PRODUCT MONOGRAPH

Pr GLUCOVISION™

Fludeoxyglucose F-18

Injection, 3.7-37GBq per vial

Positron Emitting Radiopharmaceutical (PER)

Hamilton Health Sciences Corporation
1200 Main Street West
Hamilton, Ontario
Establishment Licence No. 100479A

Date of Approval:
January 5, 2007

Submission Control No: 096178

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[Pr]GLUCOVISION[TM]

Fludeoxyglucose F-18 Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Parenteral solution, 3.7 to 37 GBq per vial at time of assay	*For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

Physical Characteristics

Glucovision[TM] (Fludeoxyglucose F-18) injection is a sterile, apyrogenic, clear, colourless aqueous solution in 0.9% sodium chloride.

Fluorine-18 (^{18}F) 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 109.7 minutes. Fludeoxyglucose F-18 (2-Deoxy-2-[^{18}F]fluoro-D-glucose) is a derivative of D-glucose with radioisotope ^{18}F substituted for OH group at C2.

Table 1: Radioactive decay rate of Fluorine-18

Radioactive decay rate:			
Hours	**Fraction Remaining**	**Hours**	**Fraction Remaining**
0	1	6	0.1
1	0.68	7	0.07
2	0.47	8	0.05
3	0.32	9	0.03
4	0.22	10	0.02
5	0.15		

External Radiation
The equilibrium dose (MIRD) constant for Fluorine-18 is:

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

The specific gamma-ray constant for Fluorine-18 is 1.39 x 10^{-4} mGy/MBq/h at 1 metre. The half value layer (HVL) for the 511 keV photons is 4.1mm lead (Pb).

Radiation Attenuation of 511 keV Photons by Lead (Pb) Shielding	
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
52.8	0.0001

INDICATIONS AND CLINICAL USE

Glucovision™ (Fludeoxyglucose F-18) injection is indicated for use with positron emission tomography in the:

- differential diagnosis of isolated indeterminate pulmonary nodules,
- staging of non-small cell lung cancer and
- 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 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 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 [^{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.

Distributions will be within 200 Km radius of manufacturing site, in a lead shielded container and will be handled according to the Transportation of Dangerous Goods Regulations, respecting 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).

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.

General

Glucovision™ (Fludeoxyglucose F-18 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 [^{18}F]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 [^{18}F]FDG. It is not known whether [^{18}F]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, [^{18}F]Fludeoxyglucose 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. Universal precautions normally used for handling blood and urine are adequate to cope with radiation risk.

Endocrine and Metabolism
The use of Glucovision™ requires particular attention in patients with diabetes mellitus. Hyperglycemia can cause reduction in the uptake of [^{18}F]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 [^{18}F]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.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview
There are no known adverse reactions to Glucovision™ (Fludeoxyglucose F-18 Injection) injections. Of 4838 patients injected with Fludeoxyglucose F-18 in the period 1996 to 2002, no adverse reactions attributable to the drug were reported. One patient studied for determination of myocardial viability developed chest pain but this was attributed to pharmacological stress testing with intravenous dipyridamole.

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

Silberstein *et al.* studied the adverse reactions from PET radiotracers both retrospectively and prospectively, publishing this data in 1998. The majority of administrations were fludeoxyglucose F-18. No adverse reactions were reported in 81, 801 intravenous administrations.

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 fludeoxyglucose F-18 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.

A single-centre prospective study was conducted in oncology patients to evaluate the safety of fludeoxyglucose F-18. 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 PET scan for evidence of adverse events; all adverse events were to be recorded on patient case report forms. No adverse events were observed and only 3 patients exhibited clinical significant abnormalities with respect to heart rate and body temperature; these abnormalities resolved spontaneously without event.

In the review of all publications presented at a detailed search of FDG PET, there were no reports of adverse events. The Food and Drug Administration's publication on PET products safety and effectiveness (FR, Vol 65, No. 48, March 10, 2000, pp 12999-13010) reports that in their extensive literature review in approving FDG as a diagnostic tool, there were no findings regarding adverse reactions. Furthermore, FDA concludes that in more than 2 decades of clinical use of the drug there have been no reports of adverse events. FDG has been approved by FDA for epilepsy at doses of 185 to 370 MBq (5 to 10 mCi) since 1994, and for detection of abnormal glucose metabolism since 2000. Silbertstein and colleagues (1998) examined 22 PET centers in the US involving a total of almost 82,000 doses of commonly used radiopharmaceuticals and found that there were no adverse events reported or observed.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Not applicable.

Abnormal Hematologic and Clinical Chemistry Findings
Not applicable.

Post-Market Adverse Drug Reactions
Not applicable.

DRUG INTERACTIONS

Overview
There are no known serious or life-threatening drug interactions with Fludeoxyglucose F-18.

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
Patients should be studied in the fasting stage. For scans performed in the morning, the patient should not eat or drink (water acceptable) from midnight. For studies performed in the afternoon, patients may be allowed a light breakfast followed by a 6 hour fast. 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 [^{18}F]Fludeoxyglucose . If the serum glucose is elevated arrangements should be made for control of the patient's blood sugars and the study re-booked. Oral hypoglycaemic agents may be continued.

Imaging is usually performed 60 minutes after injection. In order to minimize muscular uptake of [^{18}F]Fludeoxyglucose 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 at the discretion of the supervising physician, 1 hour prior to the procedure. 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 the [^{18}F]Fludeoxyglucose 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 ureter.

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.

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™ (Fludeoxyglucose F-18) is administered as an intravenous injection via an established intravenous line.

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 to 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™ concentration 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 by facsimile prior to administration to the patient.

RADIATION DOSIMETRY

The absorbed radiation dose to adult humans following an intravenous injection is presented in Table 1. The values presented were published by the International Commission on

Radiological Protection (ICRP) – 53. The following information was used in the calculation of these estimates:

1. The total body retention of ^{18}FDG may be described for dosimetry purposes by a multiexponential function with half-times of 12 minutes (0.075), 1.5 hr (0.225) and infinity (0.70).
2. Fractions of 0.04 and 0.06 are taken up by the myocardium and brain, respectively, with an uptake half-time of 8 minutes and retained for a time which is long in relation to the radioactive half-life of ^{18}F.
3. The residual activity in the total body is assumed to be uniformly distributed amongst all other tissues other than brain and heart.
4. A fraction of 0.3 is assumed to be eliminated by the renal system with half-times of 12 minutes (0.25) and 1.5 hours (0.75).

Table 2: Absorbed Dose to Various Organs Due to the Intravenous Administration of [^{18F}]FDG

ORGAN	**mGy/MBq**	**rad/mCi**
Adrenals	1.4×10^{-2}	5.2×10^{-2}
Brain	2.6×10^{-2}	9.6×10^{-2}
Breasts	1.1×10^{-2}	4.1×10^{-2}
LLI Wall	1.6×10^{-2}	5.9×10^{-2}
Small Intestine	1.3×10^{-2}	4.8×10^{-2}
Stomach	1.2×10^{-2}	4.4×10^{-2}
ULI Wall	1.3×10^{-2}	4.8×10^{-2}
Heart Wall	6.5×10^{-2}	2.4×10^{-1}
Kidneys	2.1×10^{-2}	7.8×10^{-1}
Liver	1.2×10^{-2}	4.4×10^{-2}
Lungs	1.1×10^{-2}	4.1×10^{-2}
Ovaries	1.5×10^{-2}	5.6×10^{-2}
Pancreas	1.2×10^{-2}	4.4×10^{-2}
Red Marrow	1.1×10^{-2}	4.1×10^{-2}
Bone Surfaces	1.0×10^{-2}	3.7×10^{-2}
Spleen	2.2×10^{-2}	8.1×10^{-2}
Testes	1.5×10^{-2}	5.6×10^{-2}
Thyroid	1.3×10^{-2}	4.8×10^{-2}
Urinary Bladder	1.7×10^{-1} ~	6.3×10^{-1} ~
Uterus	2.0×10^{-2}	7.4×10^{-2}
Other tissue	1.1×10^{-2}	4.1×10^{-2}
	mSv/MBq	Rem/mCi
Effective Dose Equivalent	2.7×10^{-2}	10.0×10^{-2}

NOTE: 1 mGy/MBq = 3700 mRad/mCi ~ For 2 hr void time

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

[^{18}F]-Fludeoxyglucose is a radiolabelled analogue of glucose.

The action of the drug is determined by the presence of hexokinase in an organ or tissue and the need for the tissue to utilize sugars for energy. The hexokinase will catalyze and control the phosphorylation of glucose by ATP to produce glucose-6-phosphate. The [^{18}F] 2-fluoro-2-deoxyglucose is utilized in a similar manner to glucose and [^{18}F] 2-fluoro-2-deoxyglucose-6-phosphate is produced. Unlike glucose-6-phosphate, [^{18}F]FDG-6-phosphate does not act as a substrate for phosphoglucomutase or phosphohexoseisomerase nor does it inhibit hexokinase activity. [^{18}F]FDG therefore accumulates in the tissues where there is high hexokinase activity.

Pharmacodynamics

Fludeoxyglucose F-18 has no pharmacodynamic effects.

Pharmacokinetics

After intravenous administration of [^{18}F] 2-fluoro-2-deoxy-D-glucose, the activity in the heart and brain increases over a 60 minute time period. The levels of [^{18}F]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.

The conventional pharmacokinetic model for [^{18}F]FDG employs three compartments; [^{18}F]FDG in plasma, [^{18}F]FDG in tissue and [^{18}F]FDG-6-phosphate in tissue. It only differs from glucose in that glucose-6-phosphate is further metabolized. Kuwabara et al. 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 [^{18}F]FDG and glucose uptake and phosphorylation may be utilized for qualitative as well as quantitative estimations of glucose metabolism in the human.

Absorption & Distribution: The brain receives the highest amount of FDG. The bladder wall receives high doses of radiation. 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. Glut1 expression is much lower in broncholoalveolar carcinoma compared to other types of lung cancer. FDG update is much lower in normal lung tissue than in tumour tissue.

Metabolism & Excretion: It is cleared rapidly from the blood and localizes in organs and tissues that have high 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 radiation is excreted in urine at 2 hours post-injection.

Special Populations and Conditions

Not available.

STORAGE AND STABILITY

Glucovision™ (Fludeoxyglucose F-18) should be stored upright in a lead shielded container at room temperature (between 15°C and 25°C).

Glucovision™ has an expiry time of 10 hours after calibration.

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™ (Fludeoxyglucose F-18), 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™ (Fludeoxyglucose F-18) is a parenteral solution composed of Fludeoxyglucose F-18, sterile water and 10% Sodium Chloride solution. It is packaged in 10 mL or 30 mL sterile multi-dose glass vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

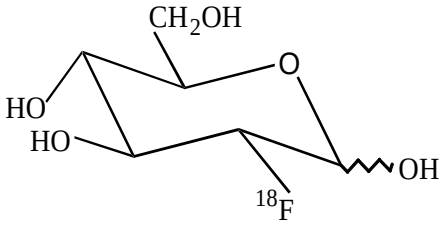
Drug Substance

Proper name: Fludeoxyglucose F-18 Injection

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

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

Structural formula:



Physicochemical properties: pH 4.5 to 7.5; Fluorine-18 decays by positron (β^+) emission and has a half-life of 109.7 minutes

Product Characteristics

[^{18}F]-FDG is supplied as a sterile, apyrogenic, clear, colourless aqueous solution in 0.9% sodium chloride. It contains not less than 95% and not greater than 105% of the labeled amount of ^{18}F expressed in GBq per vial, at time of calibration. The concentration of activity varies from 3.7 to 37GBq/ml . [^{18}F]-FDG 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 3: Summary of Clinical Trials Conducted

Study #	Sponsor	Trial Intent	Study Title	Study Method Summary
Study A	Hamilton Health Sciences	Safety	A Safety Evaluation of [^{18}F]-Fludeoxyglucose 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	Hamilton Health Sciences	Bridging Efficacy	A retrospective evaluation of [^{18}F]-Fludeoxyglucose 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 4:- Summary of Patient Demographics & Dosing for clinical trials

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean Age, (range) in years	Gender
Study A	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	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 5: Summary of Safety Results from Clinical Trials

Study # (Name)	Primary Safety Endpoints	Results
A	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. Three (3) adult patients (1%) 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.

Results of the FDG PET literature review are similar with no reports of adverse events. A review examining 22 PET centers in the US involving a total of almost 82,000 doses of commonly used radiopharmaceuticals with the vast majority of these fludeoxyglucose F-18., found no adverse events reported or observed. The USP DI Product Monograph for Fludeoxyglucose F 18 Systemic also confirms no known adverse events

Efficacy Results:

Final efficacy was determined from the Study B, a retrospective bridging efficacy study.

Table 6: Efficacy Analysis Demographic Summary

Patient Source	Patient Demographics (Tumour Type, Gender, Number)	Primary Efficacy Endpoints
Study B	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 18F-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 7 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 7: Clinical Diagnostic Parameter Results for Lung Cancer (Pulmonary Nodules) for Final Efficacy Analysis

	HHS 2006 (95%CI)	Selected Literature (95% CI)	p-value*
Prevalence	57% (46-67)	72% (68-76)	0.0031*
Sensitivity	90% (78-96)	88% (84-91)	0.9537
Specificity	81% (66-91)	65% (57-73)	0.0523
Positive Predictive Value	86% (74-93)	87% (83-90)	0.9578
Negative Predictive Value	86% (70.6-94)	68% (60-76)	0.0299*
Accuracy	86% (79-93)	82% (78-85)	0.4360

* significant difference 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% to 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% to 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.

As shown in Table 7, 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 ^{18}F- fludeoxyglucose 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, ^{18}F-

fludeoxyglucose 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 8, demonstrating that FDG PET imaging has a high sensitivity and specificity; positive FDG uptake in a lymph indicates a high likelihood of the presence of malignant nodal involvement and indicates the need for surgical confirmation.

Table 8: 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*	33 (2450)**	N0/N1 vs N2/N3 or N0 vs N1/N2/N3	86% (84 – 88)	86% (84 – 88)
Birim 2005 *	17 (833)	N0/N1 vs N2/N3	90% (86 – 95)	90% (86 – 95)
Toloza 2003	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. Subsequently 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 9 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 9: 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
476	64%(60-69)	93%(90-95)	96%(94-98)	85%(79-90)	92%(89-95)	93%(88-96)

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 Fludeoxyglucose Injection is utilized wherever there is a demand for glucose and where the levels of hexokinase are high. The concentration of [^{18}F]-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 unable to be 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 perform as a control mechanism for the utilization of glucose as an energy supply, as well as catalyzing it phosphorylation. Glucose-6-phosphate may inhibit the rate of uptake and subsequent phosphorylation of glucose.

Sols and Crane showed the affinity for the hexokinase by glucose substituted at carbon 2 is relatively unaffected by substitution even with an N-acetylamino at an N-methylamino group. The removal of the –OH at the 2 position has negligible influence on $K_{m.}$ Sols & Crane also observed that 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. This development led to the use of ^{14}C-2-deoxyglucose measurements of regional cerebral glucose metabolism using autoradiography and the development of ^{11}C-2-deoxyglucose for external detection and measurement using PET. It was shown that ^{14}C-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 . 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. In addition, 2-deoxy-2-fluoroglucose-6-phosphate did not inhibit its own formation with brain

hexokinase. This validates the use of [^{18}F]fluoro-2-deoxyglucose as an indicator of the intensity of energy metabolism in different areas of the brain. The K_m for the substrate (0.2mM) was confirmed in work by Bessell et al . [^{18}F]2-fluoro-2-deoxy glucose distribution was shown to be similar to ^{14}C-2-deoxyglucose in autoradiographic studies on rat tissue . A similarity to the ^{14}C-2-deoxyglucose in animal studies supports the prediction that the metabolic trapping of 2-[^{18}F]fluoro-2-deoxy-D-glucose-6-phosphate was responsible for its tissue distribution. Organ distribution studies in the mouse showed the percentage of the injected dose per gram in tissue was 32.7 ± 8.6% in the heart and 5.31 ± 0.43% in the muscle 30 minutes post injection with [^{18}F]2-fluoro-2-deoxyglucose. All other sites were lower. At 60 and 120 minutes post injection, the heart dose per gram in tissue was essentially the same, and the muscle dose slightly higher at 4.01 ± 0.54%, 4.97 ± 0.75%, and 3.42 ± 0.28%. In the dog, the percentage of the dose per organ was shown to be approximately 2.5 – 4% in the heart and 2 – 3.5% in the brain at 60 and 135 minutes respectively post injection. Hexokinase and phosphatase activities were determined in Swiss albino mouse tissue homogenates.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 [^{18}F]2-fluoro-2-deoxyglucose is significant in tumours with a tumour/tissue ratio as high as 4.6:1 observed . Therefore, [^{18}F]2-fluoro-2-deoxyglucose 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 affects on fertility in males and females with Glucovision ^{TM} (Fludeoxyglucose F-18).

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

[^{18}F]2-fluoro-2-deoxy-D-glucose shows no known toxic effects at the doses used in humankind. Studies with [^{18}F]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.

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.

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PART III: CONSUMER INFORMATION
Glucovision™
(Fludeoxyglucose F-18)

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 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:
Fludeoxyglucose F-18

What the important nonmedicinal ingredients are:
0.9% Sodium Chloride, 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.

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

No side effects associated with the use of Glucovision™ have been identified in clinical trials.

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. The risk from this radiation is low and is similar to the risk from smoking 5 cigarettes a day for 30 weeks.

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

There are no known serious side effects associated with the use of Glucovision™.

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, or fast heartbeat, nausea and vomiting.

HOW TO STORE IT

Glucovision™ should be stored upright in a lead shielded container at room temperature (between 15°C and 25°C).

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

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 found by contacting the sponsor, Hamilton Health Sciences Corp., at:

905-521-2100 Extension 75667

Or

glucovision@hhsc.ca

This leaflet was prepared by Hamilton Health Sciences. Corporation.

Last revised: December 19, 2006