# PRODUCT MONOGRAPH

## FluorOHmet

([$^{18}$F]Fluorodeoxyglucose, $^{18}$F-FDG)

Solution for Injection, 45 - 4240 mCi (1.665-156.88 GBq) per multi-dose vial

Diagnostic Radiopharmaceutical

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# FluorOHmet

[$^{18}$F]Fluorodeoxyglucose, $^{18}$F-FDG

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

#### a) Synthesis using the ASU COINCIDENCE

| Route of Administration | Dosage Form / Strength | ASU used in Manufacturing Process | Clinically Relevant Non medicinal Ingredients |
|---|---|---|---|
| Intravenous injection | Solution for Injection, multi-dose vial containing 45 - 4240 mCi or 1.665-156.88 GBq | COINCIDENCE | Citrate buffer in 0.9% Sodium Chloride |

#### b) Synthesis using the ASU FASTLAB

| Route of Administration | Dosage Form / Strength | ASU used in Manufacturing Process | Clinically Relevant Non medicinal Ingredients |
|---|---|---|---|
| Intravenous injection | Solution for Injection, multi-dose vial containing 45 - 4240 mCi or 1.665-156.88 GBq | FASTLAB | Phosphate buffer in 0.9% Sodium Chloride |

### DESCRIPTION

#### Physical Characteristics

FluorOHmet ([$^{18}$F]Fluorodeoxyglucose, $^{18}$F-FDG) is a sterile, apyrogenic, clear, colourless, solution for injection. FluorOHmet is a derivative of D-glucose with the radioisotope Fluorine-18 substituted for the hydroxyl group on Carbon 2.

Fluorine-18 decays by positron emission to yield two gamma photons of 0.511MeV (97%). Its

physical half-life is 109.7 minutes. A radioactive decay chart for F-18 is provided in Table 1, below.

**Table 1: Radioactive Decay Chart for Fluorine-18**

| 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 flourine-18 is:

β, γ 2.71 rads g/μCi·hour $2.03 \times 10^{-13}$ Gy kg/Bq·s
γ only 2.11 rads g/μCi·hour $1.63 \times 10^{-13}$ Gy kg/Bq·s

The specific gamma ray constant for flourine-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. The range of attenuation coefficients for this radionuclide is shown in Table 2. For example, an 8.3 mm thick lead shield has a coefficient of attenuation of 0.25 and will decrease the external radiation by 75%.

**Table 2: Radiation attenuation of 511 keV Photons by Lead Shielding**

| Lead Shield Thickness (mm) | Coefficient of 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

FluorOHmet is indicated for use in the evaluation of patients with coronary artery disease (CAD) and severe left ventricular (LV) dysfunction, or when other conventional imaging modalities are unlikely to be contributory to the diagnostic assessment, or have been equivocal or non-diagnostic (e.g., echocardiography or SPECT imaging).

FluorOHmet is typically used in conjunction with a myocardial perfusion imaging method to help define left ventricular myocardial viability in patients with dysfunctional, hypoperfused myocardial regions. This imaging may help identify persistent metabolic activity in dysfunctional and hypoperfused myocardial regions.

Imaging should be performed with an appropriate PET imaging camera.

Cardiac PET image interpretation should be carried out only by physicians with adequate training and experience in conducting and interpreting these procedures.

## 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.

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

## WARNINGS AND PRECAUTIONS

### General

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

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

As in the use of any other radioactive material, care should be taken to minimize radiation

exposure to patients consistent with proper patient management, and to minimize radiation exposure to occupational workers.

Image quality may be suboptimal in glucose intolerant or diabetic patients. Therefore it is recommended that an oral glucose load with supplemental insulin if needed or the hyperinsulinemic-euglycemic clamp methods be utilized to maintain blood sugar levels at 5-7mmol/L to ensure optimal image quality.

**Carcinogenesis and Mutagenesis**

Studies with FluorOHmet have not been performed to evaluate carcinogenic or mutagenic potential. Adequate reproductive studies have not been conducted in animals to evaluate the potential effects on fertility in human males or females. (see "SPECIAL POPULATIONS, PREGNANT WOMEN").

**Cardiovascular**

The safety and efficacy of FluorOHmet within four weeks post-MI has not been studied.

**Contamination**

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

Special precautions such as bladder catheterization should be taken following administration to incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

**Endocrine and Metabolism**

The use of FluorOHmet requires particular attention in patients with diabetes mellitus. Hyperglycemia can cause reduction in the uptake of FluorOHmet and lead to erroneous diagnosis (see DOSAGE AND ADMINISTRATION).

Blood glucose monitoring is required when using FluorOHmet for myocardial imaging. Image interpretation may be affected in those patients with unstable blood glucose levels such as hyperglycemia or diabetes.

Also, it should be noted that as CAD can be a complication of diabetes, it may be that a patient is evaluated for CAD and myocardial viability before a diagnosis of diabetes has been made.

**Special Populations**

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

**Nursing Women:** Where assessment of the risk to benefit ratio suggests the use of FluorOHmet 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 (< 16 years of age):** The safety and efficacy of FluorOHmet in pediatric patients have not been established.

**Geriatrics (> *65* years of age):** There are no known limitations to the clinical use of FluorOHmet in geriatric patients. The clinical studies conducted to demonstrate the efficacy and safety of F18 FDG for the approved indications and clinical uses included geriatric patients.

## ADVERSE REACTIONS

### Adverse Drug Reaction Overview

There have been published reports of [$^{18}$F]Fluorodeoxyglucose investigations since the early 1980s. [$^{18}$F]Fluorodeoxyglucose has an excellent safety record in the literature. The risks of use of [$^{18}$F]Fluorodeoxyglucose PET are extremely low. The absence of adverse effects is consistent with published articles on [$^{18}$F]Fluorodeoxyglucose PET and with the experience with PET agents in general: no adverse events were reported in over 80,000 administered doses of PET agents.[1]

### Clinical Trial Adverse Drug Reactions

No adverse reactions attributable to FluorOHmet injection manufactured at the University of Ottawa Heart Institute were documented as a result of administration of this product in the 803 procedures recorded in the Cardiac PET registry and CADRE registry from August 2002 to November 30, 2009. FluorOHmet produced at the University of Ottawa Heart Institute has an excellent safety profile with no observed adverse events related to its use.

*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*.

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

None observed.

**Abnormal Hematologic and Clinical Chemistry Findings**

None observed.

**Post-Market Adverse Drug Reactions**

None known.

## DRUG INTERACTIONS

**Overview**

There are no known serious or life-threatening drug interactions with FluorOHmet. 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**

No drug-food interactions are known to exist. In preparation for imaging with FluorOHmet patients should be in the fasting state. Blood glucose levels should be evaluated pre-injection and the use of either an oral glucose load with supplemental insulin as needed or the hyperinsulinemic-euglycemic clamp methods be considered for optimal image quality. (see DOSAGE AND ADMINISTRATION, ADMINISTRATION sub-heading).

**Drug-Herb Interactions**

No drug-herb interactions are known to exist.

**Drug-Laboratory Interactions**

No drug-laboratory interactions are known to exist.

## DOSAGE AND ADMINISTRATION

### Dosing Considerations

The dose of FluorOHmet is based on administering enough product to allow for effective detection via PET imaging. Typical doses ranging from 5 to 15 mCi (185-555MBq) depending on body weight result in the administration of trace quantities of the active ingredient.

### Dosage

5-15 mCi (185-555MBq) by intravenous injection, depending upon body weight, and usually calculated as 5MBq per kg to a maximum of 555MBq.

### Administration

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

FluorOHmet is administered by intravenous injection via an established intravenous line.

FluorOHmet Injection may be administered either to patients who have fasted or to patients who have received an oral glucose load.

Physicians should be aware of patient medical history, diabetes, CAD, current medications. A fasting serum glucose is required to rule out glucose intolerance.

Non-diabetic patients: It is recommended that the oral glucose loading protocol be used for non-diabetic patients.

Diabetic or glucose intolerant patients: An oral glucose load with supplemental insulin as needed or the hyperinsulinemic-euglycemic clamp protocol are recommended for use in these patients.

### Image Acquisition and Interpretation

Imaging should be performed with an appropriate PET imaging camera. ECG-gated or ungated images are typically acquired for 5 to 20 minutes, starting 30 to 60 minutes after tracer injection.

The use of attenuation-corrected PET images acquired on the same instrumentation is recommended to minimize potential attenuation artifacts. Any potential confounding effects of imaging artifacts supports that FluorOHmet be used by appropriately trained and experienced clinicians.

FluorOHmet is typically used in conjunction with a PET myocardial perfusion imaging method to help define left ventricular myocardial viability in patients with dysfunctional, hypoperfused myocardial regions.

The available product study data have not specifically examined the use of FluorOHmet PET images, when interpreted in combination with SPECT myocardial perfusion images. In instances where SPECT perfusion imaging is contemplated for use in conjunction with PET viability/metabolism, interpretation is then to consider technical and methodology aspects unique to positron imaging and differences between PET and SPECT. Such cautionary consideration must thus be given when PET metabolism and SPECT perfusion are used [versus PET-PET], or when no perfusion images are available.

Interpretation of FluorOHmet images (viability), when perfusion images have not been obtained (and/or with angiographic information or information on wall motion), is not recommended due to unreliability and difficulties.
As with all diagnostic radiopharmaceuticals, only physicians with experience in nuclear medicine should interpret FluorOHmet PET images. Physicians should be aware of patient preparation anomalies and relevant patient history.

## Instructions for Preparation and Use

FluorOHmet is available as a sterile, non-pyrogenic solution that is ready for use. The user should adhere to aseptic techniques when withdrawing a dose for administration. Administration of FluorOHmet also requires the use of appropriate radiation shielding to protect the user and patient from unnecessary exposure to the radioactive product.

## Directions for Quality Control

All quality control testing will be performed by the Manufacturer prior to release of the product. A certificate of analysis documenting the results of release testing is available for every batch of FluorOHmet.

## RADIATION DOSIMETRY

The estimated absorbed radiation Effective Dose to adult humans following an intravenous injection of FluorOHmet is presented in Table 3, below. The values presented were determined by extrapolation of animal dosimetry study data to humans, and compare favourably to the estimates in the International Commission on Radiological Protection (ICRP) publication 106 (2008). Estimates for absorbed radiation organ doses published by ICRP are shown in Table 4.

**Table 3: Effective Dose from Intravenous Administration of [$^{18}$F]fluorodeoxyglucose**

| Source | Effective Dose mSv/MBq (rem/mCi) |
|---|---|
| **Dosimetry Study** | 0.012 (0.044) |
| **ICRP 106** | 0.019 (0.070) |

**Table 4. Absorbed organ doses for $^{18}$F-FDG (ICRP 106)**

| Organ | Absorbed dose per unit activity administered (mGy/MBq) | | | | |
|---|---|---|---|---|---|
| | Adult | 15 years | 10 years | 5 years | 1 year |
| Adrenals | 1.2E-02 | 1.6E-02 | 2.4E-02 | 3.9E-02 | 7.1E-02 |
| Bladder | 1.3E-01 | 1.6E-01 | 2.5E-01 | 3.4E-01 | 4.7E-01 |
| Bone surfaces | 1.1E-02 | 1.4E-02 | 2.2E-02 | 3.4E-02 | 6.4E-02 |
| Brain | 3.8E-02 | 3.9E-02 | 4.1E-02 | 4.6E-02 | 6.3E-02 |
| Breasts | 8.8E-03 | 1.1E-02 | 1.8E-02 | 2.9E-02 | 5.6E-02 |
| Gallbladder | 1.3E-02 | 1.6E-02 | 2.4E-02 | 3.7E-02 | 7.0E-02 |
| Gastrointestinal tract | | | | | |
| Stomach | 1.1E-02 | 1.4E-02 | 2.2E-02 | 3.5E-02 | 6.7E-02 |
| Small intestine | 1.2E-02 | 1.6E-02 | 2.5E-02 | 4.0E-02 | 7.3E-02 |
| Colon | 1.3E-02 | 1.6E-02 | 2.5E-02 | 3.9E-02 | 7.0E-02 |
| (Upper large intestine | 1.2E-02 | 1.5E-02 | 2.4E-02 | 3.8E-02 | 7.0E-02) |
| (Lower large intestine | 1.4E-02 | 1.7E-02 | 2.7E-02 | 4.1E-02 | 7.0E-02) |
| Heart | 6.7E-02 | 8.7E-02 | 1.3E-01 | 2.1E-01 | 3.8E-01 |
| Kidneys | 1.7E-02 | 2.1E-02 | 2.9E-02 | 4.5E-02 | 7.8E-02 |
| Liver | 2.1E-02 | 2.8E-02 | 4.2E-02 | 6.3E-02 | 1.2E-01 |
| Lungs | 2.0E-02 | 2.9E-02 | 4.1E-02 | 6.2E-02 | 1.2E-01 |
| Muscles | 1.0E-02 | 1.3E-02 | 2.0E-02 | 3.3E-02 | 6.2E-02 |
| Oesophagus | 1.2E-02 | 1.5E-02 | 2.2E-02 | 3.5E-02 | 6.6E-02 |
| Ovaries | 1.4E-02 | 1.8E-02 | 2.7E-02 | 4.3E-02 | 7.6E-02 |
| Pancreas | 1.3E-02 | 1.6E-02 | 2.6E-02 | 4.0E-02 | 7.6E-02 |
| Red marrow | 1.1E-02 | 1.4E-02 | 2.1E-02 | 3.2E-02 | 5.9E-02 |
| Skin | 7.8E-03 | 9.6E-03 | 1.5E-02 | 2.6E-02 | 5.0E-02 |
| Spleen | 1.1E-02 | 1.4E-02 | 2.1E-02 | 3.5E-02 | 6.6E-02 |
| Testes | 1.1E-02 | 1.4E-02 | 2.4E-02 | 3.7E-02 | 6.6E-02 |
| Thymus | 1.2E-02 | 1.5E-02 | 2.2E-02 | 3.5E-02 | 6.6E-02 |
| Thyroid | 1.0E-02 | 1.3E-02 | 2.1E-02 | 3.4E-02 | 6.5E-02 |
| Uterus | 1.8E-02 | 2.2E-02 | 3.6E-02 | 5.4E-02 | 9.0E-02 |
| Remaining organs | 1.2E-02 | 1.5E-02 | 2.4E-02 | 3.8E-02 | 6.4E-02 |
| Effective dose (mSv/MBq) | 1.9E-02 | 2.4E-02 | 3.7E-02 | 5.6E-02 | 9.5E-02 |

Although the absorbed radiation dose estimates in Table 4 include values for pediatric subjects, it need be noted that the safety and efficacy of the product in pediatric patients has not been established. (See “Warnings and Precautions, Special Populations, Pediatrics”).

## OVERDOSAGE

| For management of suspected drug overdose, consult the regional poison control centre. |
|---|

Overdosage with FluorOHmet has not been reported. In case of overdose, elimination should be encouraged by means of increased fluid intake and frequent urination.

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

2-Deoxy-2-[$^{18}$F]-fluoro-D-glucose (FluorOHmet) is a $^{18}$F-labelled glucose analogue. [$^{18}$F]FDG is the most widely used diagnostic radiopharmaceutical for PET-imaging. [$^{18}$F]FDG monitors and measures glucose metabolism non-invasively by PET. [$^{18}$F]FDG behaves *in vivo* like glucose in that it enters healthy and malignant cells. In the cells it is phosphorylated by hexokinase in the way natural glucose is. It is a property of phosphorylated deoxyglucose derivatives, including phosphorylated [$^{18}$F]FDG , to be trapped in the cells. Therefore, within a given cell, the retention and clearance of [$^{18}$F]FDG reflects a balance involving glucose transporter, hexokinase and glucose-6-phophate activities. When allowances are made for the kinetic differences [$^{18}$F]FDG is used to assess glucose metabolism.

PET images are generated from the distribution of metabolically trapped $^{18}$F, and are used to distinguish scared from normal or ischemic hibernating tissue Glucose is the preferred substrate for myocardial metabolism and energy production during ischemia, when the heart switches to anaerobic metabolism. Hence [$^{18}$F]FDG uptake reflects normal viable myocardial tissue but also ischemic hibernating tissue.

### Pharmacodynamics

[$^{18}$F]FDG has no pharmacodynamic effects at the doses and concentrations used for diagnostic examination.

In comparison to background activity, regions of decreased or absent uptake of [$^{18}$F]FDG reflect a decrease or absence of glucose metabolism (scar). Regions that maintain uptake of [$^{18}$F]FDG reflect rates of glucose metabolism in normal or ischemic hibernating tissue (viable myocardium). (for additional discussion, see Part II section on Detailed Pharmacology)

### Pharmacokinetics

**Absorption:** FluorOHmet is taken up by tissues in an analogous fashion to glucose.

**Distribution:** FluorOHmet is widely distributed in the body in proportion to glucose metabolic rates.[2]

**Metabolism:** FluorOHmet is phosphorylated to [$^{18}$F]Fluorodeoxyglucose-6-phosphate by hexokinase, with no further metabolism taking place.

**Excretion:** FluorOHmet is mostly excreted unchanged in the urine; approximately 20% of the administered activity is recovered in the urine within the first 2 hours.[3]

**Special Populations and Conditions**

Dose ranging and dose adjustment studies of FluorOHmet in special populations, such as pediatric and geriatric patients, have not been undertaken.

## STORAGE AND STABILITY

FluorOHmet should be stored upright in a lead shielded container at room temperature.

FluorOHmet has an expiry time of 12 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 FluorOHmet, 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.

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

## DOSAGE FORMS, COMPOSITION AND PACKAGING

FluorOHmet is supplied in 10, 20 or 30 ml multi-dose vials for parenteral administration.

Each vial contains 45 - 4240 mCi (1.665-156.88 GBq) of FluorOHmet and may contain either citrate buffer in 0.9% sodium chloride, or phosphate buffer in 0.9% sodium chloride.

Multi-dose vials are made of Type 1 glass with gray Halo-Butyl elastomeric stoppers and aluminium crimp seals.

# PART II: SCIENTIFIC INFORMATION

## PHARMACEUTICAL INFORMATION

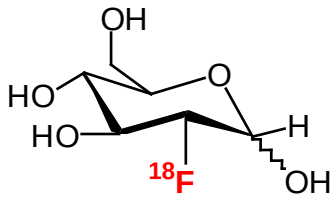
### Drug Substance

Proper name: [$^{18}$F]fluorodeoxyglucose, [$^{18}$F]FDG

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

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

Structural formula:




Physicochemical properties: FluorOHmet is a white solid with a melting point of 165 – 168°C. It is fully soluble in aqueous solutions.

### Product Characteristics

FluorOHmet is supplied as a sterile, pyrogen-free, clear, colourless solution. It contains 90-110% of the labelled amount of FluorOHmet expressed in mCi per vial, at the time of calibration. FluorOHmet does not contain any preservative.

## CLINICAL TRIALS

The trial design and demographics for the studies and data assessments undertaken to further support the use of University of Ottawa Heart Institute (UOHI) FluorOHmet are summarized below and in Table 5".

**Table 5: Summary of Clinical Trials**

| Study Title | Study Objectives | Summary of Study design | Study subjects (n=number) | Diagnosis of Patients |
|---|---|---|---|---|
| Diagnostic Performance | Sensitivity and Specificity estimates | Retrospective analysis of data | 48 (EF change ≥5%, 22 EF change <5%, 23) | Suspected coronary disease with severe LV dysfunction |
| Ottawa-FIVE | Efficacy and Safety Evaluation | Randomized, active controlled | 111 (56 [$^{18}$F]FDG, 55 active control) | suspected coronary disease with severe LV dysfunction |
| UOHI Safety | Evaluation of Safety | Retrospective analysis of data | 803 | All cardiac indications |

## Diagnostic performance – sensitivity and specificity estimates

To assess the diagnostic performance of sensitivity and specificity of FDG PET for predicting recovery of function, this can be achieved by considering the same test for LV function before and after revascularization at predefined time points. Such testing is not routinely performed, however.

For this estimation with FluorOHmet, data was gathered retrospectively on patients who had a pre-operative and follow-up evaluation of LV function at some point within a year of revascularization. The data include 19 patients from the Ottawa-FIVE FDG PET arm who had revascularization and follow-up assessment of LV function and 29 consecutive patients entered into the CADRE registry from Ottawa who underwent FDG PET, had revascularization, and had a pre- and post-revascularization assessment of LV function.

The following factors should be noted: 1. These patients had assessment of LV function on a clinical basis as directed by their attending physician and the timing of follow-up was variable and not standardized; the type of LV function evaluation was not standardized and may have been echocardiography or radionuclide angiography; as patients had a clinical need for LV function evaluation, this may have biased patient selection which could over estimate the false positive rate (lower the specificity). 2. Regional evaluation of LV function was not conducted but global LV function measurements (i.e., ejection fraction, EF) were utilized (objective, more readily obtained, and does not require image alignment). 3. For accuracy, there is no standardized method for assessing amount of viability with FDG PET, so for FluorOHmet the analysis was performed using UOHI established methods and as used in viability assessment. 4. Tercile cut-points to the nearest 5% units are amenable to clinical practice. Viablility and Non-viability are noted below and results are summarized in table 6.

a) VIABILITY was defined as either
    i. Scar < 15% of the LV
    ii. Scar 15-25% of the LV and Mismatch ≥20%
b) NON-VIABILITY was defined as either
    i. Scar 15-25% of the LV with Mismatch <20%
    ii. Scar >25% of the LV
c) LVEF recovery of ≥ 5% was considered as the standard of comparison as indicating recovery of function and therefore VIABILITY

**Table 6.**

| PET Finding | EF change >=5% | EF Change <5% | Total |
|---|---|---|---|
| With Viable Myocardium | 22 | 10 | 32 |
| Without viable Myocardium | 3 | 13 | 16 |
| Total | 25 | 23 | 48 |

Sensitivity: 22/25=88% (95%CI, 68-100%)
Specificity: 13/23=57% (95%CI, 34-77%)
PPV: 22/32=69% (95%CI, 50-84%)
NPV: 13/16=81% (95%CI, 54-96%)

Sensitivity and specificity data using FluorOHmet are within the range of those data reported in the Schinkel analysis. (See also Table 7).

Table 7: Summary of data from three studies reported in Schinkel et al, 2007

| | N | Sens % | Spec % | PPV % | NPV % |
|---|---|---|---|---|---|
| **Slart 2006** | 47 | 85 (23/27) | 100 (20/20) | 100 (23/23) | 83 (20/24) |
| **Gerber 2001** | 171 | 79 (65/82) | 55 (49/89) | 62 (65/105) | 74 (49/66) |
| **Wiggers 2001** | 35 | 100 (14/14) | 67 (14/21) | 67 (14/21) | 100 (14/14) |

**Ottawa-FIVE**:

This was a post-hoc subgroup analysis substudy of the PARR-2 study, which was a randomized, controlled, multi-centre study comparing FDG PET-directed therapy to standard care in patients with severe LV dysfunction. Eligible patients for PARR-2 were those being considered for: (1) revascularization; (2) transplantation workup; (3) referred for heart failure workup; or (4) any patient where FDG PET might be considered useful by the attending physician. Patients were randomized to either FDG PET guided management or standard care in which physicians were allowed access to any diagnostic procedure, including other imaging modalities except for PET. The study population consisted of 111 patients (PET n=56, Standard care n=55). The mean age

was 64.9 ± 9.5 in the PET arm and 63.0 ± 10.8 in the Standard arm. Two-thirds of the population was male. Prior CABG was 13% in each arm, and baseline EF (mean, SD) was 25.8 +/- 6.9 and 24.6 +/- 6.5 in PET and Standard care arms, respectively.

The primary objective of this study was to determine whether UOHI FDG PET-guided therapy achieved an outcome benefit in patients with severe LV dysfunction compared to standard care where clinical management decisions were made in the absence of FDG PET information at a centre with ready access to FDG PET imaging. The primary outcome measure was the composite clinical endpoint of cardiac death, myocardial infarction, or re-hospitalization for unstable angina or heart failure within one year of randomization.

**Ottawa-FIVE Study results**

For the composite clinical endpoint (comprising cardiac death, myocardial infarction or cardiac hospitalizations), thirty-two first events were identified at 1 year. Among first events there were 6 cardiac deaths (2 PET and 4 Standard care), 4 myocardial infarctions (1 PET and 3 Standard care) and 22 were cardiac hospitalizations (7 PET and 15 Standard care). Overall ten patients in the PET arm and 22 in the Standard care arm, experienced a composite event at one year. However, some patients were excluded from the analysis because they did not complete the one year (3/56 in PET and 1/55 in Standard care did not complete one year). The Ottawa-FIVE substudy, a *post-hoc* analysis of the PARR-2 trial (which did not meet its primary endpoint), yields results that are not consistent with results for the entire PARR-2 as a large treatment effect was observed in the smaller cohort in the Ottawa-FIVE study (25.7% of the PARR-2 population). The inconsistency in data outcome needs to be interpreted carefully as a significant interaction between treatment and centre was demonstrated based on PARR-2 and caution must be applied in interpreting the reduction in cardiac events observed in Ottawa-FIVE. The interplay of various factors (e.g., patient characteristics, access to F-18 FDG, etc) and how they may have contributed to the different results observed will need to be replicated in other studies in order to more fully resolve the unknowns and for the treatment effect observed to be characterized and considered as a true treatment effect.

Compared with the entire PARR-2 trial, it should be noted that the Ottawa-FIVE study patients were more often female, had slightly lower ejection fraction, tended to be older, and tended to have had less previous CABG.

It should be noted that 21.8% of the patients with PET-indicated revascularization in the Ottawa-FIVE cohort did not undergo revascularization procedures.

No measures of treatment compliance were obtained for the study. There was no routine or protocol-required assessment or verification as to whether the revascularization process was successful *i.e*. no follow-up perfusion or angiographic data were done to confirm the adequacy of any revascularization procedures undertaken.

The Ottawa-Five study [PARR-2] did not evaluate SPECT perfusion coupled with F-18 FDG viability image acquisition for the mismatch assessment, consequently no data was available for use of this product in that regard.

The data submitted in support of this product examined the clinical situation when PET metabolism and PET myocardial perfusion imaging were both part of the assessment undertaken.

There were no adverse events related to the administration of FluorOHmet in this study. Related adverse events were defined as events occurring within 5 half-lives of FluorOHmet administration.

**UOHI Safety Study**:

This was a retrospective, single-arm, non-blinded assessment of the safety of FluorOHmet at UOHI. All patients who received FluorOHmet manufactured at the UOHI starting in August 2002 were identified in the Cardiac PET Registry and subsequent CADRE Registry. Demographic data, cardiac history, pre and post vital signs, FluorOHmet dose, and the presence or absences of any adverse events were extracted from the database.

The population consisted of 803 patients with left ventricular dysfunction, having undergone FDG-PET myocardial imaging studies at the UOHI. The mean age was 63.5 ± 11.8 years. 79.7% of the population was male. Body mass index was 28.3 ± 5. Almost 50% of the patient population undergoing FDG-PET imaging had a history of previous heart failure. Seventy percent (70.9%) of patients had previous coronary angiography. More than 68% had a previous myocardial infarction while 36.5% had previous CABG/PCI. Pacemaker or AICD was noted in 15.7%.

**UOHI Safety Results:**

No adverse events occurred or were reported during administration or within 5 half-lives of FluorOHmet, in the 803 patients reviewed. No deaths, other serious adverse events or other significant adverse events occurred or were reported during administration or within 5 half-lives of FluorOHmet. FluorOHmet injection induced no clinically significant changes in heart rate, systolic blood pressure, or diastolic blood pressure.

Administration of doses ranging from 3-18 mCi (111MBq-666MBq) of FluorOHmet to patients presenting to the UOHI for cardiac PET imaging caused no detectable adverse events, nor meaningful clinical response.

## DETAILED PHARMACOLOGY

The hydroxyl group of the second carbon of glucose can be substituted by a group such as hydrogen or fluorine without seriously compromising the kinetic and biochemical ability of the molecule to be actively transported through the cell membrane and to act as a substrate for the

hexokinase enzyme. The 2-deoxy analogues of glucose are transported into the cell and metabolized quantitatively exactly like D-glucose up the point in the glycolytic pathway where its anomalous structure prevents the final conversion of the 2-deoxyglucose-6-phosphate by phosphohexoseixomeriase 1.[4]

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.[5,6] 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.

In mice, FDG accumulates in organs and fluids as parent FDG (or FDG-6-phosphate) and FD-Mannose (or FD-Mannose-6-phosphate) and is excreted in the urine in both forms.[7]

In rats, the percentages of [$^{18}$F]FDG and [$^{18}$F]fluorodeoxyglucose -6-phosphate 45 minutes after injection were 68 and 33%, respectively in the liver; and 70 and 27%, respectively, in the kidney.[8]

In mice bearing C3H mammary carcinoma the predominant metabolite observed in the tumour at 180 minutes was [$^{18}$F]fluorodeoxyglucose -6-phosphate, with measurable quantities of other phosphorylated species.[9]

Myocardial metabolic imaging using [$^{18}$F]FDG (as a tracer of exogenous glucose utilization) is performed in patients with dysfunctional, hypoperfused myocardial regions to determine the likelihood of benefit from revascularization. Metabolic activity can be an indicator of myocardial viability and, thus, of reversibility of contractile dysfunction. The regional myocardial concentrations of the [$^{18}$F]FDG tracer are compared with the regional distribution of myocardial perfusion. Increased regional [$^{18}$F]FDG uptake relative to myocardial perfusion (perfusion/metabolism mismatch) indicates hibernating myocardium that is viable— and more likely to be reversible contractile dysfunction if regional blood flow is improved (this is the potential for improvement when perfusion is normal), if both perfusion and [$^{18}$F]FDG uptake are normal, or if [$^{18}$F]FDG uptake is greater than regional perfusion—i.e mismatch. In contrast to this, regional reductions in [$^{18}$F]FDG uptake in proportion to perfusion (perfusion-metabolism match indicative of scar formation) is regarded to signify irreversibly damaged myocardium (contractile dysfunction that is not likely reversible— e.g., the potential for a post-revascularization improvement in contractile function is low).

## TOXICOLOGY

Non-radioactive 2-deoxy-2-fluoro-D-glucose had an LD50 of 600 mg/kg in both mice and rats when given by intraperitoneal injection in 5 or 6 consecutive daily doses.[10]

Toxicity studies in mice given three doses of 14.3 mg/kg of FDG did not reveal any immediate or long-term effects as determined by routine observations, changes in body weight, and gross

and histopathology of the internal organs. Toxicity studies in dogs injected with three doses of 0.72 mg/kg of FDG did not show any immediate or long-term effects. No significant abnormalities were detected in blood, urine, or CSF analyses, and no significant gross or microscopic abnormalities were detected in the heart, brain, spleen, liver, kidneys, lungs, ovaries, or intestines.[11]

No long-term animal studies have been performed to evaluate carcinogenic or mutagenic potential or whether 18F-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**

FluorOHmet

[$^{18}$F]Fluorodeoxyglucose, [$^{18}$F] FDG

This leaflet is part III of a three-part "Product Monograph" published when FluorOHmet was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about FluorOHmet. 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 heart.

What it does:
FluorOHmet is a sugar molecule that has a radioisotope, fluorine-18 attached to it. When it is injected into your vein, FluorOHmet will go to sites in your body where sugar is used. The radioactive part of FluorOHmet allows a picture to be taken using a Positron Emission Tomography (PET) camera. This allows your doctor to look at your heart muscle and determine if the tissue is still able to use sugar. This will help your doctor decide if you could benefit from surgery or other corrective procedures.

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

What the medicinal ingredient is:
FluorOHmet, a radioactive sugar-like molecule.

What the important nonmedicinal ingredients are:
Citrate buffer, phosphoric acid and/or 0.9% sodium chloride.

*For a full listing of nonmedicinal ingredients see Part 1 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.**
- **FluorOHmet should not be administered to pregnant women unless it is considered that the benefits to be gained outweigh the potential hazards to the fetus.**
- **FluorOHmet is excreted in human breast milk. To avoid unnecessary irradiation of the infant, formula feeding should be substituted temporarily for breast feeding**.

BEFORE you receive FluorOHmet talk to your doctor or pharmacist if:

- You have diabetes as special attention will be needed to assess your blood sugar levels prior to having the PET scan with FluorOHmet.
- You are taking any medication that changes your blood sugar level
- If you could be pregnant or are nursing
- If you have recently had surgery or radiation therapy
- If you have had a heart attack within the last 4 weeks

  If you think you have any allergies to any of the components in FluorOHmet

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, food or natural health products are known to interact with [FluorOHmet. This test normally requires fasting (restriction on food and beverages) before the test to prepare for the procedure and test that is to be conducted. Eating within 4 hours prior to undergoing the test may interfere with the diagnostic ability (how well the test works) and the reasons that your doctor is conducting this test.

## PROPER USE OF THIS MEDICATION

This product FluorOHmet 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 FluorOHmet. You may be asked to drink a sugar and water mixture prior to this test which helps define areas of the heart that can use glucose.

If you are diabetic or have elevated blood sugar levels, your blood sugars will need to be stabilized prior to testing. This may involve the use of a glucose (by mouth or intravenously) and insulin intravenously to maintain your blood sugar at a steady state for the test. 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 FluorOHmet 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 FluorOHmet. If you experience any unusual effects after receiving FluorOHmet, contact you doctor or pharmacist immediately. For example, symptoms of an allergic reaction would include rash, hives, itching, or fast heartbeat, nausea and vomiting.

### REPORTING SUSPECTED SIDE EFFECTS

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

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

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

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

## MORE INFORMATION

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

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

http://www.ottawaheart.ca/FluorOHmet or by contacting the Sponsor, University of Ottawa Heart Institute –National Cardiac PET Centre, at: 1-855-864-4334

This leaflet was prepared by University of Ottawa Heart Institute – National Cardiac PET Centre.

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