PRODUCT MONOGRAPH

CanTrace™

^{18}F-Fluorodeoxyglucose (^{18}F-FDG)

Parenteral Solution, up to 1.4 GBq/mL (38.2 mCi/mL)

Diagnostic Radiopharmaceutical

IPET Pharmaceuticals, Inc.
Suite 880, 1090 West Georgia,
Vancouver, BC V6E 3V7

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CanTrace™

^{18}F-Fluorodeoxyglucose

SUMMARY PRODUCT DESCRIP-TION: Module 3, Section 3.2.P.1.2 and Section 3.2.P.1.3

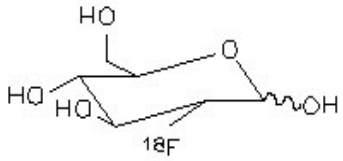
PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Parenteral solution, up to 1.4 GBq/mL	Saline

CanTrace (^{18}F-Fluorodeoxyglucose, ^{18}F-FDG) is a positron emitting radiopharmaceutical containing no-carrier added radioactive 2-deoxy-2-^{18}F-fluoro-D-glucose that is used for diagnostic purposes in conjunction with positron emission tomography (PET). It is administered by intravenous injection.

The chemical name of the active ingredient in CanTrace is 2-deoxy-2-^{18}F-fluoro-D-glucose, which has a molecular formula of $C_6H_{11}{}^{18}FO_5$ with a molecular weight of 181.1 daltons and the following chemical structure:



CanTrace is provided as a ready to use isotonic, sterile, pyrogen-free, clear and colourless solution. Each millilitre contains a calibrated amount of CanTrace and 9 mg of sodium chloride. The pH of the solution is between 4.5 and 7.5. The solution is packaged in a multi-dose glass vial and does not contain any preservatives.

DESCRIPTION

Physical Characteristics

Fluorine-18 decays by positron (β+) emission and has a half-life of 109.7 minutes. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 1).

Table 1 Principal Emission Data for Fluorine 18

Radiation / Emission	Percent per Disintegration	Mean Energy
Positron (β+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

External Radiation

The specific gamma ray constant for fluorine-18 is 0.3 Gy / hr / kBq (6.0 R / hr / mCi) at 1 cm. The lead shielding half value layer (HVL) for the 511 keV photons is 4.1 mm. A range of values for the attenuation of radiation results from the interposition of various thicknesses of lead shielding. The range of attenuation coefficients for this radionuclide is shown in Table 2. For example, the interposition of an 8.3 mm thickness of lead shielding, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 2 Radiation Attenuation of 511 keV Photons by Lead Shielding

Lead Shield Thickness (mm)	Coefficient of Attenuation
0	0.00
4.1	0.50
8.3	0.25
13.2	0.10
26.4	0.01
52.8	0.001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 3.

Table 3 Physical Decay Chart for Fluorine-18

Minutes	Fraction Remaining
0*	1.00
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250
440	0.060

*Calibration Time

INDICATIONS AND CLINICAL USE

INDICATIONS AND CLINICAL USE: Module 2, Section 2.7.3 and NON Response, March 31, 2006

CanTrace is indicated for:

Breast cancer: Evaluation of recurrence / residual disease, distant metastases (staging / restaging), and disease / therapeutic monitoring

Colorectal cancer: Evaluation of recurrence / restaging, distant metastases and disease / therapeutic monitoring.

Lung cancer: Evaluation of single pulmonary nodules (diagnosis), staging, distant metastases, recurrence / restaging, and disease / therapeutic monitoring.

For breast and lung cancer evaluation, certain thoracic area non-cancerous lesions may show CanTrace 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 CanTrace may be observed in specific lesions including bronchoalveolar, mucinous and lobular carcinoma as well as carcinoid and fibroadenoma sites.

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

General

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

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

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

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

Contamination

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

Special precautions such as bladder 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.

DIABETES MELLITUS:
Module 5, Section 5.3.5.1

Special Populations

Diabetes Mellitus

Diabetic patients may need stabilisation of blood glucose on the day preceding and on the day of the CanTrace scan.

PREGNANT $ NURSING WOMEN:
Hicks RJ et al, J Nucl Med 2001; Aug: 42 (8): 1238-42
Hamblen SM, Lowe VJ, J Nucl Med Technol 2003; 32:3-10

Pregnant Women:

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

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 outweigh the potential hazards to the fetus.

Nursing Women:

Where an assessment of the risk to benefit ratio suggests the use of this product in nursing women, formula feeding should be substituted for breast feeding.

Pediatrics (< 16 years of age):

The safety and efficacy of CanTrace in pediatric patients have not been established.

Geriatrics (> 65 years of age):

There are no known limitations on the clinical use of CanTrace in geriatric patients.

ADVERSE REACTIONS

ADVERSE DRUG REACTION OVERVIEW: Module 2, Section 2.7.4

Adverse Drug Reaction Overview

Reviews of the clinical literature and clinical trial data did not reveal any reported adverse reactions.

CLINICAL TRIAL ADVERSE DRUG REACTIONS: Module 2, Section 2.7.4.2, Module 5, Section 5.3.5.1 and Section 5.3.5.2 and NON Response, March 31, 2006

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.

Four clinical trials were conducted in a variety of cancer patients and a total of 205 patients were evaluable for safety. No adverse reactions have been observed. CanTrace has also been used in approximately 1500 patients encompassing various cancer types. No CanTrace product related adverse reactions have been observed.

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

None known.

ABNORMAL HEMATOLOGIC AND CLINICAL CHEMISTRY FINDINGS: Module 2, Section 2.7.4.3 and NON Response, March 31, 2006

Abnormal Hematologic and Clinical Chemistry Findings

Evaluation of ten (10) patients in the Safety Study found no significant changes observed in patient haematology or blood chemistry due to CanTrace injection.

Post-Market Adverse Drug Reactions

None known.

DRUG INTERACTIONS

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbs have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

DOSAGE:
Module 5, Section 5.3.5.1

Dosage

Patient dose guidelines are in the 370 to 555 MBq (10 to 15 mCi) range. Patients whose weight is greater than 50 kg and less than 100 kg have an intermediate dose calculated by:

Dose in MBq = {[(Wt in kg – 50 kg) / 50 kg] x 185} + 370
Dose in mCi = {[(Wt in kg - 50 kg) / 50 kg] x 5} + 10

Therefore, the minimum dose is 370 MBq (10 mCi) for those 50 kg and below and the maximum dose is 555 MBq (15 mCi) for those whose weight is 100 kg or greater.

Fasting serum glucose will be required to rule out uncontrolled diabetes. Blood glucose should be stabilised in non-diabetic patients by fasting before CanTrace administration. Diabetic patients may need stabilisation of blood glucose on the day preceding and on the day of the CanTrace PET scan.

Administration

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

IMAGE ACQUISITION AND INTERPRETATION:
Module 5, Section 5.3.5.1

Image Acquisition and Interpretation

Whole body images can be made using a suitable PET imaging device. Concurrent transmission images should be collected for image attenuation correction. The images should be analysed in all orthogonal planes using standard workstations.

As with all diagnostic radiopharmaceuticals, only experienced nuclear medicine physicians should interpret CanTrace PET images. Physicians should be aware of patient preparation anomalies (such as marginally acceptable blood glucose level and heightened anxiety state), relevant patient history (such as current health condition, previous / concurrent drug, surgical and radiation treatment as well as menstrual / lactation status in females) and be familiar with the normal and condition-specific physiological and anatomical variants of ^{18}F-FDG biodistribution

(such as specific muscular activity and localized trauma). CanTrace image interpretation also needs to consider potential imaging artefacts (such as patient motion during scanning and bodily metallic objects / implants).

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.

Instructions for Preparation and Use

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

Directions for Quality Control

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

DIRECTIONS FOR QUALITY CONTROL:
Module 3, Section 3.2.P.5

RADIATION DOSIMETRY

RADIATION DOSIMETRY:
Module 2, Section 2.7.2.1

Final Dose Estimates for ^{18}F-FDG administered by intravenous injection:

ORGAN	mGy / MBq	rad / mCi
Adrenals	0.014	51
Brain	0.026	96
Small Intestine	0.013	48
Heart	0.065	240
Kidneys	0.021	77
Liver	0.012	44
Lungs	0.011	41
Ovaries	0.015	55
Pancreas	0.012	44
Red Marrow	0.011	41
Spleen	0.012	44
Testes	0.015	55
Thyroid	0.0097	36
Urinary Bladder Wall	0.17	629
Uterus	0.02	74
Other tissue	0.011	41

Effective Dose: 0.027 mSv / MBq; 0.1 rem / mCi

Radiation dose estimates are based on standardised MIRD protocols and assumptions.

OVERDOSAGE

Cases of overdose are not known to have occurred with CanTrace. In case of overdose, the patient should be monitored for adverse drug reactions and managed as clinically indicated.

ACTION AND CLINICAL PHARMACOLOGY

MECHANISM OF ACTION:
Module 2, Section 2.4.2

Mechanism of Action

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

PHARMACODYNAMICS:
Module 2, Section 2.6.2 and Section 2.6.4

Pharmacodynamics

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

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

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

Pharmacokinetics

Absorption:

CanTrace is only intended for use via intravenous injection.

DISTRIBUTION:
Module 2, Section 2.6.4, Section 2.7.2.2

Distribution:

^{18}F-FDG accumulates throughout the body in proportion to glucose metabolism. Due to their high glycolytic rates, the brain and heart generally exhibit the highest accumulations post-prandially, therefore a fasting state is desirable to minimise uptake in these organs. Other tissues that exhibit the potential for moderate glucose metabolic rates and therefore ^{18}F-FDG uptake are the liver, spleen, thyroid, gut and bone marrow. As active skeletal muscle will accumulate ^{18}F-FDG, a relaxed state, especially during the initial uptake phase, is important to minimise uptake in these organs. ^{18}F-FDG has been shown to accumulate in primary and metastatic tumours throughout the body possibly related to the degree of tumour differentiation, the number of viable cancer cells present in the tumour, tumour proliferation rate and to the concentration of glucose transporters in the cell membrane.

METABOLISM:
Module 2, Section 2.6.2

Metabolism:

^{18}F-FDG is phosphorylated to ^{18}F-FDG-6-phosphate by hexokinase, with no further metabolism taking place throughout the remainder of the study.

EXCRETION:
Module 2, Section 2.6.2, Section 2.6.4, and Section 2.7.2.2

Excretion:

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

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

Special Populations and Conditions

No data available.

STORAGE AND STABILITY

Store at room temperature. Store upright in a lead shielded container. Use within 8 hours from the time of calibration.

STORAGE AND STABILITY:
Module 3, Section 3.2.P.8 and NON Response, March 31, 2006

SPECIAL HANDLING INSTRUCTIONS

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING:
Module 3, Section 3.2.P.1 and Section 3.2.P.7

DOSAGE FORMS, COMPOSITION AND PACKAGING

Supplied in a multi-dose, septum capped, 30 millilitre (mL) glass vial containing up to 18.5 GBq (500 mCi) of no carrier added 2-deoxy-2-^{18}F-fluoro-D-glucose, at end of synthesis, in approximately 13 mL (up to 1.4 GBq/mL or 38.2 mCi/mL) of normal saline.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

PHARMACEUTICAL INFORMATION:
Module 3, Section 3.2.P.1

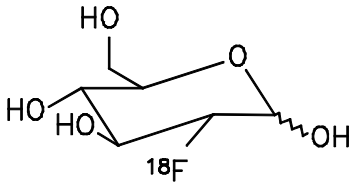
Drug Substance

Proper name: ^{18}F-fluorodeoxyglucose, ^{18}F-FDG

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

Molecular formula and molecular mass: $C_6H_{11}{}^{18}F\,O_5$, MW = 181.1

Structural formula:



Product Characteristics

CanTrace is a clear colourless solution contained in a multi-dose, septum capped, 30 mL glass vial containing up to 1.4 GBq / mL (up to 38.2 mCi / mL) of no carrier added 2-deoxy-2-^{18}F-fluoro-D-glucose, at end of synthesis, in approximately 13 mL.

The radionuclide present in the drug product is fluorine-18 (^{18}F), which decays by positron (β+) emission and has a half-life of 109.7 minutes. The principal photons useful for diagnostic imaging are the 511 keV gamma photons, resulting from the interaction of the emitted positron with an electron (Table 4).

Table 4 Principal Emission Data for Fluorine 18

Radiation / Emission	Percent per Disintegration	Mean Energy
Positron (β+)	96.73	249.8 keV
Gamma (±)*	193.46	511.0 keV

*Produced by positron annihilation

The specific gamma ray constant for fluorine-18 is 0.3 Gy/hr/kBq (6.0 R/hr/mCi) at 1 cm. The lead shielding half value layer (HVL) for the 511 keV photons is 4.1 mm. A range of values for the attenuation of radiation results from the interposition of various thicknesses of lead shielding. The range of attenuation coefficients for this radionuclide is shown in Table 5. For example, the interposition of an 8.3 mm thickness of lead shielding, with a coefficient of attenuation of 0.25, will decrease the external radiation by 75%.

Table 5 Radiation Attenuation of 511 keV Photons by Lead Shielding

Lead Shield Thickness (mm)	Coefficient of Attenuation
0	0.00
4.1	0.50
8.3	0.25
13.2	0.10
26.4	0.01
52.8	0.001

For use in correcting for physical decay of this radionuclide, the fractions remaining at selected intervals after calibration are shown in Table 6.

Table 6 Physical Decay Chart for Fluorine-18

Minutes	Fraction Remaining
0*	1.00
15	0.909
30	0.826
60	0.683
110	0.500
220	0.250
440	0.060

*Calibration Time

The specific activity of no carrier added ^{18}F-FDG has been calculated to be 62.9 Mbq / pmol or 347.8 Mbq / ng (1.7 mCi / pmol or 9.4 mCi / ng) with a total calculated amount of ^{18}F-FDG present as 151.5 pmol or 27.7 ng per vial at a concentration of approximately 2.1 ng / mL or 11.6

pmol /mL. Sodium chloride is present in the solution at a concentration of approximately 9.0 mg/mL in Sterile Water for Injection.

CLINICAL TRIALS:
Module 2, Section 2.5.4, Section 2.5.5, Section 2.7.3 and Section 2.7.4
Module 5, Section 5.3.5.1 and Section 5.3.5.2 and NON Response, March 31, 2006

CLINICAL TRIALS

Study demographics and trial design

The following tables summarise the clinical trials that have been conducted by International P.E.T. Diagnostics Inc. for CanTrace.

Table 7 Summary of Clinical Trials Conducted

Study # (Name)	Trial Intent	Study Title	Study Method Summary
1 (Safety Study)	Safety	Safety of 2-[F-18]fluoro-2-deoxy-D-glucose PET Imaging in Patients with Malignant or Potentially Malignant Neoplasms	Open label, single site, safety evaluation in 10 patients with suspected or confirmed malignant disease.
2 (Bridging Study)	Safety and Bridging Efficacy	18-Fluorodeoxyglucose Positron Emission Tomography in Staging Primary and Metastatic Tumours	Open label, single site, bridging efficacy evaluation in 75 patients encompassing seven cancer types (non-small cell lung cancer, head and neck cancer, recurrent colorectal cancer, lymphoma, melanoma, breast cancer or sarcoma.
3 (Treatment Study)	Safety and Patient Management / Treatment Study	18 – Fluorodeoxyglucose Positron Emission Tomography: Safety and Impact on Patient Management in Detecting and Evaluating Malignant or Potentially Malignant Tissue	Open label, single site, patient management effect evaluation encompassing ten cancer types (lung, breast, gastrointestinal, genitor-urinary (excluding prostate), head and neck, sarcoma, lymphoma, melanoma, gynaecological or brain). This study is currently ongoing.

Table 7 (continued)

Study # (Name)	Trial Intent	Study Title	Study Method Summary
4 (Retrospective Study)	Efficacy	A Retrospective Study of CanTrace™ (^{18}F-FDG) Diagnostic Imaging in Patients with Solitary Pulmonary Nodules, Recurrent Breast Cancer and Recurrent Colorectal Cancer	Retrospective efficacy analysis of 191 patients with SPN, recurrent breast cancer and recurrent colorectal cancer taken from the Treatment Study and Other protocol eligible patients

Table 8 Summary of Patient Demographics for Clinical Trials

Study # (Name)	Trial design	Dosage, route of administration and duration	Number of Subjects	Mean age (Range)	Gender
1 (Safety Study)	Open label, single site, safety evaluation in 10 patients with suspected or confirmed malignant disease.	Patients were given a dose of 10.2 to 14.8 mCi of CanTrace by intravenous injection followed by a PET scan.	10	62 (48-79)	Male: 6 Female: 4
2 (Bridging Study)	Open-label, Phase II/III bridging study for evaluating efficacy of CanTrace in patients with one of seven types of suspected or confirmed malignant disease.	Patients were given a dose of 10.1 to 15.6 mCi of CanTrace by intravenous injection followed by a PET scan.	75	55 (16-81)	Male: 39 Female: 36
3 (Treatment Study)	Open label, Phase II study for evaluating patient management effect of CanTrace in patients with one of ten types of suspected or confirmed malignant disease.	Patients were given a nominal dose of 10 to 15 mCi of CanTrace by intravenous injection followed by a PET scan.	Study ongoing	Study ongoing	Study ongoing

Table 8 (continued)

Study # (Name)	Trial design	Dosage, route of administration and duration	Number of Subjects	Mean age (Range)	Gender
4 (Retrospective Study)	Open-label retrospective analysis for the evaluation of efficacy of CanTrace in select patients.	Treatment Study patients received a dose of 9.5 to 15.8 mCi of CanTrace by intravenous injection followed by a PET scan. Other Protocol Eligible patients received a dose of 7.7 to 15.7 mCi of CanTrace by intravenous injection followed by a PET scan.	Treatment Study: 124 Other Protocol Eligible patients: 67 Total: 191	Treatment Study: 63 (28 to 87) Other Protocol Eligible patients: 66 (42 to 87) Total: 60 (28 to 87)	Treatment Study: Male: 66 Female: 58 Other Protocol Eligible patients: Male: 0 Female: 67 Total: Male: 66 Female: 125

Study results

Safety results:

Table 9 summarises the results of the safety analysis for CanTrace.

Table 9 Summary of Safety Results from Clinical Trials

Study # (Name)	Primary Safety Endpoints	Results
1 (Safety Study)	Evaluation of safety by assessment of adverse events, vital signs, haematology and blood chemistry before and after ^{18}F-FDG injection.	Ten (10) patients were analysed for safety. No adverse reactions observed or reported and no significant changes observed in patient vital signs, haematology or blood chemistry due to CanTrace injection.
2 (Bridging Study)	Evaluation of safety by assessment of adverse events and vital signs.	Seventy-five (75) patients were analysed for safety. No adverse reactions were observed or reported and no significant changes observed in patient vital signs due to CanTrace injection.
3 (Treatment Study)	Evaluation of safety by assessment of adverse events and vital signs.	One hundred and twenty (120) patients were analysed for safety. No adverse reactions were observed or reported and no significant changes observed in patient vital signs due to CanTrace injection.

Additional support for the safety of CanTrace was obtained from over 1500 patients administered PET scans in an open study of various cancer types, in whom no adverse reactions were observed or reported. A study of over 80,000 ^{18}F-FDG injections[a] and the USP DI Product Monograph for Fludeoxyglucose F 18 Systemic[b] confirm that there are no known side/adverse effects associated with the use of ^{18}F-FDG establishing its safety profile.

Efficacy Results:

Final efficacy was determined from the Bridging Study and the Retrospective Study (with patients taken from the Treatment Study and Other Protocol Eligible patients) as described in Table 10.

Table 10 Final Efficacy Analysis Demographic Summary

Patient Source:	Patient Demographics (Tumour Type, Gender and Number)	Primary Efficacy Endpoints
2 (Bridging Study)	Eleven (11) (8 male, 3 female) with SPN, thirteen (13) (all female) with recurrent breast cancer and ten (10) (5 male, 5 female) with recurrent colorectal cancer for a total of thirty-four (34) patients were used for the retrospective analysis.	Evaluation of efficacy by assessment of sensitivity, specificity and accuracy of ^{18}F-FDG for detection of solitary pulmonary nodules (SPN), recurrent breast cancer and recurrent colorectal cancer compared to appropriate matched literature values.
3 (Treatment Study)	Seventy-one (71) (37 male, 34 female) with SPN and fifty-three (53) (29 male, 24 female) with recurrent colorectal cancer for a total of one hundred and twenty-four (124) patients were used for the retrospective analysis.	
4 (Retrospective Study)	Sixty-seven (67) (all female) with recurrent breast cancer (Other Protocol Eligible Patients) for a total of sixty-seven (67) patients were used for the retrospective analysis.	

Diagnostic outcomes on a per patient basis were determined using CanTrace 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 CanTrace PET scans obtained were determined. Confidence intervals (95% CI) for sensitivity, specificity and accuracy were derived using the exact binomial calculations. Statistical comparison to the indication matched literature values (obtained from appropriate meta-analyses) was conducted using an exact binomial test.

Table 11 shows the overall sensitivity, specificity and accuracy of CanTrace PET imaging for the final efficacy analysis population compared to corresponding literature values for each indication.

Table 11 Clinical Diagnostic Parameter Results for Lung, Recurrent Breast and Recurrent Colorectal Cancer for Final Efficacy Analysis

Indication	Diagnostic Parameter	Literature Value	Retrospective Analysis Value	Statistical Significance*
Recurrent Breast Cancer	Sensitivity	83.1% (79.8-86.0) [n=592]	91.1% (80.4-97.0) [n=56]	p = 0.9496 Not Significantly Different
	Specificity	85.2% (81.8-88.2) [n=513]	87.5% (67.6-97.3) [n=24]	p = 0.5976 Not Significantly Different
	Accuracy	84.1% (81.8-86.2) [n=1105]	90.0% (81.2-95.6) [n=80]	p = 0.9294 Not Significantly Different
Recurrent Colorectal Cancer	Sensitivity	94.9% (92.8-99.5) [n=603]	92.6% (82.1-97.9) [n=54]	p = 0.2183 Not Significantly Different
	Specificity	81.8% (75.9-86.7) [n=214]	88.9% (51.8-99.7) [n=9]	p = 0.6719 Not Significantly Different
	Accuracy	91.4% (89.3-93.3) [n=817]	92.1% (82.4-97.4) [n=63]	p = 0.5500 Not Significantly Different
Lung Cancer (Pulmonary Nodules)	Sensitivity	94.5 (92.9-95.9) [n=965]	100% (95.8-100) [n=70]	p = 0.9905 Not Significantly Different
	Specificity	77.2% (73.1-81.0) [n=452]	58.3% (27.7-84.8) [n=12]	p = 0.0758 Not Significantly Different
	Accuracy	89.0% (87.2-90.6) [n=1417]	93.9% (86.3-97.9) [n=82]	p = 0.9273 Not Significantly Different

* Statistical significance based on exact binomial test using P< 0.05 level of confidence

Recurrent Breast Cancer

^{18}F-FDG is useful in recurrent breast cancer due to its propensity for uptake in aggressively proliferative tissue. Detection of local recurrence early in its development assists in treatment approach decisions, given that treatment options for early recurrence (radiation therapy with or without surgery) mitigate the need for more aggressive systemic chemotherapy. Breast cancer typically metastases to bone, liver, lung and brain, all of which lesions have been reported to show ^{18}F-FDG uptake.

The high overall sensitivity observed for CanTrace (91%) from 56 patients (Table 11) is similar to the supporting clinical literature values (83%). This population also had a reasonably sized cohort that presented with a target lesion that was non-malignant (n=24) providing reliable specificity data (87%) that is in excellent agreement with the literature (85%). Similarly, the

overall accuracy of CanTrace for 80 patients was highly comparable to the literature (90% vs. 84%). All values are not statistically significantly different from the literature. These results demonstrate that CanTrace is clinically effective in the evaluation of recurrent breast cancer.

The literature analysis for ^{18}F-FDG for populations of breast cancer patients assessed for distant metastases (both in a staging and restating setting) as well as for evaluation of progress of disease in response to systemic therapeutic interventions in shown in Table 12. This literature analysis indicates that ^{18}F-FDG is useful in the evaluation of distant metastases and for monitoring response to therapy.

Table 12 Summary of ^{18}F-FDG Parameter Values from Supporting Clinical Literature in Evaluation of Distant Metastases and Disease Monitoring in Breast Cancer

Sensitivity Value (%)	Specificity Value (%)	Accuracy Value (%)
81.7% (76.4-86.2) [n=262]	94.7% (91.3-97.1) [n=264]	88.2% (85.2-90.8) [n=526]

Thus the combination of clinical trial data and literature analysis (Table 11, Table 12) establishes the use of CanTrace in all claimed indications for breast cancer.

Recurrent Colorectal Cancer

Recurrence in colorectal cancer happens in approximately 1/3 of patients, usually within 2 years of their primary diagnosis and in 1/5 of cases, recurrence is localized and amenable to curative resection. Current techniques (CEA assays, CT and MRI) lack the required degree of accuracy and surgical confirmation is not suitable for all cases. Recurrent disease may also be accompanied by distant disseminated metastases, which influence the type of treatment available, namely, resection versus palliative or adjuvant treatment. Liver is the primary site of metastatic spread with lung and bone observed less frequently. Staging of recurrent disease is therefore critical to patient selection for optimal therapy irrespective of the timing of patient presentation for this indication. The literature analysis indicates that ^{18}F-FDG is effective for both assessing recurrence and staging, often leading to a change in patient management as a result.

As shown in Table 11, the high overall sensitivity observed for CanTrace (92%) from 54 patients is similar to the supporting clinical literature value (94%). This population also had a small cohort that presented with a target lesion that was non-malignant (n=9) providing limited specificity data (88%) that, nonetheless is in excellent agreement with the literature (81%). Similarly the overall accuracy of CanTrace was highly comparable to the literature (92% vs. 91%) for the 63 patients. All values are not significantly different from the literature. These

results demonstrate that CanTrace is clinically effective in the evaluation of recurrent colorectal cancer.

Thus the combination of clinical trial data and literature analysis (Table 11) establishes the use of CanTrace in all claimed indications for colorectal cancer.

Lung Cancer

The differential diagnosis of benign from malignant nodules is a critical clinical issue given the high probability of lengthy survival after resection and the general estimate of 20-40% of solitary pulmonary nodules (SPN) being malignant. Benign lesions can be classified as non-malignant tumours, infectious, inflammatory, vascular or developmental masses. The current use of sub-optimal non-invasive imaging (CT, X-rays) highlights the critical need for improved reliability of diagnostic imaging methods to correctly characterize these lesions as benign or malignant and thereby avoid unnecessary interventions. It is estimated that 50% of all SPN will be resected in spite of benign pathology.

As shown in Table 11, the high overall sensitivity observed for CanTrace (100%) from 70 patients with pulmonary nodules is similar to the supporting clinical literature values (94%). This population also had a small cohort that presented with a target lesion that was non-malignant (n=12) providing limited reliability specificity data (58%) that is in fair agreement with the literature (77%). Similarly the overall accuracy of CanTrace was highly comparable to the literature (94% vs. 89%) for the 82 patients. All values are not significantly different from the literature and the very high sensitivity and specificity translate into very high negative predictive values of approximately 87%, demonstrating a negative CanTrace PET scan can be used to reliably judge a SPN as benign, thereby vastly improving rational medical treatment decisions. These results demonstrate that CanTrace is clinically effective in differentiating benign from malignant pulmonary nodules.

Decisions regarding more advanced nodal involvement are also critical to patient management related to the type of resection and whether pre-op chemotherapy, radiotherapy or combination therapy will be necessary. Traditional methods include CT (low accuracy) and mediastinoscopy. The literature analysis (Table 13) indicates that for staging, ^{18}F-FDG has a high sensitivity (86%), specificity (90%) and accuracy (89%) with a positive ^{18}F-FDG uptake in a normal-sized mediastinal node being highly indicative of malignant nodal extension warranting surgical confirmation. Approximately 2/5 of patients will have distant metastases on presentation and even after radical treatment, 1/5 will relapse. Typical metastatic sites include the adrenals, liver, lung and brain and accurate evaluation of metastatic sites can have a major impact on therapeutic decisions. The literature analysis (Table 13) indicates that for distant metastases / recurrence / restaging, ^{18}F-FDG has a sensitivity value of 94%, a specificity value of 91% and an accuracy value of 93% indicating the clinical effectiveness of ^{18}F-FDG in evaluating the metastatic spread of lung cancer.

Table 13 Summary of ^{18}F-FDG Parameter Values from Supporting Clinical Literature in the Staging and Evaluation of Distant Metastases and Recurrence / Restaging of Lung Cancer

Indication	Sensitivity Value (%)	Specificity Value (%)	Accuracy Value (%)
Staging (including nodal involvement)	86.8 (85.0-88.4) [n=1582]	90.6 (89.6-91.5) [n=3571]	89.4 (88.5-90.2) [n=5155]
Distant Metastases, Recurrence / Restaging	94.4 (91.4-96.7) [n=324]	91.9 (88.3-94.6) [n=298]	93.2 (91.0-95.1) [n=622]

Thus the combination of clinical trial data and literature analysis (Table 11, Table 13) establishes the use of CanTrace in all claimed indications for lung cancer.

DETAILED PHARMACOLOGY: Module 2, Section 2.4.2, and Section 2.6.2

DETAILED PHARMACOLOGY

The hydroxyl group of the second carbon of glucose can be substituted by a group such as hydrogen or fluorine without seriously compromising the kinetic and biochemical ability of the molecule to be actively transported through the cell membrane and to act as a substrate for the hexokinase enzyme. The 2-deoxy analogues of glucose are transported into the cell and metabolized quantitatively exactly like D-glucose up the point in the glycolytic pathway where its anomalous structure prevents the final conversion of the 2-deoxyglucose-6-phosphate by phosphohexoseixomeriase1[c].

Gallagher *et al.*[d,e] have studied the tissue distribution of ^{18}F-FDG in animals. In mice, ^{18}F-FDG distributes uniformly to the kidneys, heart, brain, lungs and liver initially and clears rapidly from all tissue except the heart where it remains constant for at least 2 hours and, to a lesser extent, in the brain where it decreases slowly from 1 to 2 hours. The rapid clearance of ^{18}F-FDG from the liver, lungs and kidneys, and its retention by the heart and brain is a result of metabolic trapping within these organs and is reflective of glucose utilisation. Urinary excretion of intact ^{18}F-FDG was 15-25% of injected dose at 90 minutes.

Kanazawa *et al.*[f] carried out biodistribution studies of FDG in mice and using F-19 NMR determined that FDG accumulated in organs and fluids as parent FDG (or FDG-6-phosphate) and FD-Mannose (or FD-Mannose-6-phosphate) and was excreted in the urine in both forms.

Suolinna *et al.*[g] studied the biodistribution of ^{18}F-FDG in rats and determined the relative percentages of ^{18}F-FDG and ^{18}F-FDG-6-phosphate in liver (68 and 33%, respectively) and kidney (70 and 27%, respectively) at 45 minutes after injection.

Kaarstad *et al.*[h] injected mice bearing C3H mammary carcinoma with ^{18}F-FDG and determined the metabolite profile in the tumour at various time points up to 180 minutes. ^{18}F-FDG-6-

phosphate was the predominant metabolite observed with measurable quantities of other phosphorylated species.

TOXICOLOGY:
Module 2, Section 2.4.4, and Section 2.6.6

TOXICOLOGY

Fluorodeoxyglucose (FDG)

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

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

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

Actual levels of FDG in CanTrace meet pharmacopoeial standards and as such are well below any toxic level reported by the above studies.

Acetonitrile and Kryptofix 222

Potential impurities that have been observed in small amounts in CanTrace are acetonitrile and Kryptofix 222 and therefore, the potential impact of their presence on product safety was assessed.

The acute toxicity of acetonitrile has been evaluated in mice, rats and rabbits[l] and based on the maximum amount present in CanTrace provides a wide safety margin using this assessment. Based on limited human inhalational studies of acetonitrile[l], the maximum amount present in CanTrace is approximately 60 times less than the human no effect level.

The acute toxicity of Kryptofix 222 has been evaluated in rats and mice[m]. The LD_{50} of an intravenous dose in mice was 35 mg/kg and of an intraperitoneal dose in mice was 110 mg/kg. The LD_{50} of an intravenous dose in rats was 32 mg/kg and of an intraperitoneal dose was 153

mg/kg. The amount of Kryptofix 222 that may be present in CanTrace has a limit of 50 µg/ mL which is more than two orders of magnitude below the lethal dose in rodents, delivered intravenously.

Actual levels of residual acetonitrile and Kryptofix 222 in CanTrace meet pharmacopoeial standards and as such are well below any toxic level reported by the above studies.

^{18}F-Fluorodeoxyglucose (^{18}F-FDG)

No long term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether ^{18}F-FDG affects fertility in males or females.

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

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PART III: CONSUMER INFORMATION

CanTrace™

^{18}F-Fluorodeoxyglucose, ^{18}F-FDG

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

ABOUT THIS MEDICATION

What the medication is used for:
This medication is a radioactive tracer which is used as part of a nuclear medicine test called a Positron Emission Tomography (PET) scan, to help your doctor evaluate your cancer.

What it does:
CanTrace is a sugar molecule that has a radioisotope, Fluorine-18 attached to it. When CanTrace is injected into your vein, it will go to sites in your body where sugar is required. Cancer cells require lots of sugar to grow, so CanTrace will concentrate in them. The radioactive part of CanTrace (Fluorine-18) allows a picture to be taken using a Positron Emission Tomography (PET) camera that tells your doctor if you might have these cells, where they are in your body and / or to look at other features of your cancer.

When it should not be used:
- If you are pregnant or breast feeding.
- If you are allergic to any of the components of CanTrace.
- If you are diabetic and your blood sugar is not controlled.

What the medicinal ingredient is:
^{18}F-Fluorodeoxyglucose (radioactive sugar-like molecule)

What the important nonmedicinal ingredients are:
Sodium Chloride (salt) and Water

WHAT THIS MEDICATION IS USED FOR:
Module 2, Section 2.5.6 and Section 2.7.3
Module 5, Section 5.3.5

WHEN IT SHOULD NOT BE USED:
Module 2, Section 2.5,
Module 5, Section 5.3.5.1

WARNINGS AND PRECAUTIONS:
Module 2, Section 2.5

SIDE EFFECTS AND WHAT TO DO ABOUT THEM:
Module 2, Section 2.6.4,
Section and NON Response,
March 31, 2006

WHAT IT DOES:
Module 2, Section 2.4.2, and Section 2.6.2

WHAT THE MEDICINAL INGREDIENT IS:
Module 3, Section 3.2.P.1

WHAT THE IMPORTANT NON-MEDICINAL INGREDIENTS ARE:
Module 3, Section 3.2.P.1

PROPER USE OF THIS MEDICATION:
Module 2, Section 2.6.4,
Section 2.7.2.2 and NON Response, March 31, 2006

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

$ Because CanTrace 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.

$ CanTrace should not be given to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus

$ CanTrace can be passed into breast milk during nursing. To avoid unnecessary radiation exposure to your baby, formula feeding should be substituted temporarily for breast feeding.

BEFORE you receive CanTrace talk to your doctor or pharmacist if:
- you have diabetes as special attention will be needed to assess your blood glucose levels prior to having a PET scan with CanTrace
- there is a possibility that you may be pregnant
- you are breast feeding your baby
- you think you have any allergies to any of the components in CanTrace

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

It is not known whether drugs, food or natural health products interact with CanTrace.

PROPER USE OF THIS MEDICATION

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

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

Diabetic patients should stabilise 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 CanTrace have been identified in clinical trials.

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

There are no known serious side effects with the use of CanTrace. If you experience any unusual effects after receiving CanTrace, contact your doctor or pharmacist. For example, symptoms of an allergic reaction would include rash, hives, itching, or fast heartbeat, nausea and vomiting.

REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found at:

http://www.hc-sc.gc.ca/hpfb-dgpsa/bgtd-dpbtg/aboutus_e.html

http://www.petscan.ca

or by contacting the sponsor, IPET Pharmaceuticals, Inc., at: 1-604-689-7776

This leaflet was prepared by IPET Pharmaceuticals, Inc.

Last revised: July 18, 2007.

SIDE EFFECTS AND SERIOUS SIDE EFFECTS:

Module 2, Section 2.7.4.2, Module 5, Section 5.3.5.1 and Section 5.3.5.2 and NON Response, March 31, 2006