PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FDG(^{18}F)

Fludeoxyglucose (^{18}F)
Intravenous solution, >0.5 GBq/vial or syringe
Diagnostic Radiopharmaceutical

Thunder Bay Regional Health Sciences Centre
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Fludeoxyglucose F 18 Injection is indicated in Positron Emission Tomography (PET) for diagnostic use in patients for:

- the evaluation of pulmonary nodules to distinguish benign from malignant and the evaluation of non-small cell and small cell lung cancers for staging, restaging; and
- the evaluation of colorectal cancer for recurrence, restaging, and distant metastases.

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use

1.2 Geriatrics

There are no known limitations on the clinical use of fludeoxyglucose (^{18}F) injection in geriatric patients.

2 CONTRAINDICATIONS

Fludeoxyglucose F 18 Injection is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see *Dosage Forms, Strengths, Composition and Packaging*.

3 SERIOUS WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

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

FDG (^{18}F) should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.

Where an assessment of the risk-benefit ratio suggests the use of FDG (^{18}F) in nursing women, breastfeeding can be temporarily interrupted, and close contact between mother and infant minimized, for a period of at least 12 hours following the injection of FDG (^{18}F).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

Although, the dose required for the imaging study is determined by the patient's weight and the acquisition parameters of each particular PET camera, a minimum dosage of 100 MBq is used as a guideline to ensure that the PET scan is of diagnostic quality. A maximum dosage of 740 MBq is defined as the upper dosing limit, as any amount of drug exceeding that dose would not improve the diagnostic quality of the PET scan while unnecessarily increasing the absorbed radiation dose to the patient.

4.2 Dosage

The recommended dose of FDG (^{18}F) for an adult is dependent upon patient body weight and the requirements of the PET scanner used for a particular type of study, but falls within the range of 100 – 740 MBq by intravenous injection. For example, a typical PET scanner may require the administration of 5 MBq/kg of patient body weight for a whole-body scan so that for a patient weighing 70 kg, the required dose would be 350 MBq.

The final patient dose should be calculated using proper decay factors from the time of calibration and measured by a suitable radioactivity calibration system before administration. Patients should receive a single dose per day of FDG (^{18}F), with sufficient time between doses to allow for substantial decay (both physical and biological) of previous administration(s).

4.3 Administration

Patients should not eat or drink (except water) for four hours prior to the administration of FDG (^{18}F) in order to stabilize blood glucose levels. Patients with diabetes should also avoid taking insulin two hours prior to receiving FDG (^{18}F). To ensure a stable glycemic state (blood glucose ≤ 10 mmol / L), the patient's blood glucose level should be checked prior to receiving FDG (^{18}F). Patients must be able to lie still for approximately one to two hours (sedation may be required) and, for certain scan types, may be required to raise their arms over their head. Proper hydration, a urinary catheter and / or a diuretic may be required to eliminate urinary tract activity that may confound PET scan interpretation of the abdomen and /or pelvis. The patient should void prior to being positioned on the scanner table. Proper hydration and frequent urination are recommended following a PET examination to minimise radiation exposure to the bladder.

Using appropriate shielding and aseptic technique, the appropriate amount of FDG (^{18}F) should be drawn into an appropriately sized syringe and needle. The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

FDG (^{18}F), like other parenteral drug products, should be inspected visually for particulate matter and discolouration before administration whenever solution and container permit. Preparations containing particulate matter or discolouration should not be administered to the patient; rather they should be disposed of in a safe manner that is compliant with applicable regulations.

4.4 Image Acquisition and Interpretation

The acquisition parameters for imaging with FDG (^{18}F) will vary depending upon the type of PET scanner and images required. For limited-field tomographic imaging using a dedicated PET camera, careful patient positioning will allow for the clear delineation of metabolic activity in lesions previously identified through physical or other imaging examinations.

Emission imaging should begin approximately 30 to 60 minutes following administration of FDG (^{18}F). Emission image acquisition typically ranges from six to fifteen minutes, collecting between five to fifteen million total counts depending upon the number of body positions required. Whole body imaging can be obtained with correction for photon attenuation, which requires acquisition of transmission images. Elimination of image artifacts requires the exact repositioning at each level of the patient during the acquisitions of both the transmissions and emission whole body images.

For the determination of tumour metabolic rates, dynamic imaging using a dedicated PET system is recommended. Following the transmission image, a sequence of serial images is initiated at the time of use of FDG (^{18}F) and continues for approximately 60 to 90 minutes.

Standard transaxial images are reconstructed in the form of transaxial 128 x 128 pixel images or a pixel size of 4 to 5 mm. Image sets can be re-oriented into coronal and / or sagittal slices. The contiguous transaxial and / or coronal or sagittal slices can then be examined by visual inspection and interpreted relative to the normal physiological uptake of FDG (^{18}F) in the brain, myocardium, liver, spleen, stomach, intestines, kidneys or urine. Increased or abnormal FDG (^{18}F) uptake can signify neoplasms. Healing surgical wounds, infections, granulomatous tissue, or other inflammatory tissue responses may also show areas of increased FDG (^{18}F) uptake. Practitioners should be appropriately trained in the interpretation of FDG (^{18}F) PET images.

Tumour metabolism can also be estimated using semi-quantitative or quantitative methods. The semi-quantitative estimate of tumour metabolism (i.e. standard uptake values [SUV]) is based on relative lesion radioactivity normalised to the injected dose and patient body weight. It requires a static emission image acquired following the plateau of FDG (^{18}F) concentration levels (approximately 30 minutes), the total administered dose of FDG (^{18}F), and the patient's height and weight for measurement of lean body mass or of body surface area. Additional data which may be required include the measurement of arterial input function and the determination of the plasma FDG (^{18}F) levels and glucose concentrations. A calibration factor will be required between scanner events in terms of (counts / pixel / sec) and in vitro measured activity concentrations in (counts / ml / sec). This can be accomplished by imaging a cylindrical phantom with a known concentration of positron emitter and by measuring the activity of an aliquot of the cylinder solution in a well counter. This measurement can be corrected for blood glucose concentration.

Estimates of metabolic tumour rates, either using quantitative or semi-quantitative methods, are obtained by assigning regions of interest (ROI) to the tumour and the blood pool on the dynamically acquired images. The resulting time activity curves are then fitted with a tracer compartment model or submitted to graphical analysis in order to derive the phosphorylation of FDG (^{18}F).

4.5 Instructions for Preparation and Use

The components of the multi-dose vial and unit-dose syringe are sterile and non-pyrogenic. It is essential that the user follows the directions carefully and adheres to strict aseptic technique. Use aseptic technique and wear waterproof gloves throughout the entire preparation procedure. Make all transfers of radioactive solutions with an adequately shielded syringe and maintain adequate shielding around the vial and syringe during the useful life of the radioactive product.

4.6 Directions for Quality Control

The required quality control testing must be performed on the product prior to release.

5 RADIATION DOSIMETRY

The effective dose coefficient is 1.9E-02 mSv/MBq. The effective dose following the administration of 5 MBq/kg to a 70 kg adult is 6.6 mSv. The total effective dose of an FDG (^{18}F) PET/CT procedure will be higher due to the CT component of the procedure. The contribution from CT will vary according to the equipment used and the acquisition protocol.

Table 1. Absorbed dose per unit activity administered (mGy/MBq)

Organ	Adult	15 years*	10 years*	5 years*	1 year*
Adrenals	1.2E-02	1.6E-02	2.4E-02	3.9E-02	7.1E-02
Bladder	1.3E-01	1.6E-01	2.5E-01	3.4E-01	4.7E-01
Bone surfaces	1.1E-02	1.4E-02	2.2E-02	3.4E-02	6.4E-02
Brain	3.8E-02	3.9E-02	4.1E-02	4.6E-02	6.3E-02
Breasts	8.8E-03	1.1E-02	1.8E-02	2.9E-02	5.6E-02
Gallbladder	1.3E-02	1.6E-02	2.4E-02	3.7E-02	7.0E-02
Gastrointestinal tract					
Stomach	1.1E-02	1.4E-02	2.2E-02	3.5E-02	6.7E-02
Small intestine	1.2E-02	1.6E-02	2.5E-02	4.0E-02	7.3E-02
Colon	1.3E-02	1.6E-02	2.5E-02	3.9E-02	7.0E-02
(ULI	1.2E-02	1.5E-02	2.4E-02	3.8E-02	7.0E-02)
(LLI	1.4E-02	1.7E-02	2.7E-02	4.1E-02	7.0E-02)
Heart	6.7E-02	8.7E-02	1.3E-01	2.1E-01	3.8E-01
Kidneys	1.7E-02	2.1E-02	2.9E-02	4.5E-02	7.8E-02
Liver	2.1E-02	2.8E-02	4.2E-02	6.3E-02	1.2E-01
Lungs	2.0E-02	2.9E-02	4.1E-02	6.2E-02	1.2E-01
Muscles	1.0E-02	1.3E-02	2.0E-02	3.3E-02	6.2E-02
Oesophagus	1.2E-02	1.5E-02	2.2E-02	3.5E-02	6.6E-02
Ovaries	1.4E-02	1.8E-02	2.7E-02	4.3E-02	7.6E-02
Pancreas	1.3E-02	1.6E-02	2.6E-02	4.0E-02	7.6E-02
Red marrow	1.1E-02	1.4E-02	2.1E-02	3.2E-02	5.9E-02
Skin	7.8E-03	9.6E-03	1.5E-02	2.6E-02	5.0E-02
Spleen	1.1E-02	1.4E-02	2.1E-02	3.5E-02	6.6E-02
Testes	1.1E-02	1.4E-02	2.4E-02	3.7E-02	6.6E-02
Thymus	1.2E-02	1.5E-02	2.2E-02	3.5E-02	6.6E-02
Thyroid	1.0E-02	1.3E-02	2.1E-02	3.4E-02	6.5E-02
Uterus	1.8E-02	2.2E-02	3.6E-02	5.4E-02	9.0E-02
Remaining organs	1.2E-02	1.5E-02	2.4E-02	3.8E-02	6.4E-02
Effective dose (mSv/MBq)	1.9E-02	2.4E-02	3.7E-02	5.6E-02	9.5E-02

International Commission on Radiological Protection. Radiation Dose to Patients from Radiopharmaceuticals - Addendum 3 to ICRP Publication 53. ICRP Publication 106. Ann ICRP 2008;38 (1-2):87

* Although the absorbed radiation dose estimates in Table 1 include values for pediatric subjects, it need be noted that the safety and efficacy of the product in pediatric patients has not been established. (See "Warnings and Precautions, Special Populations, Pediatrics").

6 OVERDOSAGE

Cases of overdose are not known to have occurred with FDG (^{18}F). In case of overdose, elimination should be encouraged by means of increased fluid intake and frequent urination.

7 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Each 10- or 20-mL multi-dose vial and each 5-mL unit-dose syringe contain > 0.5 GBq of FDG (^{18}F) at calibration time.

The vehicle is 0.9% NaCl containing a citrate buffer. The solution does not contain any preservatives. The pH of the solution is between 4.5 and 7.5.

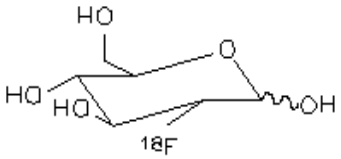
Table 2: Dosage form, strength, composition

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients	
Intravenous	Solution Fludeoxyglucose > 0.5 GBq per vial or syringe	Na-di-citrate Na-tri-citrate NaCl 0.9%	0.94 mg/mL 5.42 mg/mL qs

8 DESCRIPTION

8.1 Physical Characteristics

FDG (^{18}F) is 2-deoxy-2-^{18}F-fluoro-D- glucose. It has a molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.1 daltons and the following chemical structure:



The radionuclide present in the drug substance is fluorine-18 (^{18}F), which decays by positron (ß +) emission with a half-life of 109.7 minutes. The daughter product of this process is the stable isotope, oxygen-18 (^{18}O). The physical radiation emission data for fluorine-18 are summarised in Table 3.

Table 3. Principle Emission Data for ^{18}F

Radiation Emission	Percentage per Disintegration	Mean Energy (keV)
Positron (ß +)	96.9	249.8
Gamma (γ)	193.8	511.0

To correct for the physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 4.

Table 4. Physical decay chart for ^{18}F

Time from Calibration	Fraction remaining	Time from Calibration	Fraction remaining
60 min	68.5%	420 min	7.1%
120 min	46.9%	480 min	4.8%
180 min	32.1%	540 min	3.3%
240 min	22.0%	600 min	2.3%
300 min	15.1%	660 min	1.6%
360 min	10.3%	720 min	1.1%

Exact amounts can be calculated using the following formula:

$$A = 100 * e^{(-0.006311*t)}$$

where *A* is the fraction remaining and *t* is the time from calibration (in minutes)

8.2 External Radiation

The specific gamma ray constant for fluorine-18 is 0.3 Gy/hr/kBq at 1 cm. The lead shielding half value layer (HVL) for the 511 keV photons is 4.1 mm. The range of attenuation coefficients for this radionuclide is shown in Table 5. For example, an 8.3 mm thick lead shield has a coefficient of attenuation of 0.25 and will decrease the external radiation by 75%.

Table 5. Radiation Attenuation of 511 keV Photons by Lead Shielding

Lead Shield thickness (mm)	0	4.1	8.3	13.2	26.4	52.8
Coefficient of Attenuation	0	0.5	0.25	0.1	0.01	0.001

9 WARNINGS AND PRECAUTIONS

9.1 General

The product should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

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

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

9.2 Contamination

The following measures should be taken for up to 12 hours after receiving the radiopharmaceutical product: toilet should be used instead of urinal. Toilet should be flushed several times after use.

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

9.3 Risk for Image Misinterpretation and other Errors

For lung cancer evaluation, certain thoracic area non-cancerous lesions may show FDG (^{18}F) uptake including acute and chronic infections (such as abscesses, tuberculosis and histoplasmosis), and inflammatory / granulomatous conditions (such as sarcoidosis, bronchiectasis, or post radiotherapy sites) that could mimic tumour accumulation. Absent or less intense relative uptake of FDG (^{18}F) may be observed in specific lesions including bronchoalveolar, mucinous and lobular carcinoma as well as carcinoid and fibroadenoma sites.

For colorectal cancer evaluation, certain abdominal / pelvic area non-cancerous lesions may show FDG (^{18}F) uptake including sites of post radiation or post-surgical inflammatory response, lesion site flare following chemotherapy, colonic adenomas and bladder diverticula that could mimic tumour accumulation. Absent or less intense relative uptake of FDG (^{18}F) may be observed in specific lesions including mucinous carcinoma.

Lesion size may also affect detectability based on relative FDG (^{18}F) accumulation and PET imaging system resolution, as it has been shown that FDG (^{18}F) PET/CT imaging may have a lower sensitivity in evaluating lesion sizes of less than 1 cm.

9.4 Special Populations

9.4.1 Diabetes Mellitus

Patients with diabetes may need stabilisation of blood glucose on the day preceding and on the day of the FDG (^{18}F)-PET scan.

9.4.2 Pregnant Women

Ideally, examinations using radiopharmaceuticals, especially those elective in nature of women of childbearing capability, should be performed during the first ten days following the onset of menses, or after ensuring the woman is not pregnant. The benefit of using a diagnostic radiopharmaceutical should be weighed against the possible risk to an embryo or a fetus.

Adequate reproduction studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse reactions on the fetus.

9.4.3 Nursing Women

Where an assessment of the risk-benefit ratio suggests the use of FDG (^{18}F) in nursing women, breastfeeding can be temporarily interrupted, and close contact between mother and infant minimized, for a period of at least 12 hours following the injection of FDG (^{18}F).

Formula feeding can be substituted or, when appropriate, milk may be expressed prior to FDG (^{18}F) administration, to minimize close contact between the mother and infant to help limit radiation exposure to the infant.

9.4.4 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use

9.4.5 Geriatrics

There are no known limitations on the clinical use of fludeoxyglucose (^{18}F) injection in geriatric patients.

10 ADVERSE REACTIONS

10.1 Adverse Drug Reaction Overview

There are no known adverse drug reactions associated with the use of FDG (^{18}F).

10.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

No adverse events were reported in any published clinical trials.

10.3 Less Common Clinical Trial Adverse Drug Reactions (<1%)

None observed.

10.4 Abnormal Hematologic and Clinical Chemistry Findings

None observed.

10.5 Post-Market Adverse Drug Reactions

None observed.

11 DRUG INTERACTIONS

11.1 Drug-Drug Interactions

No drug-drug interactions are known to exist.

11.2 Drug-Food Interactions

No drug-food interactions are known to exist. In preparation for imaging with fludeoxyglucose (^{18}F), patients should be in the fasting state.

11.3 Drug-Herb Interactions

No drug-herb interactions are known to exist.

11.4 Drug-Laboratory Interactions

No drug-laboratory interactions are known to exist.

12 ACTION AND CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FDG (^{18}F) is actively transported from blood to tissue in a manner similar to glucose, where it is phosphorylated by hexokinase to FDG (^{18}F)-6-phosphate. As FDG (^{18}F)-6-phosphate is not a substrate for subsequent glycolytic pathways, and has very low membrane permeability, FDG (^{18}F) becomes trapped in tissue in proportion to the rate of glycolysis or glucose utilisation of that tissue. Imaging of the subject using a PET scanner takes advantage of the positron decay of ^{18}F to identify those tissues that have an abnormal accumulation of the radioisotope.

12.2 Pharmacodynamics

FDG (^{18}F), as a glucose analogue, concentrates in cells that rely upon glucose as a primary energy source, or in cells whose dependence on glucose increases under pathophysiologic conditions. ^{18}F-FDG is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to FDG (^{18}F)-6-phosphate by the enzyme hexokinase. Once phosphorylated, it cannot exit the cell as it is not a suitable substrate for dephosphorylation by glucose-6-phosphate. Therefore, within a given tissue or pathophysiological process, the retention and clearance of FDG (^{18}F) reflect a balance involving glucose transporter proteins, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and FDG (^{18}F) transport and phosphorylation, FDG (^{18}F) can be used to assess glucose metabolism.

In comparison to background activity of the specific organ or tissue type, regions of decreased or absent uptake of FDG (^{18}F) reflect the decrease or absence of glucose metabolism. Regions of increased uptake (relative to background) of FDG (^{18}F) reflect greater than normal rates of glucose metabolism.

In cancer, cells are generally characterised by enhanced glucose metabolism partially due to (1) an increase of the glucose transporters, (2) an increase rate of phosphorylation activity, (3) a reduction of phosphatase activity or, (4) a dynamic alteration in the balance among all of these processes. However, glucose metabolism of cancer as reflected by FDG (^{18}F) accumulation shows considerable variability. Depending upon the tumour type, stage and location, FDG (^{18}F) accumulation may be increased, normal or decreased. Also, inflammatory cells can have the same variability of uptake of FDG (^{18}F).

12.3 Pharmacokinetics

Distribution:

FDG (^{18}F) accumulates throughout the body in proportion to glucose metabolism. Due to their high glycolytic rates, the brain and heart generally exhibit the highest accumulations post-prandially, therefore a fasting state is desirable to minimise uptake in these organs. Other tissues that exhibit the potential for moderate glucose metabolic rates and therefore FDG (^{18}F) uptake are the liver, spleen, thyroid, gut and bone marrow. As active skeletal muscle will accumulate FDG (^{18}F), a relaxed state, especially during the initial uptake phase, is important to minimise uptake in these organs. FDG (^{18}F)

has been shown to accumulate in primary and metastatic tumours throughout the body, possibly related to the concentration of glucose transporters in the cell membrane, the tumour proliferation rate, the degree of tumour differentiation, and the number of viable cancer cells present in the tumour.

Metabolism:

Fludeoxyglucose (^{18}F) is phosphorylated to fludeoxyglucose (^{18}F)-6-phosphate by hexokinase, with no further metabolism taking place within the duration of the PET scan.

Excretion:

FDG (^{18}F) is excreted unchanged in the urine (approximately 20 % of the administered activity is excreted within the first 2 hours) therefore the urinary tract can show intense accumulation of FDG (^{18}F). Seventy-five (75) % of the administered activity of FDG (^{18}F) is retained with an effective half-life of 1.83 hours; 19% has an effective half-life of 0.26 hours and the remaining 6 % has an effective half-life of 1.53 hours.

The time to peak concentration is approximately 30 minutes in highly metabolic tissues such as the brain. Since the time to peak concentration depends on the glucose metabolic rate and whole-body clearance of FDG (^{18}F), less metabolically active tissues such as many tumours may not reach peak concentrations until nearly 2 hours. The time also depends on the balance between the uptake of FDG (^{18}F), the clearance of FDG (^{18}F) from the blood and radioactive decay.

Special Populations and Conditions

No data available.

13 STORAGE AND STABILITY

FDG (^{18}F) should be stored upright in a lead shielded container at controlled room temperature. FDG (^{18}F) should be used within 12 hours from calibration.

14 SPECIAL HANDLING INSTRUCTIONS

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

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

PART II: SCIENTIFIC INFORMATION

15 PHARMACEUTICAL INFORMATION

15.1 Drug Substance

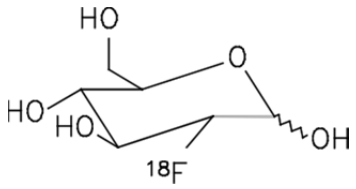
Proper name: Fludeoxyglucose (^{18}F)

Chemical name: 2-deoxy-2-(^{18}F)fluoro-D-glucose

Molecular formula: $C_6H_{11}{}^{18}FO_5$

Molecular mass: 181.26 daltons

Structural formula:



15.2 Product Characteristics

Fludeoxyglucose (^{18}F) Injection is a clear, colorless ready-to-use sterile, pyrogen free solution. Each vial or syringe contains > 0.5 GBq of 2-deoxy-2-[^{18}F]fluoro-D glucose at calibration time. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multiple-dose glass vials or unit-dose syringes and does not contain any preservative.

16 CLINICAL TRIALS

The Thunder Bay Regional Health Research Institute's FDG (^{18}F) was authorized as an Abbreviated New Drug Submission (ANDS). The focus of the ANDS was a physicochemical-based comparison; no clinical trial data were generated and submitted for this product. The Canadian Reference Product (CRP) cited in this ANDS was the Winnipeg Regional Health Authority's fludeoxyglucose (^{18}F).

17 NON-CLINICAL TOXICOLOGY

Fludeoxyglucose (FDG)

Bessell *et al* studied the toxicology of FDG injected intraperitoneally in mice and rats and reported the LD_{50} in mice as 600 mg/kg.

Reivich *et al* studied the toxicology of FDG in mice and dogs. Mice were injected intraperitoneally with FDG (3 weekly doses of 14.3 mg/kg – 3000 times the human dose). No effect was noted on animal weight, no gross or microscopic abnormalities were noted and no immediate or long-term effects were noted. Dogs were injected intravenously with three doses of 0.72 mg/kg and showed no clinical signs or symptoms of adverse effects. No significant abnormalities were detected in the blood, urine or cerebrospinal fluid. No significant gross or microscopic abnormalities were noted in internal organs.

Som *et al* studied the toxicology of FDG in mice and dogs. Mice were injected intraperitoneally with FDG (3 weekly doses of 14.3 mg/kg – 3000 times the human dose). No effect was noted on animal weight and no gross or microscopic abnormalities were noted. Dogs were injected intravenously with three doses of 0.72 mg/kg and no significant abnormalities were detected in the blood, urine or cerebrospinal fluid. No significant gross or microscopic abnormalities were noted in internal organs. No abnormalities of body temperature, blood pressure, pulse or breathing were observed in the dogs.

Acetonitrile, Ethanol, and Kryptofix 222

Potential impurities that have been observed in very small amounts in Fludeoxyglucose (^{18}F) Injection are acetonitrile, and Kryptofix 222 (Kryptofix) and therefore, the potential impact of their presence on product safety was assessed.

The acetonitrile limit for Fludeoxyglucose (^{18}F) Injection follows the ICH Q3C(R3) specification for this residual solvent and thus provides a large safety factor for exposure of the patient to this potentially toxic chemical.

The ethanol limit for Fludeoxyglucose (^{18}F) Injection follows the ICH Q3C(R3) specification for this residual solvent and thus provides a large safety factor for exposure of the patient to this low toxicity chemical.

The acute toxicity of Kryptofix has been evaluated in rats and mice. The LD50 of an intravenous dose in mice was 35 mg/kg and of an intraperitoneal dose was 110 mg/kg. The LD50 of an intravenous dose in rats was 32 mg/kg and of an intraperitoneal dose was 153 mg/kg. Doses of up to 188.25 mg/kg (route not specified) in rats demonstrated transient elevations in liver enzymes but no other histopathological changes were evident. The Kryptofix limit (≤ 50 µg/mL) for Fludeoxyglucose (^{18}F) Injection follows the USP 39 specification and is more than two orders of magnitude below the lethal dose in rodents, delivered intravenously. Thus a more than reasonable safety margin is realised for the (worst case) Kryptofix content in Fludeoxyglucose (^{18}F) Injection based on these assessments.

18 SUPPORTING PRODUCT MONOGRAPHS

Fludeoxyglucose (^{18}F) Injection

Parenteral Solution, > 0.5 GBq/vial

Submission control #: 153940

Winnipeg Regional Health Authority

November 6, 2012

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

FDG (^{18}F)

Fludeoxyglucose (^{18}F) Injection

Read this carefully before you receive FDG. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about FDG.

Serious Warnings and Precautions

- FDG should not generally be administered to pregnant women.
- If you are breastfeeding, breastfeeding can be temporarily interrupted, and close contact between mother and infant minimized, for a period of at least 12 hours following the injection of FDG (^{18}F).

What is FDG used ford:

Fludeoxyglucose (^{18}F) Injection, or ^{18}FDG, is a radioactive drug which is used in conjunction with a diagnostic Positron Emission Tomography (PET) scan to help your physician evaluate your cancer.

How does FDG work?

FDG is a radioactive form of sugar with the radioisotope, Fluorine-18, attached to it. When it is injected into a vein, it is distributed throughout your body. Cancer cells require more sugar to function and, therefore, FDG will concentrate in them. A diagnostic scanning test, called a PET scan, uses the radioisotope in FDG to make whole-body images. These images can help your physician detect the presence and the location of cancer cells within your body.

What are the ingredients in FDG?

FDG contains fludeoxyglucose (^{18}F) and the non-medicinal ingredient sodium citrate.

FDG comes in the following dosage forms:

Injectable solution

Do not use FDG if:

Fludeoxyglucose (^{18}F) Injection should not be used if you are pregnant, are allergic to any component of fludeoxyglucose (^{18}F) injection, or if you are diabetic with uncontrolled blood sugar levels.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive FDG. Talk about any health conditions or problems you may have, including if you:

- are pregnant
- are breast feeding
- are diabetic

Other warnings you should know about:

- Fludeoxyglucose (^{18}F) should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the foetus.
- Fludeoxyglucose (^{18}F) can be passed through breast milk to your nursing infant. Breastfeeding babies can also be exposed to radiation by being held close to the breast. Minimizing close contact between mother and infant, and temporarily interrupting breastfeeding by substituting formula feeding, both for about 12 hours following the FDG(^{18}F) injection, will help avoid unnecessary exposure of your infant to the radiation.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions between fludeoxyglucose (^{18}F) Injection and other drugs, herbal remedies, and food or food products have not been established.

Before taking FDG:

Diabetic patients should ensure that their blood sugar levels are stable the day preceding and the day of the PET scan with fludeoxyglucose (^{18}F).

You may be asked to eat nothing and drink only water for four hours before your scheduled PET scan with fludeoxyglucose (^{18}F).

To decrease the radiation exposure to your bladder, you should drink plenty of water and urinate as often as possible when the PET scan is finished.

What are possible side effects from using FDG?

There are no known side effects with the use of fludeoxyglucose (^{18}F) injection. If you experience any troublesome symptoms unusual effects after receiving fludeoxyglucose (^{18}F) injection, contact your health care professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Keep out of reach and sight of children.

If you want more information about FDG:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website.

This leaflet was prepared by the Thunder Bay Regional Health Sciences Centre, 980 Oliver Rd, Thunder Bay ON P7B 6V4.

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