PRODUCT MONOGRAPH

GLUCOVISION®

[F-18]-Fludeoxyglucose (FDG) Injection

[F-18]-FDG Phosphate, 1 - 540 GBq per batch at EOS

[F-18]-FDG Citrate, 1 - 453 GBq per batch at EOS

Diagnostic Radiopharmaceutical

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Table of Contents

GLUCOVISION®

[F-18]-Fludeoxyglucose (FDG) Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Parenteral solution, 1 - 540 GBq/batch ([F-18]-FDG Phosphate) or 1 - 453 GBq/batch ([F-18]-FDG Citrate) at End of Synthesis	*For a complete listing see Dosage Forms, Composition and Packaging section.*

Glucovision® ([F-18]-Fludeoxyglucose (FDG) Injection) is a sterile, apyrogenic, clear, colourless aqueous solution formulated in 35.2 mg/mL phosphate buffer with 0.275% anhydrous ethanol (USP) or 4.2 mg/mL citrate buffer with 4.5 mg/mL sodium chloride. The pH is 4.5 - 7.5.

DESCRIPTION

Physical Characteristics

Fluorine 18 (F-18) is a radioactive isotope of fluorine. It decays by positron emission yielding two gamma photons at 0.511 MeV (97%) or orbital electron capture (3%). Its physical half-life is 109.8 minutes. [F-18]-FDG (2-Deoxy-2-[F-18]fluoro-D-glucose) is a derivative of D-glucose with the radioisotope F-18 substituted for OH group at C2.

Table 1: Radioactive decay rate of Fluorine 18

Hours	Fraction Remaining	Hours	Fraction Remaining
0	1	10	0.023
1	0.685	11	0.016
2	0.469	12	0.011
3	0.321	13	0.007
4	0.220	14	0.005
5	0.151	15	0.003
6	0.103	16	0.0023
7	0.071	17	0.0016
8	0.048	18	0.0011
9	0.033	19	0.0008

External Radiation

The equilibrium dose (MIRD) constant for Fluorine 18 is:[1]

β, γ	2.71 rads g/μCi-hour	2.03E-13 Gy kg/Bq s
γ only	2.11 rads g/μCi-hour	1.63E-13 Gy kg/Bq s

The specific gamma-ray constant for F-18 is 1.39 x 10^{-4} mGy/MBq/h at 1 metre. The narrow-beam half value layer (HVL) for the 511 keV photons is 4.1 mm lead (Pb) (Table 2).[2] The broad-beam half value layer (HVL) for the 500 keV photons is 5.6 mm lead (Pb) and 3.2 mm tungsten (W).[3]

Table 2: Radiation Attenuation of Narrow Beam 511 keV Photons

Shield Thickness (Pb) mm	Fractional Attenuation
4.1	0.5
8.3	0.25
13.2	0.1
26.4	0.01
41.4	0.001

INDICATIONS AND CLINICAL USE

Glucovision® ([F-18]-FDG Injection) is indicated for use with positron emission tomography (PET) in the following:

- differential diagnosis of isolated indeterminate pulmonary nodules,
- staging of non-small cell lung cancer
- detection of residual or recurrent mass after initial non-small cell lung cancer therapy

For lung cancer evaluation, certain thoracic area non-cancerous lesions may show Glucovision® uptake. These may include 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 Glucovision® 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 [F-18]-FDG relative accumulation and to resolution of PET imaging instrumentation systems should also be considered as it has been shown that [F-18]-FDG PET imaging may have a lower sensitivity in evaluating lesion sizes of less than 1 cm.

Glucovision® will be shipped within the 19 hour shelf life at room temperature in a lead or tungsten shielded container. At the product expiry of 19 hours post-end of synthesis, it may not be possible to obtain the required radioactive dose to image an adult patient. It will be handled according to the Transportation of Dangerous Goods Regulations, with respect to the Handling, Offering for Transport and Transporting of Dangerous Goods (Transport Canada) and the

Packaging and Transport of Nuclear Substances Regulations (Canadian Nuclear Safety Commission).

Glucovision® must be administered by appropriately trained personnel in a licensed facility.

CONTRAINDICATIONS

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

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.
- Glucovision® should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.
- Glucovision® is excreted in human breast milk. To avoid unnecessary irradiation of the infant, formula feeding should be substituted temporarily for breast feeding.[4,5]

General

Glucovision® ([F-18]-FDG Injection) should be administered under the supervision of a health professional who is experienced in the use of radiopharmaceuticals.

Glucovision® 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.

Carcinogenesis and Mutagenesis

Studies with [F-18]-FDG have not been performed to evaluate carcinogenic or mutagenic potential or effects on fertility in human males or females.

Animal reproduction studies have not been performed using [F-18]-FDG. It is not known whether [F-18]-FDG can have adverse effects on the fetus when administered to a pregnant female. Radionuclides administered to a pregnant female also give a dose of radiation to the

fetus. Therefore, [F-18]-FDG should not be administered to a pregnant female unless the potential benefit justifies the potential risk to the unborn fetus (see TOXICOLOGY).

Contamination

The following measures should be taken for up to 6 hours after receiving Glucovision®: Toilet should be used instead of urinal. Toilet should be flushed several times after use. Universal precautions normally used for handling blood and urine are adequate to cope with radiation risk. Special precautions such as bladder catheterisation should be taken following administration to incontinent patients to minimise the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Endocrine and Metabolism

The use of Glucovision® requires particular attention in patients with diabetes mellitus. Hyperglycemia can cause reduction in the uptake of [F-18]-FDG and lead to erroneous diagnosis (see DOSAGE AND ADMINISTRATION).

Peri-Operative Considerations

Foci of inflammation or areas of healing after surgery or radiotherapy also may have high uptake of [F-18]-FDG and it may not be possible to distinguish tumour foci from inflammatory foci.

Special Populations

Pregnant Women: Ideally examinations using radiopharmaceuticals, especially those elective in nature, of women of childbearing capability, should be performed during the first 10 days following the onset of menses.

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 benefits to be gained outweigh the potential hazards to the fetus.

Nursing Women: Where assessment of the risk to benefit ratio suggests the use of Glucovision® Injection in lactating mothers, breast feeding should be suspended for at least 12 hours after the administration of the radiopharmaceutical and the milk expressed during this period should be discarded. Milk may be expressed before the administration of the radiopharmaceutical and saved for use during this period; alternatively formula feeding can be substituted.[4,5]

Pediatrics: The safety and efficacy of Glucovision® in pediatric patients have not been established.

Geriatrics (>65 years of age): There are no known safety or efficacy concerns in the clinical use of Glucovision® in geriatric patients. The clinical studies conducted to demonstrate the efficacy and safety of [F-18]-FDG for the approved indications and clinical uses included geriatric patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

There are no known serious adverse reactions to Glucovision® ([F-18]-FDG Injection). Of 4838 patients injected with [F-18]-FDG from 1996 - 2002, no adverse reactions attributable to the drug were reported. One adverse event experienced by a patient was attributed to a severe vasovagal reaction to IV catheter insertion.

No safety concerns or adverse events occurred in a total of 410 patients studied in retrospective efficacy or prospective safety clinical studies.[6,7]

No [F-18]-FDG adverse events were reported in two publications covering an approximate 20 year period (1980 - 2000); one of these reports included over 80,000 administered doses of PET agents (the majority of which were [F-18]-FDG), while the second report was based on an extensive literature review.[8,9]

Subsequent to these earlier publications, there have been isolated case reports in the literature of adverse events attributed to [F-18]-FDG.[10-12] These adverse events were all hypersensitivity-related and included cutaneous flushing, pruritic body rash, itching, abdominal pain, hypotension, head tremors and chills.

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.

A single-centre retrospective study was conducted with [F-18]-FDG PET imaging in lung neoplasms. A total of 99 patients evaluated were visually observed during PET scan for evidence of adverse events. No adverse events were observed.[6]

A single-centre prospective study was conducted in oncology patients to evaluate the safety of [F-18]-FDG. Three hundred and twelve adult patients and 15 pediatric patients with various types of cancer were evaluated. Patient vital signs (sitting systolic and diastolic blood pressure, and temperature) were measured and patients were visually observed during the PET scan for evidence of adverse events; all adverse events were to be recorded on patient case report forms. No drug-related adverse events were observed and only 3 patients exhibited clinically significant abnormalities with respect to heart rate and body temperature; these abnormalities resolved spontaneously without event.[7]

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

Not applicable.

Abnormal Hematologic and Clinical Chemistry Findings

Not applicable.

Post-Market Adverse Drug Reactions
Isolated reports of hypersensitivity reactions have been reported in the post-market setting .[10-12]
Have emergency resuscitation equipment and personnel immediately available.

DRUG INTERACTIONS

Overview
There are no known serious or life-threatening drug interactions with [F-18]-FDG. Any medication, which could cause a change in blood glucose or metabolic activity of tissues, could affect the sensitivity of the diagnostic test.

Drug-Drug Interactions
No drug-drug interactions are known to exist.

Drug-Food Interactions
Elevated blood glucose levels diminish tumour FDG uptake therefore it is important that patients fast prior to injection.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions
Not applicable

DOSAGE AND ADMINISTRATION

Dosing Considerations

GENERAL POPULATION

- Patients should be studied in the fasting state.
- For scans performed in the morning, the patient should not eat or drink (water is acceptable) from midnight onwards.
- For studies performed in the afternoon, patients may be allowed a light breakfast followed by a 6 hour fast.
- Imaging is usually performed 60 minutes after injection.
- In order to minimize muscular uptake of [F-18]-FDG, the patient should be at rest from the time of injection to the end of imaging.
- Lorazepam 50 μg/kg, sublingually, to a maximum of 2 mg may be administered, 1 hour prior to the procedure, at the discretion of the supervising physician. This will encourage muscular relaxation and reduce muscle uptake.
- Patients should be well hydrated and, where feasible, drink 500 mL of water after injection. Within 10 minutes following administration of [F-18]-FDG Injection, 20 mg of furosemide may be injected. This will promote diuresis and avoid difficulties in the interpretation of activity in the area of the kidneys or ureters.

SPECIAL CONSIDERATIONS

- Insulin dependent diabetics are best studied following a light breakfast and the routine morning administration of insulin.
- There should be a minimum of a 3 hour wait following the last administration of insulin.
- Blood glucose levels should be measured prior to administration of [F-18]-FDG Injection.
- If the serum glucose is elevated arrangements should be made for control of the patient's blood sugar and the study re-booked.
- Oral hypoglycaemic agents may be continued.

Dosage

Dependent upon the camera used for imaging, a dose of 3 - 5 MBq (0.08 - 0.14 mCi) per kilogram of body weight, with a maximum of 370 MBq (10 mCi) is recommended for adults.[6,7,13] The maximum injection volume is 10 mL.

The patient dose should be measured by a suitable radioactivity calibration system prior to administration. If the Standardized Uptake Value (SUV) of FDG is to be calculated, the remaining activity in the syringe must also be measured after delivery of the dose to the patient.

Administration

Glucovision® ([F-18]-FDG Injection) is administered as an intravenous injection via an established intravenous line. The dose should be measured in a suitable dose calibration system, prior to administration.

Instructions for Preparation and Use

Waterproof gloves should be worn when handling this product. Adequate shielding around the vial should be maintained as appropriate and an adequately shielded syringe should be used for administration of the drug product.

Image Acquisition and Interpretation

Images should be acquired with a PET scanner or gamma camera modified for acquisition of 511 keV photons. Image acquisition should begin 60 - 90 minutes following injection over an axial field of view extending from the skull base to the mid abdomen for patients studied to characterize a solitary indeterminate pulmonary nodule; or from the skull base to mid-thigh in patients studied for staging or recurrence of non-small cell lung cancer.

A thorough knowledge of the normal distribution of intravenously administered Glucovision® is essential in order to accurately interpret pathological studies.

The finding of abnormal Glucovision® uptake usually indicates the presence of underlying pathology, either neoplasm or inflammation. Further diagnostic studies may be necessary to determine the exact etiology of zones of abnormal activity.

Directions for Quality Control

The manufacturer will determine the radiochemical purity of the radiopharmaceutical product. A certificate of analysis to document the radiochemical purity of Glucovision® should be obtained from the manufacturer prior to administration to the patient.

RADIATION DOSIMETRY

The absorbed radiation dose to adult humans following an intravenous injection is presented in Table 3. The values presented were published by the International Commission on Radiological Protection (ICRP 2008). The following biokinetic model was used in the calculation of these estimates:[14]

1. There is an initial uptake in heart (0.04), brain (0.08), liver (0.05), lungs (0.03) and all other tissues (0.8).
2. Retention is considered to be infinite, without consideration of a delayed uptake.
3. A fraction of 0.3 of the activity in other organs and tissues is considered to be excreted in urine with biological half-times of 12 minutes (25%) and 1.5 h (75%), according to the kidney-bladder model.

Table 3: Absorbed Dose to Various Organs Due to the Intravenous Administration of [F-18]-FDG (F-18 half-life =1.83 h)[14]

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	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-0l
Bone surfaces	1.lE-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
(Upper large intestine)	1.2E-02	1.5E-02	2.4E-02	3.8E-02	7.0E-02
(Lower large intestine)	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.IE-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	I.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

NOTE: 1 mGy/MBq = 3700 mRad/mCi

Although the absorbed radiation dose estimates in Table 3 include values for pediatric subjects, it should 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

Overdosage of [F-18]-FDG has not been reported. In case of overdose of [F-18]-FDG, elimination should be encouraged by means of increased fluid intake and frequent urination.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

[F-18]-FDG is a radiolabelled analogue of glucose.

The uptake of the drug is determined by the cellular expression of facilitative glucose transporters (GLUT) in the plasma membrane and intracellular hexokinase. Following uptake, hexokinase will catalyze and control the phosphorylation of glucose by ATP to produce glucose-6-phosphate. [F-18]-FDG is utilized in a similar manner to glucose and [F-18]-FDG-6-phosphate is produced. Unlike glucose-6-phosphate, [F-18]-FDG-6-phosphate does not act as a substrate for phosphoglucomutase or phosphohexoseisomerase nor does it inhibit hexokinase activity. [F-18]-FDG therefore accumulates in the tissues where there is high hexokinase activity.

Pharmacodynamics

[F-18]-FDG has no pharmacodynamic effects.

Pharmacokinetics

After intravenous administration of [F-18]-FDG, the activity in the heart and brain increases over a 60 minute time period. The levels of [F-18]-FDG in the other organs or tissues decrease following tri-exponential kinetics. The half-time of the fast phase is about 25 seconds, the intermediate 3.4 minutes and the longer clearance phase from the blood and organs and tissues of low hexokinase activity is longer with a half-life of approximately 47 minutes.[15]

The conventional pharmacokinetic model for [F-18]-FDG uptake employs three compartments; [F-18]-FDG in plasma, [F-18]-FDG in tissue and [F-18]-FDG-6-phosphate in tissue. It only differs from glucose in that glucose-6-phosphate is further metabolized. Kuwabara *et al.* (1990) have suggested that a new model which combines the 2 rate constants of transfer and phosphorylation might be more physiologically meaningful for use in the clinical setting. Nevertheless, the measurement of the rate of [F-18]-FDG and glucose uptake and phosphorylation may be utilized for qualitative as well as quantitative estimations of glucose metabolism in the human.[16]

Absorption & Distribution: The brain receives the highest amount of [F-18]-FDG. The bladder wall receives high doses of radiation. [F-18]-FDG uptake into tumour tissue is directly related to the expression of GLUT1 protein. GLUT1 is expressed at a higher rate in adenocarcinomas and squamous cell carcinomas and at a much lower level in broncholoalveolar carcinoma compared to other types of lung cancer. [F-18]-FDG uptake is much lower in normal lung tissue than in tumour tissue.[15,17-21]

Metabolism & Excretion: [F-18]-FDG is cleared rapidly from the blood and localizes in organs and tissues that have high GLUT expression and hexokinase activity such as the heart, brain, and tumours. It is excreted unchanged via the kidney and the lack of tubular reabsorption results in clinically significant target tissue/ blood ratios. Approximately 30% of activity is excreted in urine at 2 hours post-injection.[15,17,18]

Special Populations and Conditions

Not available.

STORAGE AND STABILITY

Glucovision® ([F-18]-FDG Injection) should be stored upright in a lead or tungsten shielded container at room temperature (15 - 30°C).

Glucovision® has an expiry time of 19 hours post-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.

In the event of a spill of Glucovision® ([F-18]-FDG Injection), the spill should be contained by absorbent material and entrance to the area restricted. Personnel trained in the safe handling of radioactive materials should clean the spill. Materials used in decontamination should be stored in a shielded area until no longer radioactive and then disposed of in regular garbage. Radiation monitoring must demonstrate that radiation readings in the area of the spill have returned to background prior to returning the area to use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Glucovision® ([F-18]-FDG Injection) is a parenteral solution composed of [F-18]-FDG in 35.2 mg/mL phosphate buffer with 0.275% anhydrous ethanol (USP) or 4.2 mg/mL citrate buffer with 4.5 mg/mL sodium chloride. It is packaged in 10 mL or 30 mL sterile multi-dose glass vials, or in 1 mL, 3 mL or 5 mL sterile unit-dose syringes.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

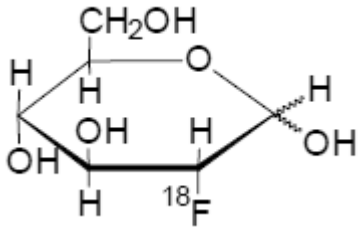
Drug Substance

Proper name: [F-18]-Fludeoxyglucose, [F-18]-FDG

Chemical name: 2-Deoxy-2-[F-18]fluoro-D-glucose

Molecular formula and molecular mass: $C_6H_{11}{}^{18}FO_5$, 181.26 g/mol

Structural formula:



Physicochemical properties: F-18 decays by positron (β^+) emission and has a half-life of 109.8 minutes

Product Characteristics

Glucovision® ([F-18]-FDG Injection) is supplied as a sterile, apyrogenic, clear, colourless aqueous solution in 35.2 mg/mL phosphate buffer with 0.275% anhydrous ethanol or 4.2 mg/mL citrate buffer with 4.5 mg/mL sodium chloride. It contains, at the time of calibration, the radioactive amount of Glucovision® (± 10%) stated on the label. The activity per batch for [F-18]-FDG Phosphate and [F-18]-FDG Citrate is 1 - 540 GBq and 1 - 453 GBq, respectively, at End of Synthesis. [F-18]-FDG Injection does not contain any preservative.

CLINICAL TRIALS

Study demographics and trial design

The following tables summarize the clinical trials that have been conducted by Hamilton Health Sciences using Glucovision®.

Table 4: Summary of Clinical Trials Conducted

Study #	Sponsor	Trial Intent	Study Title	Study Method Summary
Study A[7]	Hamilton Health Sciences	Safety	A Safety Evaluation of [^{18}F]-FDG PET imaging in oncology patients	Open label, retrospective and prospective, single centre safety study in 327 patients with suspected or confirmed malignant disease
Study B[6]	Hamilton Health Sciences	Bridging Efficacy	A retrospective evaluation of [^{18}F]-FDG PET imaging in indeterminate Solitary Pulmonary Nodules	Open Label, retrospective, single-centre bridging efficacy evaluation in 84 patients with solitary pulmonary nodules (85 exams)

Table 5: Summary of Patient Demographics & Dosing for Clinical Trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean Age, (range) in years	Gender
Study A[7]	Retrospective and prospective, single centre safety study	3 MBq/kg (min 110, max 300) FDG, intravenous single dose	327	**Adult** 59.3 (17 – 88) **Pediatric** 12.3 (6 – 16)	**Adult** 165 Male 147 Female **Pediatric** 11 Male 4 Female
Study B[6]	Retrospective, single-centre efficacy study	3 MBq/kg (min 110, max 300) FDG, intravenous, single dose	84	**Evaluable:** 66.79, (24-86) **Non-evaluable:** 65.31, (34-86)	**Evaluable:** 40 Male, 44 Female **Non-evaluable:** 50 Male, 61 Female

Study Results

Safety Results:

The table below summarizes the safety results for Glucovision®.

Table 6: Summary of Safety Results from Clinical Trials

Study # (Name)	Primary Safety Endpoints	Results
Study A[7]	Evaluation of safety by assessment of adverse events and vital signs	Three hundred and twelve (312) adult and fifteen (15) paediatric patients were analyzed for safety. No adverse events were observed. There were no significant changes in vital signs observed in the paediatric patients. Four (4) adult patients (1.3%) exhibited clinically significant changes in vital signs that resolved spontaneously.

Additional support for the safety of Glucovision® was obtained from over 4,838 patients injected with Glucovision® with no adverse reactions observed or reported.

Efficacy Results:

Final efficacy was determined from Study B[6], a retrospective bridging efficacy study.

Table 7: Efficacy Analysis Demographic Summary

Patient Source	Patient Demographics (Tumour Type, Gender, Number)	Primary Efficacy Endpoints
Study B[6]	Eighty-four (84) (40 male, 44 female) patients with solitary pulmonary nodule underwent eighty-five (85) studies that were used for the retrospective analysis.	Evaluation of efficacy by assessment of sensitivity, specificity and accuracy of [F-18]-FDG for detection of solitary pulmonary nodules (SPN), and comparison to appropriate matched literature values.

Diagnostic outcomes were determined on a per scan basis using Glucovision® scan outcome and all applicable clinical information. Sensitivity (ratio of true positive target lesions to total positive target lesions), specificity (ratio of true negative target lesions to total negative target lesions and accuracy (ratio of total correct studies to the total number of target lesions) of Glucovision® PET scans were determined. Confidence intervals (95% CI) for sensitivity, specificity and accuracy were derived using exact binomial calculations (Wilson's method). Statistical comparison to literature values was conducted using a binomial test for a single proportion with a $p < 0.05$ defined as representing a significant difference.

Literature for comparison was selected on the following basis:

- Studies using dedicated PET instrumentation (as opposed to a modified gamma camera)
- Prospective studies published in English reporting on 35 or more patients
- Grade A or B rating for quality according by a grading scheme used by the Veteran's Administration and National Health Services Technology Assessment of PET scanning.
- Study reports PET specificity and sensitivity, and accuracy

Cumulative literature values were calculated from the selected studies. Table 8 shows the overall sensitivity, specificity, accuracy, positive and negative predictive values of Glucovision® PET imaging for the final efficacy analysis population compared to corresponding literature values for solitary pulmonary nodules.

Table 8: Clinical Diagnostic Parameter Results for Lung Cancer (Pulmonary Nodules) for Final Efficacy Analysis

Diagnostic Parameter	Final Efficacy Analysis	Literature Value [n=472]	p-value
Prevalence	57% (46-67)	72% (68-76)	0.0031
Sensitivity	90% (78-96)	88% (84-91)	NS 0.9537
Specificity	81% (66-91)	65% (57-73)	NS 0.0523
Positive Predictive Value	86% (74-93)	87% (83-90)	NS 0.9578
Negative Predictive Value	86% (70.6-94)	68% (60-76)	0.0299*
Accuracy	86% (79-93)	82% (78-85)	NS 0.4360

* Statistical significance based on exact binomial test using $p<0.05$ level of confidence, NS = not significant

The NPV from the HHS 2006 study is statistically significantly higher than the corresponding value from the literature. The potential cause of this difference may be due to the low specificity of the FDG PET imaging that was identified in one study which then influenced the pooled results.

Lung Cancer

The differential diagnosis of benign from malignant pulmonary nodules is an important clinical issue. Most pulmonary nodules are discovered incidentally on chest radiograph or chest computed tomography and 15 - 75% of such nodules are malignant, depending on the population studied. Benign lesions can be classified as non-malignant tumours, infections, inflammatory, vascular or developmental masses. When present, malignancy must be promptly identified and treated in order to improve patient survival. Patients with Stage Ia disease (T1N0M0) have a 61 - 75% 5 year survival following surgical resection; whereas the average patient with lung cancer has a 5 year survival of only 10 - 15%. Strategies that improve the ability to reach a timely and accurate diagnosis of lung cancer and its stage are essential for providing patients with the most appropriate treatment and, when possible, the best opportunity for cure.[22-25]

As shown in Table 8, the overall high sensitivity for Glucovision® (90%) from 85 studies of pulmonary nodules is similar to the supporting clinical literature values (88%). The specificity (81%) is not significantly different than the selected published literature (65%). The overall accuracy of Glucovision® was highly comparable to the literature (86% vs 82%) despite a lower prevalence of disease in the population we studied. These values translate to high positive and negative predictive values of 86% respectively, demonstrating that Glucovision® can be used to reliably judge a SPN as malignant or benign, improving medical treatment decisions.

We have demonstrated that Glucovision® used as diagnostic radiotracer with positron emission tomography has a diagnostic accuracy comparable to [F-18]-FDG produced by other manufacturers in the diagnosis of isolated solitary pulmonary nodules, across a wide variety of pulmonary neoplasms. The literature demonstrates that, in this same group of malignancies,

[F-18]-FDG can be used for both the staging of malignancy and detection of residual or recurrent malignant disease with high sensitivity and specificity.

After lung cancer is diagnosed, accurate staging is essential to enable appropriate treatment decisions to be made. Patients without metastatic lymph nodes (N0 disease) or with only intrapulmonary or hilar nodes (N1) are generally considered operable. Those with ipsilateral (N2) or contralateral (N3) metastatic mediastinal lymph nodes have locally advanced disease and are usually not considered for surgical treatment. Conventional staging procedures (CXR and CT) are imperfect in their ability to spare patients from the morbidity and mortality of stage inappropriate procedures. FDG-PET imaging appears to play a role in improving stage assignment. Three meta-analyses have been published which evaluate the diagnostic accuracy of FDG PET imaging in distinguishing operable (N0/N1) from non-operable (N2/N3) lung cancer. The results of these analyses are shown in Table 9, demonstrating that FDG PET imaging has a high sensitivity and specificity; positive FDG uptake in a lymph node indicates a high likelihood of the presence of malignant nodal involvement and indicates the need for surgical confirmation.

Table 9: Summary of Meta-analyses of Diagnostic Accuracy of FDG PET Scanning for Mediastinal Staging

	Number of Studies (patients)	Parameter Studied	Se (95% CI)	Sp (95% CI)
Gould 2003*[26]	33 (2450)**	N0/N1 vs. N2/N3 or N0 vs. N1/N2/N3	86% (84 – 88)	86% (84 – 88)
Birim 2005*[27]	17 (833)	N0/N1 vs. N2/N3	90% (86 – 95)	90% (86 – 95)
Toloza 2003[28]	18 (1045)	N0/N1 vs. N2/N3	84% (78 – 89)	89% (83 – 93)

*Gould and Birim both report the maximal joint sensitivity and specificity from SROC curves
**Data extracted available only in the on-line version of the paper www.annals.org. Studies reporting with the patient as the unit assessed were utilized.

The literature regarding the detection of extrathoracic metastases by FDG PET has been summarized in a Health Technology Board of Scotland (HTBS) systematic review of 17 observational trials.[29] Subsequently, the National Institute for Clinical Evidence of England (NICE) identified 2 additional papers. From these data the NICE has constructed a summary receiver operator characteristic curve illustrating the distribution of values for the detection of distant metastases. The calculated pooled weighted sensitivities and specificities were calculated to be 93% and 96%. NICE concluded that FDG PET has a high sensitivity and specificity for the detection of extrathoracic disease.

Furthermore the NICE reported on 18 studies which reported the rate of unexpected distant metastases detected and subsequent patient management changes. The studies recruited a combination of patients eligible for radical therapy (surgery: 4 studies, radiotherapy: 1 study, both: 5 studies). An average of 15% of patients had unexpected distant metastases detected by FDG PET (range 8 – 39%), which resulted in management changes (as a result of detected metastases only) in 25% of patients.
After initial therapy for non-small cell lung cancer, early detection of recurrence is important as salvage therapies can both improve longevity and quality of life. Findings on conventional

anatomical imaging (CT and CXR) can be difficult to characterize as surgery or radiotherapy result in distortion of anatomy, fibrotic changes and necrosis which can be difficult to distinguish from disease recurrence. Table 10 provides synthesized diagnostic efficacy parameters from 10 papers published between 1994 and 2006. The joint sensitivity, specificity, positive predictive, and negative predictive value is high at 96%, 85%, 92% and 93% respectively indicating the clinical effectiveness of FDG PET scanning in evaluating the metastatic spread of cancer.

Table 10: Synthesized Diagnostic Accuracy Parameters in the Diagnosis of Lung Cancer Recurrence or Metastasis

Total # Subjects	Prevalence	Accuracy	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
47	64% (60-69)	93% (90-95)	96% (94-98)	85% (79-90)	92% (89-95)	93% (88-96)

In a study of preoperative NSCLC, patients were randomized to either conventional staging with PET-CT (n = 98) or conventional staging alone (n = 91), Fischer *et al.* found that the PET-CT group had significantly fewer thoracotomies (p = 0.004) and that there was a reduction of futile thoracotomies in this group (p = 0.05).[30] In a similar study Van Tinteren *et al.* showed that the addition of FDG PET scanning to the diagnostic workup of patients with suspected NSCLC resulted in a significant reduction of thoracotomies (relative reduction of 51%, 95% CI 32 – 80% ; p = 0.003).[31] In a third study (Maziak *et al.* 2009), patients with early-stage NSCLC were randomized to either PET-CT (n = 170) or conventional staging (n = 167).[32] Disease was correctly upstaged in 23 of 167 patients in the PET-CT group and 11 of 162 in the control group. Thus 13.8% and 6.8% patients were spared surgery in the two groups respectively (difference, 7.0% [95% CI, 0.3 to 13.7%]). Disease was incorrectly upstaged in 8 and 1 recipients in the PET-CT and conventional groups respectively and was incorrectly understaged in 25 and 48 patients respectively (14.9% vs. 29.6%; difference, 14.7% [CI, 5.7 to 23.4%]). These studies provide evidence that FDG PET-CT imaging incorporated into the diagnostic workup of NSCLC patients can have a positive impact on staging of disease.

Thus the combination of clinical trial data and literature analysis establishes the use of Glucovision® in all claimed indications for lung cancer.

DETAILED PHARMACOLOGY

[F-18]-FDG is utilized wherever there is a demand for glucose and where the levels of hexokinase are high. The concentration of [F-18]-FDG in cells relies on the phosphorylation of the 2-fluoro-2-deoxy-D-glucose to 2-fluoro-2-deoxy-D-glucose-6-phosphate that is catalyzed by the hexokinase enzyme (ATP: D-hexose-6-phosphotransferase). The 2-deoxy sugar phosphates are not utilized as substrates for the phosphoglucomutase and phosphohexoseisomerase enzymes and their subsequent conversion to the glucose and fructose 1,6 diphosphate sugars. The hexokinase enzymes provide as a control mechanism for the utilization of glucose as an energy supply, as well as catalyzing its phosphorylation. Glucose-6-phosphate may inhibit the rate of uptake and subsequent phosphorylation of glucose.[33,34]

Sols and Crane showed the affinity for hexokinase by glucose substituted at carbon 2 is relatively unaffected by substitution even with an N-acetylamino at an N-methylamino group.[35] The removal of the –OH at the 2 position has negligible influence on $K_{m.}$ The phosphate ester produced when 2-deoxyglucose is administered is not inhibitory to the hexokinase enzyme nor does it act as a substrate for phosphohexoseisomerase or glucose-6-phosphate dehydrogenase.[35] This development led to the use of [C-14]-2-deoxyglucose measurements of regional cerebral glucose metabolism using autoradiography [36] and the development of [C-11]-2-deoxyglucose for external detection and measurement using PET.[37] It was shown that [C-14]-2-deoxyglucose-6-phosphate concentrations in various parts of the brain could vary during altered stimulus to the brain. These variances related to their known effect of the stimuli.[36] Machado de Domenech and Sols observed that the K_m for the reaction of 2-fluoro-2-deoxyglucose with hexokinase was 0.2 mM in both yeast and animal enzyme preparations.[38] In addition, [F-18]-FDG-6-phosphate did not inhibit its own formation with brain hexokinase. This validates the use of [F-18]-FDG as an indicator of the intensity of energy metabolism in different areas of the brain. The K_m for the substrate (0.2 mM) was confirmed in work by Bessell *et al*.[39] [F-18]-FDG distribution was shown to be similar to [C-14]-2-deoxyglucose in autoradiographic studies on rat tissue.[40] A similarity to the [C-14]-2-deoxyglucose in animal studies supports the prediction that the metabolic trapping of [F-18]-FDG -6-phosphate was responsible for its tissue distribution.[41-43]

[F-18]-FDG organ distribution studies in the mouse showed tissue uptake at 30 min post-injection (p.i.) was 32.7 ± 8.6 %ID/g in the heart, 5.31 ± 0.94 %ID/g in the brain and 3.21 ± 0.43 %ID/g in muscle. All other sites were lower. By 120 minutes p.i., the heart dose was essentially the same, while the brain dose fell to 3.42 ± 0.28 %ID/g and the muscle dose increased to 4.97 ± 0.78 %ID/g.[41] In two dogs, the %ID/organ was approximately 2.8 – 4.1% (60 min p.i.) and 2.4 – 2.5% (135 min p.i.) [heart], and 2.1 (60 min p.i.) and 2.1 – 3.5% (135 min p.i.) [brain].[41] Hexokinase and phosphatase activities were determined in Swiss albino mouse tissue homogenates.[42] Not only did the substitution of the fluorine in the 2-position result in a high rapid uptake in the heart and brain homogenates, but analysis of the urine of the mice in their organ distribution study showed the fluorinated compound was excreted unchanged. This resulted in low blood background radioactivity relative to the high and rapid uptake and radioactivity levels in those organs with high hexokinase activity (e.g. as brain and heart). Since tumour cells also have increased hexokinase activity, the uptake of [F-18]-FDG is significant in tumours with a tumour/tissue ratio as high as 4.6:1 observed.[43] Therefore, [F-18]-FDG will localize in tissue or organs having a high hexokinase activity, will be quickly cleared from the blood unchanged by the kidney resulting in high tissue or organ to blood radioactivity ratios.

TOXICOLOGY

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or the effects on fertility in males and females with Glucovision® ([F-18]-FDG Injection).

As with other radiopharmaceuticals which distribute intracellularly, there may be increased risk of chromosome damage from Auger electrons if nuclear uptake occurs.

[F-18]-FDG shows no known toxic effects at the doses used in humans. Studies with [F-18]-FDG have not been performed to evaluate carcinogenic or mutagenic potential or effects on fertility. At doses of 0.5 – 1 g/kg in rats, deoxyglucose has been shown to inhibit the glycolytic pathway but not cause death.[44,45]

Som *et al.* (1980) investigated the tumor imaging properties and toxicity of [F-18]-FDG in a variety of rodents and mongrel dogs. The toxicity evaluation in mice using 1000 times the human tracer dose of [F-18]-FDG per week for 3 weeks and in dogs using 50 times human tracer dose per week for 3 weeks did not show any evidence of acute or chronic toxicity .[43]

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PART III: CONSUMER INFORMATION
GLUCOVISION®
([F-18]-Fludeoxyglucose (FDG) Injection)

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

ABOUT THIS MEDICATION

What the medication is used for:
Glucovision® (FDG) is used with positron emission tomography (PET scanning) for investigation of the following stages of lung cancer:

- differential diagnosis of isolated indeterminate pulmonary nodules
- staging non-small cell lung cancer
- detecting residual or recurrent mass after initial therapy for non-small cell lung cancer.

What it does:
Glucovision® acts as glucose and goes to malignant cells because these cells have a high glucose uptake rate. Within the malignant cells, Glucovision® breaks down, gets trapped, and then accumulates. The radioactive part of Glucovision® helps the cancer to show on the PET scan.

FDG should be used with PET imaging in cases where it is difficult to diagnose a mass seen on a conventional CT scan and where it is difficult to tell if the mass is cancerous or not. FDG should be used with PET imaging in order to determine the stage of non-small cell lung cancer so that your doctor can determine the appropriate therapy. FDG should also be used with PET imaging to determine whether a surgically removed tumour or a tumour treated with chemotherapy or radiotherapy has any remaining malignant tissue.

When it should not be used:
Glucovision® should not be used if you have had an allergic reaction to it in the past.

Glucovision® should only be used under the supervision of a health professional experienced in the use of radioactive drugs.

Glucovision® should not be used in pregnant women unless the benefits are considered to be greater than the risk to the baby.

What the medicinal ingredient is:
[F-18]-Fludeoxyglucose (FDG)

What the important nonmedicinal ingredients are:
Sodium Phosphate and 0.275% Ethanol in Sterile Water or Sodium Citrate and Sodium Chloride in Sterile Water.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Because Glucovision® 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.**
- **Glucovision® should not be given to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.**
- **Glucovision® can be passed into breast milk during nursing. To avoid unnecessary radiation exposure to your baby, formula feeding should be substituted temporarily for breastfeeding.**

BEFORE you receive Glucovision® talk to your doctor or pharmacist if you:

- have diabetes
- are taking any medication or supplement that changes your blood sugar level or metabolism
- could be pregnant
- are nursing
- have recently had surgery or radiation therapy
- have had an allergic reaction to Glucovision® in the past

- You may experience claustrophobia from being in the PET scanner ring or discomfort from lying on the PET scanner table for up to 60 minutes
- 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.
- Only a toilet (not a urinal) should be used for 24 hours after receiving Glucovision®. The toilet should be flushed several times after use.

INTERACTIONS WITH THIS MEDICATION

No other drugs are known to interact with Glucovision®.

PROPER USE OF THIS MEDICATION

Glucovision® should not be self-administered.

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

You may be asked to fast for 4 to 6 hours (nothing to eat but allowed to drink water) before you have a PET scan with Glucovision®.

Diabetic patients should stabilize their blood glucose levels the day preceding and on the day of the PET scan.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects associated with the use of Glucovision® are very rare. However, allergic reactions with rash, flushing, abdominal pain, low blood pressure, head tremors and chills have been known to occur.

You may experience some mild discomfort or bruising at the site of injection. You will be exposed to radiation contained in Glucovision®. The radiation will be gone from your body in 6 hours. The radiation dose is similar to the amount of the radiation you would receive from a CT scan.

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

If you experience any unusual effects after receiving Glucovision®, contact your doctor or pharmacist. For example, symptoms of an allergic reaction would include rash, hives, itching, flushing, fast heartbeat, abdominal pain, low blood pressure, head tremors, chills, nausea and vomiting.

HOW TO STORE IT

Glucovision® should be stored upright in a lead or tungsten shielded container at room temperature (15 - 30°C)

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:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- 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 0701E
    Ottawa, Ontario
    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, Centre for Probe Development and Commercialization, at:

905-525-9140 extension 21212

or

glucovision@imagingprobes.ca

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