy or contains particulate matter. [^{13}N] Half-life = 9.96 min. Calculate correct dosage from date and time of calibration. Manufactured by _____.* (radioactivity caution statement and symbol)

EOS = End of Synthesis

Caution: **Rx Only.**

* All missing information should be filled in by the applicant.

Fludeoxyglucose F 18 Injection - [^{18}F] FDG Diagnostic — For Intravenous Administration

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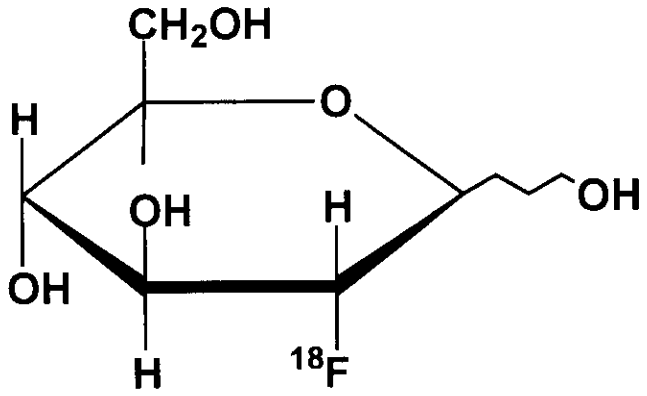
Fludeoxyglucose F 18 Injection - [^{18}F] FDG
Diagnostic - For Intravenous Administration

DESCRIPTION

Fludeoxyglucose F 18 Injection is a positron emitting radiopharmaceutical containing no-carrier added radioactive 2-deoxy-2-[^{18}F]fluoro-D-g1ucose, which is used for diagnostic purposes in conjunction with Positron Emission Tomography (PET). It is administered by intravenous injection.

The active ingredient 2-deoxy-2-[^{18}F]fluoro-D-g1ucose, abbreviated [^{18}F] FDG, has a molecular formula of $C_8H_{11}{}^{18}FO_5$ with a molecular weight of 181.26 daltons, and has the following chemical structure:



Fludeoxyglucose F 18 Injection is provided as a ready to use isotonic, sterile, pyrogen free, clear, colorless solution. Each mL contains between _____ to _____ MBq * (__ – __ mCi) * of 2-deoxy-2-[^{18}F]fluoro-D glucose at the end of synthesis (EOS), and 9 mg of sodium chloride. The pH of the solution is between ___ to ___ .*,[5] The solution is packaged in a multiple-dose glass vial and does not contain any preservative.

Physical Characteristics

Fluorine F 18 decays by positron (β+) emission and has a half-life of 109.7 minutes. 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).

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* All missing information should be filled in by the applicant.

[5] Current USP standard states the pH <791> should be "between 4.5 and 8.5." The FDA approved reference listed drug has a pH range between 5.5 and 7.5. The current USP standards for Fludeoxyglucose F 18 13 Injection are being revised.

Table 1. Principal Emission Data for Fluorine F 18

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

** Produced by positron annihilation
From: Kocher, D.C. "Radioactive Decay Tables" DOE/TIC-i 1026, 89 (1981).

External Radiation

The specific gamma ray constant for fluorine F 18 is 6.0 R/hr/mCi (0.3 Gy/hr/kB) at 1cm. 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 2. For example, the interposition of an 8.3 mm thickness of Pb, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 2. Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0	0.00
4.1	0.50
8.3	0.25
13.2	0.10
26.4	0.01
52.8	0.001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 3.

Table 3. Physical Decay Chart for Fluorine F 18

Minutes	Fraction Remaining
0	1.00
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250
440	0.060

*Calibration Time

CLINICAL PHARMACOLOGY

General

Fludeoxyglucose F 18 Injection is a radiolabeled analog of glucose that is rapidly distributed to all organs of the body after intravenous administration. After background clearance of Fludeoxyglucose F 18 Injection, optimal PET imaging is generally achieved between 30 to 40 minutes after administration.

Pharmacodynamics

Fludeoxyglucose F 18 Injection is a glucose analog that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F 18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [^{18} F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it can not exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of fludeoxyglucose F 18 reflect a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and fludeoxyglucose F 18 transport and phosphorylation (expressed as the “lumped constant” ratio), fludeoxyglucose F 18 is used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of fludeoxyglucose F 18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of fludeoxyglucose F 18 reflect greater than normal rates of glucose metabolism.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (1) an increase in the activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by fludeoxyglucose F 18 accumulation shows considerable variability. Depending on tumor type, stage, and location,

fludeoxyglucose F 18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of uptake of fludeoxyglucose F 18.

In the heart under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolized immediately instead of being converted into glycogen. Under these conditions, phosphorylated fludeoxyglucose F 18 accumulates in the myocyte and can be detected with PET imaging.

Normally, the brain relies on anaerobic metabolism. In epilepsy, the glucose metabolism varies. Generally during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic.

Pharmacokinetics

In four healthy male volunteers, receiving an intravenous administration of 30 seconds in duration, the arterial blood level profile for fludeoxyglucose F 18 was described as a triexponential decay curve. The effective half-life ranges of the three phases were 0.2-0.3 minutes, 10-13 minutes with a mean and standard deviation (STD) of 11.6 $\pm$ 1.1 min, and 80-95 minutes with a mean and STD of 88 $\pm$ 4 min.

Within 33 minutes, a mean of 3.9% of the administrated radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at 2 hours postadministration suggests that 20.6% (mean) of the radioactive dose was present in the bladder. (See the Metabolism section for additional clearance times.)

Distribution

The extent of binding of fludeoxyglucose F 18 to plasma proteins is not known.

Metabolism

Fludeoxyglucose F 18 Injection is transported into cells and phosphorylated to [^{18}F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [^{18}F]FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[^{18}F]fluoro-6-phospho-D-mannose ([^{18}F]FDM-6-phosphate).

Fludeoxyglucose F 18 Injection may contain several impurities (e.g., 2-deoxy-2-chloro-D-glucose (ClDG)). Biodistribution and metabolism of C1DG are presumed to be similar to fludeoxyglucose F 18 and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (C1DG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, C1DG, and ClDM) presumably leave cells by passive diffusion.

Fludeoxyglucose F 18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours.

Fludeoxyglucose F 18 that is not involved in glucose metabolism in any tissue is excreted unchanged in the urine.

Elimination

Fludeoxyglucose F 18 is cleared from most tissues within 24 hours and can be eliminated from the body unchanged in the urine. Three elimination phases have been identified in the reviewed literature. In one study, there is an early elimination phase ("alpha": half-life of 0.2-0.3 minutes) and two late phases ("beta": half life of 11.6 ±1.1 minutes and "gamma": half life of 88± 4 minutes). Another study reported a "beta" phase (half life of 4.2 ±1.1 minutes) and "gamma" phase (half life of 50.1 ±14.6 minutes). Within 33 minutes, a mean of 3.9% of the injected dose was measured in the urine of normal subjects. Within 2 hours of administration, a mean of 20.6% of the injected dose was found in the bladder.

Pharmacokinetics in Special Populations

Extensive dose range and dose adjustment studies with this drug product in normal and special populations have not been completed. In pediatric patients with epilepsy, doses given have been as low as 2.6 mCi.

The pharmacokinetics of Fludeoxyglucose F 18 Injection in renally impaired patients have not been characterized. Fludeoxyglucose F 18 is eliminated through the renal system. Care should be taken to prevent excessive and unnecessary radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on fludeoxyglucose F 18 distribution in humans have not been ascertained. Diabetic patients may need stabilization of blood glucose levels on the day before and on the day of the Fludeoxyglucose F 18 Injection study.

Drug-Drug Interactions

Drug-drug interactions with Fludeoxyglucose F 18 Injection have not been evaluated.

CLINICAL TRIALS

Oncology: [6] The efficacy of Fludeoxyglucose F 18 Injection in positron emission tomography cancer imaging was demonstrated in 16 independent literature reports. These studies prospectively evaluated the sensitivity and specificity of fludeoxyglucose F 18 for detecting malignancies. All these studies had at least 50 patients and used pathology as a standard of truth to compare the results of PET imaging with Fludeoxyglucose F 18 Injection. The studies encompassed a variety of cancers: non-small cell lung cancer, colo-rectal, pancreatic, breast, thyroid, melanoma, Hodgkin's and non-Hodgkin's lymphoma, and various types of metastatic cancers to lung, liver, bone, and axillary nodes. The doses in the studies ranged from 200 MBq to 740 MBq with a median and mean dose of 370 MBq.

[6] See the Agency's March 2000 PET Safety and Effectiveness Federal Register Notice.

In these studies the patients had a clinical reason for the evaluation of malignancy (e.g., the patients had an abnormality identified by a prior test and were seeking a diagnosis, or the patients had an existing diagnosis of cancer and were having further work-up or monitoring). None of these studies evaluated the use of Fludeoxyglucose F 18 Injection in routine population screening in which healthy, asymptomatic people are tested for purposes of cancer early detection. The efficacy of fludeoxyglucose F 18 PET imaging in cancer screening, including its ability to decrease cause-specific mortality, is unknown.

In PET imaging with Fludeoxyglucose F 18 Injection, sensitivity is restricted by the biologic variability of cancer glucose utilization found in individual patients, with different cancers (see Clinical Pharmacology and Pharmacodynamic sections). In the reviewed studies, the sensitivity and specificity varied with the type of cancer, size of cancer, and other clinical parameters. Also, there were false negatives and false positives. Negative PET imaging results with Fludeoxyglucose F 18 Injection do not preclude the diagnosis of cancer and further work-up is indicated. Also, positive PET imaging results with Fludeoxyglucose F 18 Injection can not replace biopsy to confirm a diagnosis of cancer. There are non-malignant conditions such as fungal infections, inflammatory processes, and benign tumors that had patterns of increased glucose metabolism that give rise to false-positive examinations.

Cardiology:[7] The efficacy of Fludeoxyglucose F 18 Injection for cardiac use was demonstrated in ten independent literature reports, which, in general, shared the characteristics summarized below. The studies were prospective and enrolled patients with coronary artery disease and chronic left ventricular systolic dysfunction of a mild to moderate degree. The patients were scheduled to undergo coronary revascularization with either coronary artery bypass surgery or angioplasty. Before revascularization, patients underwent PET imaging with Fludeoxyglucose F 18 Injection and perfusion imaging with other diagnostic radiopharmaceuticals. Doses of Fludeoxyglucose F 18 Injection ranged from 74-370 MBq (2-10 mCi). Segmental, left ventricular, wall-motion assessments of asynergic areas made before revascularization were compared to those made after successful revascularization to identify myocardial segments with functional recovery. Segmental wall motion assessments were made blinded to the results of metabolic/perfusion imaging, and PET image analyses were quantitative.

Left ventricular myocardial segments were predicted to have reversible loss of systolic function if they showed fludeoxyglucose F 18 accumulation and reduced perfusion (i.e., flow-metabolism mismatch). Conversely, myocardial segments were predicted to have irreversible loss of systolic function if they showed concordant reductions in both fludeoxyglucose F 18 accumulation and perfusion (i.e., matched defects). Diagnostic performance measures such as sensitivity, specificity, positive predictive value, and negative predictive value were calculated. None of the studies prospectively determined the degree to which mismatch, or the location of mismatch, is associated with improvements in global ventricular function, clinical symptoms, exercise tolerance, or survival.

Findings of flow-metabolism mismatch in a myocardial segment suggest that successful revascularization will restore myocardial function in that segment. However, false-positive tests

[7] See the Agency's March 2000 PET Safety and Effectiveness Federal Register Notice.

occur regularly, and the decision to have a patient undergo revascularization should not be based on PET findings alone. Similarly, findings of a matched defect in a myocardial segment suggest that myocardial function will not recover in that segment, even if it is successfully revascularized. However, false-negative tests occur regularly, and the decision to recommend against coronary revascularization, or to recommend a cardiac transplant, should not be based on PET findings alone. The reversibility of segmental dysfunction as predicted with fludeoxyglucose F 18 PET imaging depends on successful coronary revascularization. Therefore, in patients with a low likelihood of successful revascularization, the diagnostic usefulness of PET imaging with Fludeoxyglucose F 18 Injection is limited.

Epilepsy:[8] In a prospective, open label trial, Fludeoxyglucose F 18 Injection was evaluated in 86 patients with epilepsy. Each patient received a dose of Fludeoxyglucose F 18 Injection in the range of 185-370 MBq (5-10 mCi). Demographic characteristics of race and gender are not available. The mean age was 16.4 years (range: 4 months - 58 years; of these, 42 patients were < 12 years and 16 patients were <2 years old). Patients had a known diagnosis of complex partial epilepsy and were under evaluation as surgical candidates for treatment of their seizure disorder. Seizure foci had been previously identified on ictal EEGs and sphenoidal EEGs. In 16% (14/87) of patients, the pre-Fludeoxyglucose F 18 Injection findings were confirmed by fludeoxyglucose F 18; 34% (30/87) of patients, images of Fludeoxyglucose F 18 Injection provided new findings. In 32% (27/87), imaging with Fludeoxyglucose F 18 Injection was not definitive. The influence of these findings on surgical outcome, medical management, or behavior is not known.

Several other studies comparing imaging with Fludeoxyglucose F 18 Injection results to subsphenoidal EEG, MRI and/or surgical findings supported the concept that the degree of hypometabolism corresponds to areas of confirmed epileptogenic foci.

The safety and effectiveness of Fludeoxyglucose F 18 Injection to distinguish idiopathic epileptogenic foci from tumors or other brain lesions that may cause seizures have not been established.

INDICATIONS AND USAGE

Fludeoxyglucose F 18 Injection is indicated in positron emission tomography (PET) imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnoses of cancer.

Fludeoxyglucose F 18 Injection is indicated in positron emission tomography (PET) imaging in patients with coronary artery disease and left ventricular dysfunction, when used together with myocardial perfusion imaging, for the identification of left ventricular myocardium with residual glucose metabolism and reversible loss of systolic function.

Fludeoxyglucose F 18 Injection is indicated in positron emission tomography (PET) imaging in patients for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures.

[8] NDA #20-306.

CONTRAINDICATIONS

None known

WARNINGS

None known

PRECAUTIONS

General

Use in patients with diabetes or hyperglycemia has not been well studied. It is recommended that patients be normoglycemic when undergoing PET imaging with Fludeoxyglucose F 18 Injection.

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 radionuclides. (See Drug Handling section.) 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 by using the smallest dose of radioactivity consistent with safety and relative value of diagnostic information.

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

Information for Patients

To minimize radiation absorbed dose to the bladder, adequate hydration should be encouraged to permit frequent voiding during the first few hours after intravenous administration of Fludeoxyglucose F 18 Injection. This may be achieved by having patients drink at least an 8 oz glass of water prior to drug administration. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible a toilet should be used and should be flushed several times after each use and hands should be washed thoroughly after each voiding or fecal elimination. If blood, urine or feces soil clothing, the clothing should be washed separately.

Diabetic Patients

Transport of fludeoxyglucose F 18 into cells may be affected by fasting or by blood glucose changes associated with diabetes mellitus. Diabetic patients may need stabilization of blood glucose levels on the day before and on the day of administration of Fludeoxyglucose F 18 Injection.

Carcinogenesis, Mutagenesis, Impairment or Fertility

Studies with Fludeoxyglucose F 18 Injection have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been conducted with Fludeoxyglucose F 18 Injection. It is not known whether Fludeoxyglucose F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, Fludeoxyglucose F 18 Injection should not be administered to a pregnant woman unless the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

The effects of Fludeoxyglucose F 18 Injection on human breast milk are unknown. Because many drugs are excreted in human milk, caution should be exercised when Fludeoxyglucose F 18 Injection is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of Fludeoxyglucose F 18 Injection in pediatric patients with epilepsy is established on the basis of studies in adult and pediatric patients. In pediatrics, the recommended dose is 2.6 mCi. The optimal dose adjustment on the basis of body size or weight has not been determined. (See Radiation Dosimetry section.)

The safety and effectiveness of Fludeoxyglucose F 18 Injection for the evaluation of malignancy or for the identification of left ventricular myocardium with reversible loss of systolic function in pediatric patients below the age of 16 years have not been established. (See Clinical Trials and Radiation Dosimetry section.)

ADVERSE REACTIONS

The Fludeoxyglucose F 18 Injection safety database for epilepsy included of 374 patients. Of these, 245 were male and 105 were female. For 24 patients, gender was not specified. The mean age was 47.8 years (range under 2 to over 65 years). Eighteen patients were between the age of 0 and 2 years; 42 patients were between the ages of 2 and 21 years; 213 patients were between 21 and 65 years; 98 patients were older than 65 years; and the ages of 3 male patients were not specified. A racial distribution is not available. In this database, adverse drug reactions that required medical intervention were not reported. In a small, 42 patient subset of the 374 patients studied, 4 patients had transient hypotension, 6 had hypo- or hyperglycemia and 3 had transient increases in alkaline phosphatase.

In a 1999 review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems indicated that adverse reactions have not been reported for Fludeoxyglucose F 18 Injection. However, patients should be appropriately monitored for adverse drug reactions and should be reported to FDA, if they occur.

OVERDOSAGE

Overdoses of Fludeoxyglucose F 18 Injection have not been reported. (See Radiation Dosimetry section for related information.)

DOSAGE AND ADMINISTRATION

The recommended dose of Fludeoxyglucose F 18 Injection for an adult (70 kg) is 185-370 MBq (5-10 mCi), as an intravenous injection for studies of malignancy, cardiology, and epilepsy.

In general, Fludeoxyglucose F 18 Injection should be administered after patients have fasted for 4-6 hours. For cardiac use, Fludeoxyglucose F 18 Injection may be administered either to patients who have fasted or to patients who have received a glucose load. (See Patient Preparation section.)

The optimum rates of administration and upper safe dose for Fludeoxyglucose F 18 Injection have not been established. The time interval between doses of Fludeoxyglucose F 18 Injection should be long enough to allow substantial decay (physical and biological) of previous administrations.

The final dose for the patient should be calculated using proper decay factors from the time of the end of synthesis (EOS) and measured by a suitable radioactivity calibration system before administration. (See decay factors in Table 3.)

Patient Preparation

Blood glucose levels should be stabilized before Fludeoxyglucose F 18 Injection is administered. In non-diabetic patients this may be accomplished by fasting 4-6 hours before Fludeoxyglucose F 18 Injection. Diabetic patients may need stabilization of blood glucose on the day preceding and on the day of administration of Fludeoxyglucose F 18 Injection.

For cardiac imaging, administration of Fludeoxyglucose F 18 Injection to fasting patients limits the accumulation of fludeoxyglucose F 18 to ischemic myocardium. This may make localization of the ischemic region difficult because the surrounding myocardium will not be well visualized. Conversely, administration of Fludeoxyglucose F 18 Injection to patients who have received a glucose load (e.g., 50-75 grams, 1-2 hours before administration of Fludeoxyglucose F 18 Injection) allows the surrounding, non-ischemic myocardium to be seen and facilitates localization of ischemic areas.

Imaging

Optimally, it is recommended that positron emission tomography (PET) imaging be initiated within 40 minutes of administration of Fludeoxyglucose F 18 Injection.

Static emission scans are acquired 30-100 minutes after the time of injection.

Drug Handling

Fludeoxyglucose F 18 Injection, like other parenteral drug products, should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit. Fludeoxyglucose F 18 Injection preparations containing particulate matter or discoloration should not be administered. They should be disposed of in a safe manner, in compliance with applicable regulations.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves and effective shielding should be worn when handling the product.

The contents of each vial are sterile and non-pyrogenic. To maintain sterility, aseptic technique must be used during all operations involved in the manipulation and administration of Fludeoxyglucose F 18 Injection.

The current reference listed drug (RLD) states that Fludeoxyglucose F 18 Injection should be used within 8 hours of the end of synthesis (EOS).

As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other persons.

Fludeoxyglucose F 18 Injection, like other radioactive drugs, must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Care should be taken to minimize exposure to the patient consistent with proper patient management. 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 authorized to license the use of radionuclides.

Radiation Dosimetry

The estimated absorbed radiation doses (rem/mCi) to a 1-year old (9.8 kg), 5-year old (19 kg), 10-year old (32 kg), 15-year old (57 kg), and adult human (70 kg) from intravenous injection of Fludeoxyglucose F 18 Injection are shown in Table 4. These estimates were calculated based on human[9] data and using the data published by the International Commission on Radiological

Protection[10] for Fludeoxyglucose F 18 Injection. The dosimetry data obtained and presented in this table show that there are slight variations in absorbed radiation dose for various organs in each of the age groups. These dissimilarities in absorbed radiation dose are understood to be due to developmental age variations (e.g., organ size, location, and overall metabolic rate for each age group). The identified critical organs (in descending order) across all age groups evaluated (i.e., newborn, 1, 5, 10, 15 year(s) and adults) are the urinary bladder, heart, pancreas, spleen, and lungs. The absolute values for absorbed radiation in each of these organs vary in each of the age groups.

[9] Jones, S. C., A. Alavi, D. Christman, I. Montanez, A. P. Wolf, and M. Reivich. 1982. The Radiation Dosimetry of 2-F-18 fluoro-2-deoxy-D- glucose in Man. *J. Nucl. Med*. 23, 613-617.

[10] ICRP Publication 53,Volume 18, No. l-4,1987, pages 75-76.

Table 4. Estimated Absorbed Radiation Doses (rem/mCi) After Intravenous Administration of 2-deoxy-2-[18F]fluoro-D-glucose, Fludeoxyglucose F 18 Injection.

Organ	Newborn[1] (3.4 kg)	1-year old[1] (9.8 kg)	5-year old[1] (19 kg)	10-year old[1] (32 kg)	15-year old[1] (57 kg)	Adult[1] (70 kg)
Bladder wall[2]	4.3	1.7	0.93	0.60	0.40	0.32
Heart wall	2.4	1.2	0.70	0.44	0.29	0.22
Pancreas	2.2	0.68	0.33	0.25	0.13	0.096
Spleen	2.2	0.84	0.46	0.29	0.19	0.14
Lungs	0.96	0.38	0.20	0.13	0.092	0.064
Kidneys	0.81	0.34	0.19	0.13	0.089	0.074
Ovaries	0.80	0.8	0.19	0.11	0.058	0.053
Uterus	0.79	0.35	0.19	0.12	0.076	0.062
LLI wall *	0.69	0.28	0.15	0.097	0.060	0.051
Liver	0.69	0.31	0.17	0.11	0.076	0.058
Gallbladder wall	0.69	0.26	0.14	0.093	0.059	0.049
Sm intestine	0.68	0.29	0.15	0.096	0.060	0.047
ULI wall **	0.67	0.27	0.15	0.090	0.057	0.046
Stomach wall	0.65	0.27	0.14	0.089	0.057	0.047
Adrenals	0.65	0.28	0.15	0.095	0.061	0.048
Testes	0.64	0.27	0.14	0.085	0.052	0.041
Red marrow	0.62	0.26	0.14	0.089	0.057	0.047
Thymus	0.61	0.26	0.14	0.086	0.056	0.044
Thyroid	0.61	0.26	0.13	0.080	0.049	0.039
Muscle	0.58	0.25	0.13	0.078	0.049	0.039
Bone surfaces	0.57	0.24	0.12	0.079	0.052	0.041
Breast	0.54	0.22	0.11	0.068	0.043	0.034
Skin	0.49	0.20	0.10	0.060	0.037	0.030
Brain	0.29	0.13	0.09	0.078	0.072	0.070
Other tissues	0.59	0.25	0.13	0.083	0.052	0.042

[1] MIRDOSE 2 software was used to calculate the radiation absorbed dose. Assumptions on the biodistribution based on data from Gallager et al. (*JNM* 18:10,990-996) and Jones et al. (*JNM* 23:7,613-617).

[2] The dynamic bladder model with a uniform voiding frequency of 1.5 hours was used.

* LLI = lower large intestine. ** ULI = upper large intestine

HOW SUPPLIED

NDC _ _ _ _ _ - _ _ _ - _ _ *

Fludeoxyglucose F 18 Injection is supplied in a _____-dose* septum capped ___ mL* glass vial containing between _____ - _____ MBq/mL* (___ – ___ mCi/mL)*,[11] of no carrier added 2-deoxy-2-[^{18}F]fluoro-D-glucose, at end of synthesis, in approximately ___ mL.*

This radiopharmaceutical is licensed by [YOUR STATE],* Department of Nuclear Safety, for distribution to persons licensed pursuant to [YOUR STATE's Section Regulatory Code for Radioactive material specified in Section of YOUR STATE'S Code],* as appropriate, or under the equivalent licenses of an Agreement State or Licensing State.

Storage

Fludeoxyglucose F 18 Injection should be stored upright in a lead shielded container at controlled room temperature.

Storage and disposal of Fludeoxyglucose F 18 Injection should be in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

Expiration Date and Time

The expiration date and time are provided on the container label. Fludeoxyglucose F 18 Injection should be used within 8 hours from the time of the end of synthesis.

Caution: Rx ONLY

Manufactured by:*
Distributed by: *

Your Facility Name
Complete Address
City, State and Zip Code*

* All missing information should be filled in by the applicant.
[11] The FDA approved reference listed drug has a specific concentration (strength) between 4 - 40 mCi/mL at EOS.

LABELING
IMMEDIATE CONTAINER
VIAL/LEAD PIG

Fludeoxyglucose F 18 Injection - [^{18}F] FDG
Diagnostic-For Intravenous Administration

Lot#_____ Expiration Date/Time:_____/_____ *
(12 hours after EOS)

Calibration: Date_____ * Time_____ * (EOS)

Activity Concentration:_____mCi* in_____mL*@ EOS

Each mL contains _____ - _____MBq* (___ - ___ mCi)*,[12] of no carrier added 2-deoxy-2-[^{18}F]fluoro-D-glucose @ EOS and 9 mg of sodium chloride. Store upright in a shielded container at controlled room temperature. Do not use if cloudy or contains particulate matter. ^{18}F Half-life = 110 min. Calculate correct dosage from date and time of calibration. Manufactured by _____.* (radioactivity caution statement and symbol)

EOS = End of Synthesis

Caution: **Rx Only.**

* All missing information should be filled in by the applicant.
[12] The FDA approved reference listed drug has a specific concentration (strength) between 4 - 40 mCi/mL at EOS.

Sodium Fluoride F 18 Injection
Diagnostic — For Intravenous Administration

This guidance has been prepared by the PET Steering Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on the content and format of NDAs and ANDAs for certain positron emission tomography (PET) drug products. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

Sodium Fluoride F 18 Injection
Diagnostic - For Intravenous Administration

DESCRIPTION

Sodium Fluoride F 18 Injection is a positron emitting radiopharmaceutical, containing no-carrier added, radioactive fluoride F 18 that is used for diagnostic purposes in conjunction with positron emission tomography (PET) imaging. It is administered by intravenous injection and is produced by particle acceleration in a ^{20}Ne (d, α) ^{18}F nuclear reaction.

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

$$Na^{+}\ ^{18}F^{-}$$

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 between _____MBq to _____MBq * (____to_____mCi)* fluoride F 18, at the end of synthesis (EOS) reference time, in 0.9% aqueous sodium chloride. The pH of the solution is between 6 to 8. The solution does not contain any preservatives. The only known source of nonradioactive fluorine ion present is that found in the distilled water and saline solutions used in preparing this product.

Physical Characteristics

Fluorine F 18 decays by positron ($+) emission and has a half-life of 110 (109.7) minutes. 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).

Table 1. Principal Emission Data for Fluorine F18

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

** Produced by positron annihilation

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

* All missing information should be filled in by the applicant.

External Radiation

The specific gamma ray constant for Fluorine F 18 is 6.0 R/hr/mCi (0.3 Gy/hr/kB) at 1cm. 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 2. For example, the interposition of an 8.3 mm thickness of Pb with a coefficient of attenuation of 0.25 will decrease the external radiation by 75%.

Table 2. Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding

Shield Thickness (Pb) mm	Coefficient of Attenuation
0	0.00
4.1	0.50
8.3	0.25
13.2	0.10
26.4	0.01
52.8	0.001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 3.

Table 3. Physical Decay Chart for Fluorine F 18*

Minutes	Fraction Remaining
0	1.00
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250
440	0.060

*Calibration Time

CLINICAL PHARMACOLOGY

General

Fluorine F 18 ions normally 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.

Pharmacodynamics

Increased fluorine F 18 ion deposition around joints can occur in arthritis or following trauma; increased deposition has also been documented in bone around fracture sites, in osteomyelities, fibrous dysplasia, spondylitis tuberculosa, Paget's disease, hyperstosis frontalis interna, myositis ossificans, and in rapidly growing epiphyses. The tendency for fluorine F 18 ions to accumulate in the vicinity of primary and metastatic malignancy in bone has proven clinically useful in detection of such lesions (3-10).

Pharmacokinetics

Following intravenous administration, Sodium Fluoride F 18 Injection provides fluorine F 18 ions that rapidly equilibrate, primarily within the extracellular fluid space. These fluorine F 18 ions are then rapidly cleared by bone deposition and by excretion into the urine.

Distribution

Deposition of the fluorine F 18 ions in bone appears to be primarily a function of blood flow to the bone and the efficiency of the bone in extracting the fluorine F 18 ions from the blood perfusing the bone (1). Fluorine F 18 ions do not appear to be bound to serum proteins.

Elimination

In patients with normal renal function, 20% or more of the fluorine F 18 ions are cleared from the body in the urine within the first 2 hours after intravenous administration (3). Subsequently, small amounts of fluorine 18 ions continue to be excreted in the urine further diminishing the radioactivity of the fluorine F 18 ions in soft tissues of the body. (See Pharmacokinetics section)

The clearance of fluorine F 18 ions from the blood is rapid (2). Fluorine F 18 ions are rapidly eliminated via the renal system.

Drug-Drug Interactions

Drug-drug interactions with Sodium Fluoride F 18 Injection have not been studied.

INDICATIONS

Sodium Fluoride F 18 Injection is used as a bone imaging agent to define areas of altered osteogenic activity.

CONTRAINDICATIONS

None known.

WARNINGS

None known.

PRECAUTIONS

General

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. (See Drug Handling section.) 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 by using the smallest dose of radioactivity consistent with safety and relative value of diagnostic information.

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

Information for Patients

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 of Sodium Fluoride F 18 Injection. This may be achieved by having patients drink at least an 8 oz. glass of water prior to drug administration. To help protect themselves and others in their environment, patients should take the following precautions for 12 hours after injection: whenever possible a toilet should be used and should be flushed several times after each use; wash hands thoroughly after each voiding or fecal elimination. If blood, urine, or feces soil clothing, the clothing should be washed separately.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Teratogenic Effects: Pregnancy Category C

Animal reproduction studies have not been conducted with Sodium Fluoride F 18 Injection. It is not known whether Sodium Fluoride F 18 Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction 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.

Nursing Mothers

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.

Pediatric Use

The safety and effectiveness of Sodium Fluoride F 18 Injection has not been established in pediatric patients. Like other bone imaging agents, Sodium Fluoride F 18 Injection is known to localize in the rapidly growing epiphyses in developing long bones. (See Clinical Pharmacology section.)

ADVERSE REACTIONS

Fluorine ions are a normal body constituent. The amount of fluorine ions in Sodium Fluoride F 18 Injection at the indicated dose has 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. In a 1999 review of the published literature, publicly available reference sources and adverse drug reaction reporting systems indicated that adverse reactions have not been reported for Sodium Fluoride F 18 Injection. However, patients should be appropriately monitored for adverse drug reactions, and such reactions should be reported to FDA, if they occur.

OVERDOSAGE

Overdoses of Sodium Fluoride F 18 Injection have not been reported. (See also Radiation Dosimetry section.)

DOSAGE AND ADMINISTRATION

The recommended dose of Sodium Fluoride F 18 Injection is 16.5 to 74.0 MBq (0.5 to 2.0 mCi), as an intravenous injection.

The maximum recommended dose should not exceed 148.0 MBq (4.0 mCi)

However, it has been estimated that use of 148.0 MBq(4.0 mCi) fluorine F 18 may result in a calculated whole body radiation dose one-sixth of that associated with approximately 100 µCi of ^{85}Sr, an impurity. The dose of Sodium Fluoride F 18 Injection used in a given patient should be minimized consistent with the objectives of the study, and the nature of the radiation detection devices employed. (See Radiation Dosimetry section.)

The final dose for the patient should be calculated using proper decay factors from the time of the end of synthesis (EOS), and measured by a suitable radioactivity calibration system before administration. (See decay factors in Table 3.)

Patient Preparation

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 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 fluorine F 18 radioactivity in the lumbar spine or bony pelvis.

Imaging

Optimally, it is recommended that imaging of Sodium Fluoride F 18 Injection can begin 1 to 2 hours after administration; however, the longer the imaging procedure is delayed, the greater will be the ratio of the activity in bone to that in soft tissue. Voiding immediately prior to imaging the fluorine F 18 biodistribution in the pelvis is recommended to reduce background radioactivity.

Drug Handling

Sodium Fluoride F 18 Injection, like other parenteral drug products, should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit. Sodium Fluoride F 18 Injection preparations containing particulate matter or discoloration should not be administered. They should be disposed of in a safe manner in compliance with applicable regulations.

Aseptic techniques and effective shielding should be employed in withdrawing doses for administration to patients. Waterproof gloves and effective shielding should be worn when handling the product.

The contents of each vial are sterile and non-pyrogenic. To maintain sterility, aseptic technique must be used during all operations involved in the manipulation and administration of Sodium Fluoride F 18 Injection.

As with any other radioactive material, appropriate shielding should be used to avoid unnecessary radiation exposure to the patient, occupational workers, and other persons.

Sodium Fluoride F 18 Injection, like other radioactive drugs, must be handled with care, and appropriate safety measure should be used to minimize radiation exposure to clinical personnel. Care should be taken to minimize exposure to the patient consistent with proper patient management. 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 authorized to license the use of radionuclides.

Radiation Dosimetry

Following are the estimated absorbed radiation doses (rem/mCi) to a human adult (70 kg) from intravenous injection of Sodium Fluoride F 18 Injection. These estimates were calculated based on human data and using the data published by the International Commission on Radiological

Protection for Sodium Fluoride F 18 Injection.[13] Fluorine F 18 ions decay with a physical half-life of 109.7 minutes (1.828 hrs.). Ninety-seven percent (97%) of the decay results in emission of a positron with a maximum energy of 0.635 MeV, and 3% of the decay results in electron capture with subsequent emission of characteristic X-rays of oxygen. The bone and bone marrow are considered the target and critical organs. The absolute values for absorbed radiation in relation to age have not been established.

Table 4. Estimated Absorbed Radiation Doses (rem/mCi) after Intravenous Administration of Sodium Fluoride F 18 Injection in Adult Humans (70kg).

	Estimated Radiation Dose	
ORGAN	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
LLI wall *	0.012	0.043
Small intestine	0.0066	0.025
Stomach	0.0038	0.014
ULI 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

*LLI – lower large intestine. ** ULI = upper large intestine

[13] ICRP Publication 53, Volume 18, No. l-4,1987, pages 73 - 74.

Estimates were calculated using phantom of Cristy & Eckerman (Report ORNL/TM-8381/V1 & V7). Models for bone and marrow are adopted from Eckerman (Aspects of dosimetry of radionuclides within the skeleton with particular emphasis on the active marrow, In Fourth International Radiopharmaceutical Dosimetry Symposium; A.T. Schlafke-Stelson and E. E. Watson eds. CONF-851113, Oak Ridge Associated Universities, Oak Ridge, TN 37831, 1986. pp 514-534.). Additio nal information was obtained from the Radiation Internal Dose Information Center, Oak Ridge Associated Universities, Oak Ridge, TN 37831.

HOW SUPPLIED

NDC _ _ _ _ _ - _ _ _ - _ _ *

Sodium Fluoride F 18 Injection is supplied in_____mL* single-dose /multiple-dose, septum capped glass vial containing between_____-_____MBq/mL* (_____-_____mCi/mL)* of no carrier added sodium [^{18}F] fluoride, at end of synthesis (EOS) reference time, in approximately_____mL volume.*

This radiopharmaceutical is licensed by [YOUR STATE]* Department of [Name of Nuclear Licensing or Safety]* for distribution to persons licensed pursuant to [YOUR STATE's Regulatory Section for Radioactive material specified in YOUR STATE's LAW],* as appropriate, or under the equivalent licenses of an Agreement State or Licensing State.

Storage

Sodium Fluoride F 18 Injection should be stored upright in a lead shielded container at controlled room temperatures.

Storage and disposal of Sodium Fluoride F 18 Injection should be in accordance with the regulations and a general license, or its equivalent, of an Agreement State or a Licensing State.

Expiration Date and Time

The expiration date and time are provided on the container label. Sodium Fluoride F18 Injection should be used within _____hours* from the time of the end of synthesis (EOS) reference time.

Caution: **Rx ONLY**

Manufactured by:_____*
Distributed by:_____*

Your Facility Name
Complete Address
City, State and Zip Code*

* All missing information should be filled in by the applicant.

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LABELING
IMMEDIATE CONTAINER
VIAL/LEAD PIG

Sodium Fluoride F 18 Injection
Diagnostic-For Intravenous Administration

Lot#_____Expiration Date/Time:_____/_____ *
(___ hours after EOS*)

Calibration: Date_____ Time_____ * (EOS)

Activity Concentration:_____mCi* in_____mL*@ EOS

Each mL contains _____ - _____MBq* (___ - ___ mCi)*,[14] of no carrier added sodium [^{18}F] fluoride @ EOS* and 9 mg of sodium chloride. Store upright in a shielded container at controlled room temperature. Do not use if cloudy or contains particulate matter. ^{18}F Half-life = 110 min. Calculate correct dosage from date and time of calibration. Manufactured by _____*. (radioactivity caution statement and symbol)

EOS = End of Synthesis

Caution: **Rx Only.**

* All missing information should be filled in by the applicant.

[14] The FDA approved reference listed drug has a specific concentration (strength) of 2.0 mCi/mL at the time of calibration ranging from 4.2 - 0.22 mCi/mL for an eight hour period.