PRODUCT MONOGRAPH

GLUDEF®

(Fludeoxyglucose F18 Injection)

Solution for Injection containing 185 - 11420 MBq (5 mL unit-dose syringes) and 740 - 90000 MBq (20 mL multi-dose vials) at the date and time of calibration.

Diagnostic agent in conjunction with Positron Emission Tomography (PET)

For Intravenous Use

Bristol-Myers Squibb Medical Imaging
2365 Cote-de-Liesse
Saint-Laurent, Quebec H4N 2M7
Canada

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GLUDEF

(Fludeoxyglucose F18 Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
IV	Solution for Injection, containing 185 - 11420 MBq (5 mL unit-dose syringes) and 740 - 90000 MBq (20 mL multi-dose vials) Fludeoxyglucose (18F) at the date and time of calibration.	Citrate buffer, Normal Saline 0.9% sterile for injection

DESCRIPTION

Physical Characteristics

GLUDEF (fludeoxyglucose F18) is provided as a ready to use, isotonic, sterile, pyrogen-free solution for intravenous injection. The solution is clear, colourless or slightly yellow with a pH between 4.5 and 7.5. GLUDEF is packaged in 5 mL unit-dose syringes and 20 mL multiple dose glass vials and does not contain any preservatives. The fluorine F18 atom in GLUDEF 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 (see Table 1).

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-11026, 89 (1981).

External Radiation

The specific gamma ray constant for fluorine F18 is 6.0 R/hr/mCi (0.3 Gy/hr/kBq) at 1 cm. The half-value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb). A range of values for the attenuation of radiation results from the interposition of the various thickness of Pb. The range of attenuation coefficients for this radionuclide is shown in Table 2. As shown, 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

The fractions remaining at selected intervals after calibration for use in correcting for physical decay of the F18 radionuclide 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

INDICATIONS AND CLINICAL USE

Oncology

Lung Cancer: GLUDEF is indicated for imaging in patients undergoing oncologic diagnostic procedures for the evaluation of single pulmonary nodules (diagnosis).

For lung cancer evaluation, certain thoracic area non-cancerous lesions may show GLUDEF

uptake including acute and chronic infections (such as abscesses, tuberculosis and histoplasmosis), inflammatory/granulomatous conditions (such as sarcoidosis, pleurodesis and bronchiectasis, radiotherapy sites), and atherosclerotic vessels that could mimic tumour accumulation. Absent or less intense relative uptake of GLUDEF may be observed in specific lesions including bronchoalveolar, mucinous and lobular carcinoma as well as carcinoid and fibroadenoma sites.

An understanding of lesion size (such as micrometastases) with respect to ^{18}F-FDG relative accumulation and to PET imaging instrumentation system resolution should also be considered as it has been shown that ^{18}F-FDG PET imaging may have a lower sensitivity in evaluating lesion sizes of less than 1 cm.

CONTRAINDICATIONS

GLUDEF should not be administered to patients who are hypersensitive to fludeoxyglucose F18 or to any ingredient in the formulation or component of the container. For a complete listing of ingredients, see DOSAGE FORMS, COMPOSITION and PACKAGING section.

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.
- GLUDEF should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.
- GLUDEF is excreted in human breast milk. To avoid unnecessary irradiation of the infant,

General

Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

Radiopharmaceuticals including GLUDEF should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and appropriate licences of the competent authorities.

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.

GLUDEF should be stored and handled in adequate shielding in order to protect patients and hospital staff as much as possible. In particular, it is recommended to protect oneself from the effects of beta+ radiation and annihilation photons by using an appropriate shielding when performing withdrawals from the vial and injections.

It is recommended to avoid any close contact between the patient and young children during the initial 12 hours following the injection.

Radiopharmaceuticals should be prepared by the user in a manner that satisfies both radiation safety and pharmaceutical quality requirements.

Carcinogenesis and Mutagenesis

Studies with GLUDEF (fludeoxyglucose F18 Injection) have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Contamination

The following measures should be taken for up to 6 hours after receiving the radiopharmaceutical product: Toilet should be used instead of urinal. Universal precautions normally used for handling blood and urine are adequate to cope with radiation risk.

Special Populations

Diabetes Mellitus

Diabetic patients may need stabilization of blood glucose on the day preceding and on the day of the GLUDEF scan.

Pregnant Women

GLUDEF must not be administered during pregnancy.

There is no clinical experience with the use of [18F]-fludeoxyglucose in pregnant women. No studies of reproductive function have been performed in animals.

When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques that do not involve ionising radiation have to be considered.

Radionuclide procedures carried out on pregnant women involve radiation doses to the fetus.

Administration of GLUDEF (fludeoxyglucose F18 injection) at an activity of 400 MBq results in an absorbed dose to the uterus of 8.4 mGy. In general, a radiation burden to the fetus above the natural radiation exposure should be avoided.

Nursing Women

Fludeoxyglucose F18 is excreted into breast milk. Before administration of GLUDEF to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding. If administration during lactation is unavoidable, breast feeding must be interrupted for at least 12 hours and the expressed milk must be discarded. When appropriate, expressed milk may be drawn off prior to administration of GLUDEF. To avoid unnecessary irradiation of the infant, formula feeding should be substituted temporally for breast feeding. For radioprotection, it is recommended to avoid close contact between the mother and the infant during the initial 12 hours following injection.

Pediatrics

Few clinical data exist regarding the safety and diagnostic efficacy of fludeoxyglucose F18 for patients under 18 years of age. Therefore, use in such patients is not recommended.

Geriatrics

There are no studies on the use of GLUDEF in geriatric patients.

Reduced Kidney Function

In patients with reduced kidney function, a very careful indication is required since an increased radiation exposure is possible in these patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Since the administration of the fludeoxyglucose F18 substance quantity is very low, the major risk for an undesirable effect is caused by the radiation. Exposure to ionising radiation may lead to cancer or development of hereditary defects. Most nuclear medicine procedures involve levels of radiation (effective dose) less than 20 mSv. These effects can be expected with a low probability. After administration of an activity of 400 MBq of fludeoxyglucose F18, the effective dose is about 7.6 mSv.

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.*

Fludeoxyglucose F18 is the most commonly used Positron Emission Tomography (PET) agent and has a long history of safe use in basic research and in clinical settings. The results of two PET radiopharmaceutical studies demonstrating a favorable safety profile are summarized below.

The results of a prospective 4-year study from approximately 70 functioning PET centers including all positron emitting radiopharmaceuticals, primarily ^{18}F-FDG, but also ^{11}C-CO_2, ^{11}C-methionine, ^{13}N-NH_3, and ^{15}O-H_2O were analyzed. A total of 33,925 radiopharmaceutical doses were recorded in a retrospective examination of the records by the 22 participating institutions and the prospective number of administered doses recorded by the participants was 47,876. This represented a total of 81,801 administered doses. No adverse reactions were found from any PET radiopharmaceutical dose. There were no deaths or hospitalizations caused by non-radioactive interventional pharmaceuticals used adjunctive to PET studies.

A review of the PET registry at the Centre Hospitalier Universitaire de Sherbrooke (Canada) revealed that approximately 15,000 doses of fludeoxyglucose F18 were administered between 1998 and 2006, with approximately 8,295 of these administered under a clinical trial setting since 2003. No serious adverse events related to the fludeoxyglucose F18 injection were observed at that site. Four patients experienced a brief vagal reaction shortly after the fludeoxyglucose F18 injection. These effects were considered minor and probably unrelated to the fludeoxyglucose F18 injection and more likely related to the placement of an intravenous needle and the fasting state.

Less Common Trial Adverse Drug Reactions (<1%)

Not observed.

Abnormal Hematologic and Clinical Chemistry Findings

Not observed.

Post-Market Adverse Drug Reactions

Not observed.

DRUG INTERACTIONS

Overview

The administration of glucose or insulin influences the influx of fludeoxyglucose F18 into the cells. In the case of high blood glucose levels as well as low plasma insulin levels, the influx of fludeoxyglucose F18 into organs and tumours is reduced. Therefore, medicinal products that modify blood glucose levels may affect the sensitivity of the fludeoxyglucose F18 examination.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosage

The recommended activity for adults is 280 to 553 MBq depending on the body weight of the patient (usually calculated as 5 MBq per Kg) and the type of camera used.

GLUDEF must be administered by direct intravenous injection. The administered volume is consequently based on the period of time between initial calibration and administration and must be calculated using the appropriate decay correction factors.

The emission scans are usually started 40 to 60 minutes after the injection of fludeoxyglucose (F-18). Provided that the tumour uptake has reached an activity plateau and sufficient activity remains for adequate counting statistics, emission scans can also be performed up to two or three hours after administration, thus reducing background activity.

Administration

The patient dose should be measured by a suitable radioactivity calibration system prior to administration.

The activity of fludeoxyglucose F18 has to be measured with calibrator immediately prior to injection. The injection must be intravenous in order to avoid irradiation as a result of local extravasation as well as imaging artefacts.

Provided a sufficient amount of activity remains for adequate counting statistics, fludeoxyglucose F18 PET can also be performed up to two or three hours after administration, thus reducing background activity. If required, repeated examinations can be carried out on a short notice.

For all patients, the radiation exposure must be justifiable by the expected diagnostic results to be achieved with the lowest possible radiation dose. In addition, it is possible that increased radiation exposure occurs in patients with reduced kidney function.

GLUDEF should be given to sufficiently hydrated patients fasting for a minimum of 4 hours, in order to obtain a maximum enrichment of activity, since glucose uptake in the cells is limited (saturation kinetics). The amount of liquid taken should not be limited, however, **beverages containing glucose must be avoided**.

In order to reduce radiation exposure to the bladder, patients should be encouraged to drink sufficient amounts of fluids and to empty prior to and after the PET examination.

In order to avoid hyperfixation of the tracer in muscle, it is advisable for patients to avoid all strenuous physical activity prior to the examination and to remain at rest between the injection and examination and during acquisition of images. Patients should be comfortably lying down without reading or speaking.

A blood glucose test should be performed prior to administration since hyperglycaemia may result in a reduced sensitivity of GLUDEF, especially when glycaemia is greater than 8 mmol/L. Similarly, GLUDEF should not be administered to patients with uncontrolled diabetes.

Image Acquisition and Interpretation

Infectious and/or inflammatory diseases as well as regenerative processes after surgery can result in a significant uptake of fludeoxyglucose F18 and therefore lead to false positive results.

False positive or false negative fludeoxyglucose F18 results cannot be excluded after radiotherapy within the first 2-4 months.

A delay of at least 4-6 weeks after the last administration of chemotherapy is optimal, in

particular to avoid false negative results. If the patient requires an earlier diagnosis with fludeoxyglucose F18, the reason for earlier fludeoxyglucose F18-PET examination must be reasonably documented. In the case of chemotherapy regimen with cycles shorter than 4 weeks, the fludeoxyglucose F18-PET examination should be done just before re-starting a new cycle.

When applying a coincidence PET (positron emission tomography) scanner system, sensitivity is reduced in comparison to a dedicated PET, resulting in a reduced detection of lesions smaller than 1 cm. It is recommended that fludeoxyglucose F18-PET images should be interpreted in relation with tomographic anatomical imaging modalities (e.g. CT, ultrasonography, MRI).

Instructions for Preparation and Use

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 GLUDEF.

Prior to administration, the GLUDEF packaging container (ie. glass vials, syringes) should be verified and the activity of the solution measured using a calibrator. The product may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection. Withdrawals should be performed under aseptic conditions. The vials must not be opened after disinfecting the stopper and the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle. The solution should also be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

The administration of radiopharmaceuticals creates risks for other people from external radiation or contamination from spills such as urine and vomit. Radiation protection precautions in accordance with national regulations must therefore be taken in these situations. Radioactive waste must be disposed of in conformity with the relevant national and international regulations.

RADIATION DOSIMETRY

Table 4 below shows the dosimetry as calculated according to the ICRP 80 publication.

Table 4: Dose absorbed per unit of activity administered (mGy/MBq)

Organ	Dose (mGy/MBq)	Organ	Dose (mGy/MBq)
Adrenal glands	0.012	Lungs	0.01
Bladder wall	0.160	Muscles	0.011
Bone surfaces	0.011	Oesophagus	0.011
Brain	0.028	Ovaries	0.015
Breasts	0.009	Pancreas	0.012
Bile duct	0.012	Bone marrow	0.011
Intestinal wall	0.011	Skin	0.008
Small intestine	0.013	Spleen	0.011
Colon	0.013	Testes	0.012
Upper Large Intestine (ULI) wall	0.012	Thymus	0.011
Lower Large Intestine (LLI) wall	0.015	Thyroid	0.010
Heart	0.062	Uterus	0.021
Kidneys	0.021	Other organs	0.011
Liver	0.011	**Effective dose (mSv/MBq)**	**0.019**

OVERDOSAGE

Overdoses of fludeoxyglucose F18 Injection have not been reported.

An overdose in the pharmacological sense is unlikely given the doses used for diagnostic purposes. If an overdose of GLUDEF has been administered, the radiation dose delivered to the patient must be reduced by increasing as much as possible the elimination of the radionuclide by forced diuresis and frequent mictions.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

GLUDEF (Fludeoxyglucose F18) is a glucose analog with a unique mechanism of action that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose F18 is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [18F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of fludeoxyglucose F18 reflects a balance involving the glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose, fludeoxyglucose F18 transport and phosphorylation (expressed as the "lumped constant" ratio), fludeoxyglucose F18 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 F18 reflect the decrease or absence of glucose metabolism. Regions of increased uptake of fludeoxyglucose F18 reflect greater than normal rates of glucose metabolism.

Pharmacodynamics

Fludeoxyglucose F18 has no pharmacodynamic effects.

Pharmacokinetics

The pharmacokinetics data indicate that heart and brain (organs with high hexokinase activity) show high activity per gram of tissue. The arterial blood level profile for fludeoxyglucose F18 is described as a triexponential decay curve.

Absorption

Fludeoxyglucose F18 is a glucose analog which accumulates in all cells using glucose as primary source of energy. Approximately 3% of the injected activity is absorbed by the myocardium within 40 minutes.

Distribution

In the first distribution phase, there is a homogenous distribution in kidneys, heart, brain, lung and liver. In all organs, with the exception of heart and brain which show an activity plateau over 1-2 hours, a rapid clearance can be observed. Fludeoxyglucose F18 passes the blood-brain barrier. Approximately 7% of the injected dose is accumulated in the brain within 80-100 minutes after injection. The distribution of fludeoxyglucose F18 in normal heart is mainly

homogenous, however, regional differences of up to 15% are described for the interventricular septum.

Metabolism

Fludeoxyglucose F18 is transported into cells and phosphorylated to [18F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [18F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[18F]fluoro-6-phospho-D-mannose ([18F]FDM-6-phosphate). Epileptogenic foci exhibit a reduced glucose metabolism in the phases free of attacks.

Excretion

Fludeoxyglucose F18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Fludeoxyglucose F18 can be eliminated from the body unchanged in the urine. Clearance from the cardiac tissue may require more than 96 hours. Within 33 minutes, a mean of 3.9% of the administered radioactive dose was measured in the urine. The amount of radiation exposure of the urinary bladder at two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Special Populations and Conditions

Extensive dose range and dose adjustment studies with GLUDEF in normal and special populations have not been completed.

Pediatrics

Few clinical data exist regarding the safety and diagnostic efficacy of fludeoxyglucose F18 for oncologic patients under 18 years of age. Therefore, use in such patients is not recommended.

Geriatrics

There are no studies on the use of GLUDEF in geriatric patients.

STORAGE AND STABILITY

GLUDEF (fludeoxyglucose F18) injection, like all other parenteral products, should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit. GLUDEF preparations containing particulate matter or discoloration should not be administered and 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.

GLUDEF undiluted solutions should be used within 12 hours following the end of synthesis (EOS) and stored at room temperature (15-30^{o}C). The diluted GLUDEF solutions should be used within 8 hours following the end of synthesis (EOS) and stored at room temperature (15-30^{o}C).

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

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Unit-dose syringes:

Each syringe of GLUDEF contains 185-11420 MBq of 2-deoxy-2-[18F]fluoro-D glucose at the end of synthesis (EOS) for an individual dose of 185-740 MBq at injection. The unit-dose syringes also contain 0.1 to 4.0 mL of a citrate buffer solution and 0 to 3.9 mL of sodium chloride (0.9%) solution. The solution does not contain any preservatives.

Multi-dose glass vials:

Each vial of GLUDEF contains 0.74 to 90 GBq of 2-deoxy-2-[18F]fluoro-D glucose at the end of synthesis (EOS). The multi-dose vials also contain 0.1 to 16 mL of a citrate buffer solution and 0 to 15.9 mL of sodium chloride (0.9%) solution. The solution does not contain any preservatives.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name

Fludeoxyglucose F18 Injection

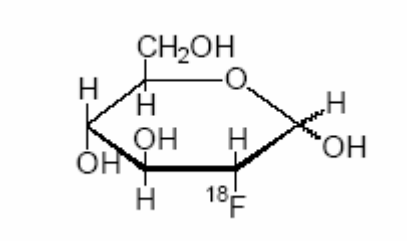
Chemical Name

2-deoxy-2-[^{18}F]fluoro-D-g1ucose

Molecular Formula and Molecular Mass

$C_6H_{11}{}^{18}FO_5$, 181.26 daltons

Structural Formula



Physicochemical Properties

GLUDEF (fludeoxyglucose F18) injection is provided as a ready to use isotonic, sterile, pyrogen free, clear, colorless citrate buffered solution. The pH of the solution is between 4.5 and 7.5.

Product Characteristics

GLUDEF is a solution for injection containing 185 - 11420 MBq (5 mL unit-dose syringes) and 740 - 90000 MBq (20 mL multi-dose vials) at the date and time of calibration. Each undiluted vial and syringe of GLUDEF contains fludeoxyglucose F18 and citrate buffer. Each diluted vial and syringe of GLUDEF contains fludeoxyglucose F18, citrate buffer as well as sterile normal saline (0.9%) for injection.

CLINICAL TRIALS

A clinical trial (BMS-FDG-01) was performed in order to evaluate the diagnostic parameters associated with GLUDEF. These diagnostic parameters were compared with those historically observed for the use of Fludeoxyglucose F18 in the diagnosis of Solitary Pulmonary Nodules. The primary goal of the trial was to determine if the sensitivity of GLUDEF was comparable to that seen in the literature. Secondary goals included evaluation of specificity, positive predictive value, negative predictive value, accuracy and the likelihood ratio.

The cumulative values for diagnostic parameters derived from the literature are estimated using meta-analysis statistical methods. These values were derived from 13 publications which specifically examined Solitary Pulmonary Nodules (7-19).

Table 6, below, describes the demographics of the patient population for the GLUDEF trial.

Table 6 - Summary of patient demographics for BMS-FDG-01

Trial No.	Trial Design	Mean Dose (^{18}F-FDG) / Route of Administration	Trial Subjects	Mean Age (Range)	Gender
BMS-FDG-01	Retrospective, non-randomized clinical trial with blinded reading of ^{18}F-FDG PET data by two independent observers	357 MBq IV	n = 102	64 (39-88)	Male n = 62 Female n = 40

Efficacy

Table 7, below, illustrates that the primary goal of the trial was achieved as GLUDEF was found to have comparable sensitivity to the cumulative results derived from the literature.

Table 7 – Primary Endpoint of Trial BMS-FDG-01

Diagnostic Parameter	GLUDEF (% [95% CI (%)])[2]	Historical[1] (% [95% CI (%)])	P-Value[3]
Sensitivity	96.7 [90.8 – 99.3]	92.8 [88.5-95.6]	0.141

1 Historical values for 18F-FDG used in the diagnosis of Solitary Pulmonary Nodules based on a cumulative analysis of 13 studies (7-19)
2 Exact confidence intervals are reported
3 P-Value based on Z-scores for proportions

The results obtained for the secondary endpoints were affected by the low number of cases with a negative biopsy result (approximately 7%), see Table 8, below. This low number of negative cases did not allow for a precise estimate of specificity or negative predictive value for GLUDEF.

Table 8 - Secondary Endpoints of Trial BMS-FDG-01

Diagnostic Parameter[1]	GLUDEF (% [95% CI])[2]	Historical[3] (% [95% CI])	P-Value[4]
Specificity	33.3 [4.3 – 77.7]	81.8 [73.6 - 87.9]	0.002
PPV	95.7 [89.4 – 98.8]	90.1 [85.9 – 93.1]	0.068
NPV	40.0 [5.3 – 85.3]	85.7 [78.0 – 91.0]	0.001
Accuracy	92.9 [85.8 – 97.1]	89.1 [85.6 – 91.9]	0.219
Likelihood ratio	1.441 [0.821 – 2.556]	N/A	N/A

1 PPV – Positive Predictive Value, NPV – Negative Predictive Value
2 Exact confidence intervals are reported
3 Historical values for 18F-FDG used in the diagnosis of Solitary Pulmonary Nodules based on a cumulative analysis of 13 studies (7-19)
4 P-Value based on Z-score for proportions

Safety

There were no adverse events reported in the trial.

DETAILED PHARMACOLOGY

Pharmacodynamics

Fludeoxyglucose F18 Injection is rapidly distributed to all organs of the body after intravenous administration. After background clearance of fludeoxyglucose F18 Injection, optimal PET imaging is generally achieved between 45 to 60 minutes after administration.

In cancer, the cells are generally characterized by enhanced glucose metabolism partially due to (i) an increase in the activity of glucose transporters, (ii) an increased rate of phosphorylation activity, (iii) a reduction of phosphatase activity or, (iv) a dynamic alteration in the balance among all these processes. However, glucose metabolism of cancer as reflected by fludeoxyglucose F18 accumulation shows considerable variability. Depending on tumour type, stage, and location, fludeoxyglucose F18 accumulation may be increased, normal, or decreased. Also, inflammatory cells can have the same variability of fludeoxyglucose F18 uptake.

Pharmacokinetics

The pharmacokinetics data indicate that heart and brain (organs with high hexokinase activity) show high activity per gram of tissue. In four healthy male subjects receiving an intravenous bolus injection over approximately 30 seconds, the arterial blood level profile for fludeoxyglucose F18 was described as a triexponential decay curve.

Absorption

Fludeoxyglucose F18 is a glucose analog which accumulates in all cells using glucose as primary source of energy. After cell uptake and phosphorylation [18F]-FDG-6-phosphate cannot leave the cell before dephosphorylation. Regions with an increased fludeoxyglucose F18 uptake correlate well with an increased glucose turnover. Regions with a reduced or missing enrichment exhibit a missing glucose turnover. Normal cells usually show an enrichment in the range of the background activity whereas inflammatory cells show an unclear behavioural pattern (reduced, normal, or increased).

Approximately 3% of the injected activity is absorbed by the myocardium within 40 minutes. 0.3% and 0.9-2.4% of the injected activity are accumulated in the pancreas and lung.

Distribution

After an intravenous bolus injection over approximately 30 seconds in healthy volunteers as described above, the arterial blood activity curve of fludeoxyglucose F18 can be described as a triexponential clearance 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 ± 1.1 min, and 80-95 minutes with a mean and STD of 88 ± 4 min.

In the first phase there is a homogenous distribution in kidneys, heart, brain, lung and liver. In all organs with the exception of heart and brain which show an activity plateau over 1-2 hours, a rapid clearance can be observed. The rapid excretion of fludeoxyglucose F18 in liver, lung and kidneys in contrast to the retention in heart and brain is based on the mechanism of metabolic trapping and reflects the glucose utilisation in the different tissues. Since fludeoxyglucose F18 competes with glucose for the cellular transport mechanism (the cellular uptake is proportional to the respective substrate), it is assumed that the cellular fludeoxyglucose F18 uptake is inversely proportional to the blood sugar level.

Fludeoxyglucose F18 passes the blood-brain barrier. Approximately 7% of the injected dose is accumulated in the brain within 80-100 minutes after injection. The distribution of fludeoxyglucose F18 in normal heart is mainly homogenous, however, regional differences of up to 15% are described for the interventricular septum. Fludeoxyglucose F18 is also bound to a lesser extent to ocular muscle, pharynx and intestine. Binding to muscle may be seen following recent exertion and in the event of muscular effort during the examination.

Metabolism

Fludeoxyglucose F18 is transported into cells and phosphorylated to [18F]-FDG-6-phosphate at a rate proportional to the rate of glucose utilization within that tissue. [18F]-FDG-6-phosphate presumably is metabolized to 2-deoxy-2-[18F]fluoro-6-phospho-D-mannose ([18F]FDM-6-phosphate).

Fludeoxyglucose F18 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 F18 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 the cells by passive diffusion.

Excretion

Fludeoxyglucose F18 and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Fludeoxyglucose F18 can be eliminated from the body unchanged in the urine. Clearance from the cardiac tissue may require more than 96 hours. Three elimination phases have been identified in the reviewed literature. 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 two hours post-administration suggests that 20.6% (mean) of the radioactive dose was present in the bladder.

Fludeoxyglucose F18 that is not involved in glucose metabolism in any tissue is excreted in the urine.

TOXICOLOGY

Single Dose Toxicity

The LD50 for 2-deoxy-2-fluoro-D-glucose (FDG) in both mice and rats was determined to be approximately 600 mg/kg. When a single dose of 400 mg/kg of fludeoxyglucose F18 was administered by intraperitoneal injection into male Chester Beatty Wistar rats of approximately 200 g, no morphological changes were observed in the tissues examined.

No toxicity was observed after intravenous injection of up to 200 mg/kg and 100 mg/kg of non radioactive FDG to rats and dogs in single-dose toxicity tests.

Repeat-Dose Toxicity

Mice suffered no immediate or long-term effects. Their weight remained stable and did not differ significantly from that of controls. No gross or microscopic abnormalities were present in the brain, heart, spleen, liver, kidneys or lungs.

No clinical signs or symptoms of adverse effects were observed in the dogs. No significant abnormalities were detected in the blood, urine or cerebrospinal fluid analyses, and no significant gross or microscopic abnormalities were present in the brain, heart, spleen, liver, kidneys, lungs, ovaries or intestines.

Genotoxicity

By deducing the biological effects of fludeoxyglucose F18 from those of Iodine-131 administered at high activity (in average 3.7 GBq), it can be concluded that since I-131 does not induce genetic effects or causes low chromosomal aberrations, F-18 administered at lower activity (0.1 to 0.4 GBq) would not produce mutagenic effects.

The effective dose for 3.7 GBq of I-131 is 407 Sv for only a dose lower than 10 mSv for 370 MBq of fludeoxyglucose F18. Since the effective dose is related to the stochastic effects, it follows that 370 MBq of fludeoxyglucose F18 has no or low mutagenic effects.

Reproductive and Development Toxicity

A study performed on hypoxic pregnant rats showed that in a hypoxic condition, the function of the placenta as a barrier was unpaired. A higher and heterogeneous accumulation of the tracer was observed in the placenta and in the feotal organs compared to normal pregnant rats.

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PART III: CONSUMER INFORMATION
< GLUDEF >
<Fludeoxyglucose F18 Injection>

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

ABOUT THIS MEDICATION

What the medication is used for:
GLUDEF is a diagnostic agent that will allow your doctor to evaluate images obtained during your medical examination. This will help with the diagnosis and treatment of your disease.

What it does:
GLUDEF contains a special glucose or sugar molecule which is in a chemical state referred to as an "excited state". As time goes by, this molecule emits energy which is captured by a camera called a PET camera. This is what allows your doctor to obtain a PET-Scan image of your disease. GLUDEF will be given to you by a healthcare professional using an IV. This is called an injection. This means that a small amount of GLUDEF will be given to you through a needle placed in a vein in your arm. After waiting for approximately 40 to 60 minutes after receiving GLUDEF, a picture of your disease will be taken with the PET camera.

When it should not be used:
GLUDEF should not be used if you are allergic to any of its components or if you have ever had an allergic reaction to GLUDEF. Please see below for a complete listing of the ingredients.
GLUDEF should not be used if you have diabetes and your blood sugar is not controlled.

What the medicinal ingredient is:
The name of the special glucose or sugar molecule in GLUDEF is called "fludeoxyglucose F18".

What the important nonmedicinal ingredients are:
Citrate buffer and Normal Saline 0.9%.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Because GLUDEF is a radiopharmaceutical, it can only be given by doctors and other health professionals who are specially trained and experienced in the safe use and handling of radioisotopes.**
- **GLUDEF should not be given to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.**
- **GLUDEF can be passed into breast milk during nursing. To avoid unnecessary exposure to your baby, formula feeding should be substituted temporarily for breast feeding.**

BEFORE you receive GLUDEF, talk to your doctor or pharmacist if you:

- Have diabetes, as special precautions are needed to assess your blood glucose levels prior to having a PET-scan
- Are allergic to any components of GLUDEF
- Are pregnant or are planning to become pregnant
- Are breastfeeding
- Have reduced kidney function

INTERACTIONS WITH THIS MEDICATION

It is important to tell your doctor if you are taking any other medicines including corticosteroids, valproate, carbamazepine, phenytoin, phenobarbitol and catecholamines. These can all affect the quality of your image scan.

Also tell your doctor if you are undergoing a certain kind of therapy called Colony-Stimulating Factor (CSF) therapy.

PROPER USE OF THIS MEDICATION

GLUDEF will be administered under the supervision of a health professional who is experienced with radiopharmaceuticals, a class of products to which GLUDEF belongs.

It is also important to drink plenty of fluids and to empty before and after your examination. Fluids containing glucose or sugar must be avoided as this can affect the results of your scan.

Patients with diabetes should stabilize their blood glucose levels the day preceding and on the day of the PET-scan.

Should an accidental spill of GLUDEF occur, it is important to notify the appropriate personnel immediately.

It is also recommended that you avoid close contact with young children for a period of 12 hours after you examination.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all other radiopharmaceutical products, GLUDEF can cause side effects. It is important to let your doctor know should you experience any side effects during or after the administration of GLUDEF.

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

Toll-free telephone: 866-234-2345
Toll-free fax 866-678-6789
By email: cadrmp@hc-sc.gc.ca

By regular mail:
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9

NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Bristol-Myers Squibb Medical Imaging at 1-866-463-6267.

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