PRODUCT MONOGRAPH

TRADE NAME

Fludeoxyglucose (^{18}F) Injection

Parenteral Solution, > 0.5 GBq/ vial

Diagnostic Radiopharmaceutical

BC Cancer, part of the Provincial Health Services Authority
600 West 10th Avenue
Vancouver, BC
V5Z 4E6.

Date of Approval:
August 2, 2019

Control #: 227258

Table of Contents

TRADE NAME

Fludeoxyglucose (^{18}F) Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

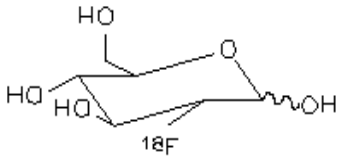
Table 1. Summary Information

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous	Parenteral solution >0.5 GBq / vial	None

DESCRIPTION

Fludeoxyglucose F 18 Injection (^{18}F-FDG) is an intravenous diagnostic radiopharmaceutical for Positron Emission Tomography (PET).

^{18}F-FDG 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:



Fludeoxyglucose F 18 Injection is supplied as a multi-dose (10 mL or 30 mL), sterile, non-pyrogenic injection vial containing a calibrated amount of ^{18}F-FDG in approximately 29 mL of citrate buffer without preservatives. The final product may be diluted with saline to ensure a radioactivity concentration that is suitable for clinical use. The pH of the solution is between 4.5 and 7.5.

Physical Characteristics

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 radionuclide, oxygen-18 (^{18}O). The physical radiation emission data for fluorine-18 are summarised in Table 2.

Table 2. 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

External Radiation

The specific gamma ray constant for flourine-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 3. 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%.

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

Table 3. Radiation Attenuation of 511 keV Photons by Lead Shielding

Lead Shield thickness (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

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

Calibration time (min)	Fraction remaining
120	0.47
240	0.22
360	0.10
480	0.05
540	0.03
600	0.02
720	0.01

INDICATIONS AND CLINICAL USE

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 and restaging; and
- the evaluation of colorectal cancer for recurrence, restaging, and distant metastases.

For lung cancer evaluation, certain thoracic area non-cancerous lesions may show ^{18}F-FDG 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 ^{18}F-FDG 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 ^{18}F-FDG 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 ^{18}F-FDG may be observed in specific lesions including mucinous carcinoma.

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

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing of ingredients, see the *Dosage Forms, Composition and Packaging* section of the product monograph.

WARNINGS AND PRECAUTIONS

Precautions related to the handling of radioactive material must be observed in the handling and utilisation of this product including those concerning radioactive patients. Radiopharmaceuticals should only be used by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans.

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.

^{18}F-FDG 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 ^{18}F-FDG injection 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 PET scan.

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.

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.

Special Populations

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

Pregnant Women: Since 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, this radiopharmaceutical preparation should not be administered to pregnant women unless it is considered that the potential benefits outweigh the potential hazards to the fetus.

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.

Nursing Women: Where an assessment of the risk-benefit ratio suggests the use of this product in nursing women, breast feeding can be temporarily interrupted for at least 12 hours following the PET scan. Formula feeding can be substituted or, when appropriate, milk may be expressed prior to ^{18}F- FDG administration to minimize close contact between the mother and infant to help limit radiation exposure to the infant.

Pediatrics: The safety and effectiveness of fludeoxyglucose (^{18}F) injection in the approved indication have not been established in pediatric patients.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

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.

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

None observed.

Abnormal Hematologic and Clinical Chemistry Findings

None observed.

Post-Market Adverse Drug Reactions

None observed.

DRUG INTERACTIONS

Drug-Drug Interactions

No drug-drug interactions are known to exist.

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.

Drug-Herb Interactions

No drug-herb interactions are known to exist.

Drug-Laboratory Interactions

No drug-laboratory interactions are known to exist.

DOSAGE AND ADMINISTRATION

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.

Dosage

The recommended dose of ^{18}F-FDG 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 ^{18}F-FDG, with sufficient time between doses to allow for substantial decay (both physical and biological) of previous administration(s).

Administration

Patients should not eat or drink (except water) for four hours prior to the administration of ^{18}F-FDG in order to stabilize blood glucose levels. Patients with diabetes should also avoid taking insulin two hours prior to receiving ^{18}F-FDG. To ensure

a stable glycemic state (blood glucose ≤ 10 mmol / L), the patient's blood glucose level should be checked prior to receiving ^{18}F-FDG. 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 ^{18}F-FDG 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.

^{18}F-FDG, 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.

Image Acquisition and Interpretation

The acquisition parameters for imaging with ^{18}F-FDG 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 ^{18}F-FDG. 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 ^{18}F-FDG 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 ^{18}F-FDG in the brain, myocardium, liver, spleen, stomach, intestines, kidneys or urine. Increased or abnormal ^{18}F-FDG uptake can signify neoplasms. Healing surgical wounds, infections, granulomatous tissue, or other inflammatory tissue responses may also show areas of increased ^{18}F-FDG uptake. Practitioners should be appropriately trained in the interpretation of ^{18}F-FDG 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 ^{18}F-FDG concentration levels (approximately 30 minutes), the total administered dose of ^{18}F-FDG, 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 ^{18}F-FDG 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 ^{18}F-FDG.

Instructions for Preparation and Use

The components of the vial 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 during the useful life of the radioactive product.

Directions for Quality Control

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

RADIATION DOSIMETRY

The effective dose following the administration of 5 MBq/kg to a 70 kg adult is 6.6 mSv.

Table 5. 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	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 5 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").

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

^{18}F-FDG is actively transported from blood to tissue in a manner similar to glucose, where it is phosphorylated by hexokinase to ^{18}F-FDG-6-phosphate. As ^{18}F-FDG-6-phosphate is not a substrate for subsequent glycolytic pathways, and has very low membrane permeability, ^{18}F-FDG 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.

Pharmacodynamics

^{18}F-FDG, 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 ^{18}F-FDG-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 ^{18}F-FDG reflect a balance involving glucose transporter proteins, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and ^{18}F-FDG transport and phosphorylation, ^{18}F-FDG 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 ^{18}F-FDG reflect the decrease or absence of glucose metabolism. Regions of increased uptake (relative to background) of ^{18}F-FDG 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 ^{18}F-FDG accumulation shows considerable variability. Depending upon the tumour type, stage and location, ^{18}F-FDG accumulation may be increased, normal or decreased. Also, inflammatory cells can have the same variability of uptake of ^{18}F-FDG.

Pharmacokinetics

Distribution:

^{18}F-FDG 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 ^{18}F-FDG uptake are the liver, spleen, thyroid, gut and bone marrow. As active skeletal muscle will accumulate ^{18}F-FDG, a relaxed state, especially during the initial uptake phase, is important to minimise uptake in these organs. ^{18}F-FDG 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:

^{18}F-FDG 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 ^{18}F-FDG. Seventy-five (75) % of the administered activity of ^{18}F-FDG 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 ^{18}F-FDG, 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 ^{18}F-FDG, the clearance of ^{18}F-FDG from the blood and radioactive decay.

Special Populations and Conditions

No data available.

STORAGE AND STABILITY

^{18}F-FDG should be stored upright in a lead shielded container at controlled room temperature. ^{18}F-FDG should be used within 12 hours from the end of synthesis.

SPECIAL HANDLING INSTRUCTIONS

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

^{18}F-FDG is supplied in a multi-dose, septum-capped, 10 mL or 30 mL glass vial containing >0.5 GBq of no-carrier-added 2-deoxy-2-[^{18}F]fluoro-D-glucose, at end of synthesis, in approximately 29 mL. The final drug product may be diluted with saline to achieve a radioactivity concentration that is suitable for clinical use.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

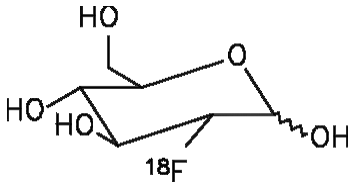
Proper name: Fludeoxyglucose (^{18}F)

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:



Product Characteristics

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

CLINICAL TRIALS

The BC Cancer's ^{18}F-FDG was authorized as an Abbreviated New Drug Submission (ANDS). The focus of the ANDS was a physicochemically-based comparison; no clinical trial data were generated and submitted for this product. The Canadian Reference Product (CRP) cited in this ANDS was Winnipeg Regional Health Authority's Fludeoxyglucose (^{18}F) Injection.[1]

DETAILED PHARMACOLOGY

The hydroxyl group of the second carbon of glucose can be substituted by a group such as hydrogen or fluorine without seriously compromising the kinetic and biochemical ability of the molecule to be actively transported through the cell membrane and to act as a substrate for the hexokinase enzyme. The 2-deoxy analogues of glucose are transported into the cell and metabolized quantitatively exactly like D-glucose up the point in the glycolytic pathway where its anomalous structure prevents the final conversion of the 2-deoxyglucose-6-phosphate by phosphohexoseixomeriase.[2]

Gallagher et al.[3,4] have studied the tissue distribution of ^{18}F-FDG in animals. In mice, ^{18}F-FDG distributes uniformly to the kidneys, heart, brain, lungs and liver initially and clears rapidly from all tissue except the heart where it remains constant for at least two hours and, to a lesser extent, in the brain where it decreases slowly from one to two hours. The rapid clearance of ^{18}F-FDG from the liver, lungs and kidneys, and its retention by the heart and brain is a result of metabolic trapping within

these organs and is reflective of glucose utilisation. Urinary excretion of intact ^{18}F-FDG was 15 to 25% of injected dose at 90 minutes.

Kearfott et al.[5] studied groups of mice (CD-1 strain) and rats (Sprague-Dawley strain) injected intravenous (IV) with tracer amounts of ^{18}F-FDG and sacrificed at 1, 5, 30, 60, and 120 minutes for tissue biodistribution analysis. They also studied two mongrel dogs with imaging at 40 to 80 minutes post IV injection of tracer doses for tissue biodistribution analysis with arterial blood sampling at 0 to 10, 15, 20, 30, 40, 45, 60, and 90 minutes. The dogs were sacrificed at 60 and 120 minutes. Tissue biodistribution (percent of injected dose per gram - %ID/gram) for blood, brain, liver, spleen, lung, heart, kidney, bone, muscle and bladder over the time periods indicated for mice and rats was reported. Tissue biodistribution (percent of injected dose per one percent of body weight - %ID/gram/1%body weight) for blood, brain (left and right hemisphere, cerebellum), liver, spleen, lung, heart (left and right atria and ventricle), kidney, bone, muscle, and bladder wall for the dogs was determined. Tissue pharmacokinetic parameters in heart and brain were estimated.

TOXICOLOGY

Fludeoxyglucose (FDG)

Bessell et al.[6] 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.[7] 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.[8] 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 (18F) 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 (18F) 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.[9] The LD_{50} of an intravenous dose in mice was 35 mg/kg and of an intraperitoneal dose was 110 mg/kg. The LD_{50} 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.[10] The Kryptofix limit ($\leq$ 50 µg/mL) for

Fludeoxyglucose ($_{18}$F) Injection follows the USP 30 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.

REFERENCES

1 Fludeoxyglucose (18F) Injection, Canadian Product Monograph, Date of Preparation September 28, 2012. (Manufacturer: Winnipeg Regional Health Authority. The Great-West Life PET/CT Centre Suite 751, 7th Floor 715 McDermot Avenue Winnipeg, MB R3E 3P4.

2 Pauwels EKJ, Sturm EJC, Bombardieri E, Cleton FJ, Stokkel MPM. Positron-emission tomography with [18F]fluorodeoxyglucose: Part I. Biochemical uptake mechanism and its implication for clinical studies J Cancer Res Clin Oncol 2000;126:549-59.

3 Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan C-N, Wolf AP. Metabolic Trapping as a Principle of Radiopharmaceutical Design: Some Factors Responsible for the Biodistribution of [$_{18}$F] 2-Deoxy-2-Fluoro-D-Glucose. J Nucl Med 1978 Oct; 19(10):1154-61.

4 Gallagher BM, Ansari A, Atkins H, Casella V, Christman DR, Fowler JS, et al. Radiopharmaceuticals XXVII. ^{18}F-Labeled 2-Deoxy-2-Fluoro-D-Glucose as a Radiopharmaceutical for Measuring Regional Myocardial Glucose Metabolism In Vivo: Tissue Distribution and Imaging Studies in Animals. J Nucl Med 1977 Oct; 18(10):990-6.

5 Kearfott KJ, Elmaleh DR, Goodman M, Correira JA, Alpert NM, Ackerman RH, et al. Comparison of 2- and 3-18F-Fluoro-deoxy-D-glucose for Studies of Tissue Metabolism. Int J Nucl Med Biol 1984;11(1):15-22.

6 Bessell EM, Courtney VD, Foster AB, et al. Some in vivo and in vitro antitumor effects of the deoxyfluoro-D-glucopyranoses. Eur J Cancer 1973;9:463-70.

7 Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, Casella V, Fowler J, Hoffman E, Alavi A, Som P, Sokoloff L. The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ Res. 1979 Jan;44(1):127-37.

8 Som P, Atkins HL, Bandoypadhyay D, Fowler JS, MacGregor RR, Matsui K, et al. A Fluorinated Glucose Analog, 2-fluoro-2-deoxy-D-glucose (F-18): Nontoxic Tracer for Rapid Tumor Detection. J Nucl Med 1980 Jul; 21(7):670-5.

PART III: CONSUMER INFORMATION

Fludeoxyglucose (^{18}F) Injection

This leaflet is part III of a three-part "Product Monograph" published when Fludeoxyglucose (^{18}F) Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fludeoxyglucose (^{18}F) Injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
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

What it does:
Fludeoxyglucose (^{18}F) Injection 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, Fludeoxyglucose (^{18}F) Injection will concentrate in them. A diagnostic scanning test, called a PET scan, uses the radioisotope in Fludeoxyglucose (^{18}F) Injection to make whole-body images. These images can help your physician detect the presence and the location of cancer cells within your body.

When it should not be used:
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

What the medicinal ingredient is:
Fludeoxyglucose (^{18}F) (a radioactive form of sugar).

What the important non-medicinal ingredients are:
There are no important non-medicinal ingredients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Because Fludeoxyglucose (^{18}F) Injection is a radio-pharmaceutical, it should be used only by those health professionals who are appropriately qualified in the use of radioactive prescribed substances in or on humans**.**
- **F**ludeoxyglucose (^{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 (18F) 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 PET scan, will help avoid unnecessary exposure of your infant to the radiation.

BEFORE you receive Fludeoxyglucose (^{18}F) Injection talk to your doctor or pharmacist if:

- you have any allergies to the Fludeoxyglucose (^{18}F) Injection or its ingredients
- you have diabetes, as your blood sugar levels may have to be assessed prior having your PET scan with Fludeoxyglucose (^{18}F) Injection
- you think you may be or are pregnant
- you are breast feeding your baby

INTERACTIONS WITH THIS MEDICATION

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

PROPER USE OF THIS MEDICATION

This product will be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

No side effects have been associated with the use of fludeoxyglucose (^{18}F) injection.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

There are no known serious side effects with the use of fludeoxyglucose (^{18}F) injection. If you experience any unusual effects after receiving fludeoxyglucose (^{18}F) injection, contact you doctor or pharmacist immediately. For example, symptoms of an allergic reaction would include rash, hives, itching, or fast heartbeat, nausea and vomiting.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

1. Report online at www.healthcanada.gc.ca/medeffect
2. Call toll-free at 1-866-234-2345
3. Complete a Canada Vigilance Reporting Form and:
   - Fax toll-free to 1-866-678-6789, or
   - Mail to: Canada Vigilance Program
     Health Canada
     Postal Locator 0701D
     Ottawa, ON K1A 0K9

   Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, BC Cancer, part of the Provincial Health Services Authority.

This leaflet was prepared by BC Cancer.

Last revised: August 2, 2019