Safeguarding public health

MHRA

Public Assessment Report

Mutual Recognition Procedure

Steripet 250 MBq/ml Solution for Injection

Fludeoxyglucose (^{18}F)

MRP no: UK/H/0814/001/MR
UK licence no: PL 00221/0171

Applicant: GE Healthcare Limited

Steripet 250 MBq/ml Solution for Injection
PL 00221/0171; UK/H/0814/001/MR

LAY SUMMARY

On 5th December 2005, Denmark, Norway, Italy, Portugal, Spain and The Netherlands, approved Marketing Authorisations (licence) for the medicinal product Steripet 250 MBq/ml Solution for Injection (UK/H/0814/001/MR). This application was made by mutual recognition procedure (MRP), with the UK as reference member state (RMS). The original national licence was granted in the UK on 16th May 2005.

This is a prescription-only medicine (POM) used for scanning procedures called Positron Emission Tomography (PET) imaging. Sometimes, the hospital centres that carry out the procedure are called PET Centres.

Steripet 250 MBq/ml Solution for Injection is a radiopharmaceutical product used for diagnostic purposes. A diagnostic radiopharmaceutical is a product that, when injected, temporarily collects in a specific organ or area of the body. It can be detected from outside the body using special cameras because it contains a small amount of radioactivity, and a picture, known as a scan, can be taken. The scan will show the distribution of radioactivity within the organ and the body. This can give the doctor valuable information about the structure and function of that organ. The radiopharmaceuticals used have very short half-lives, which mean that they rapidly change into harmless, non-radioactive material.

The amount of radioactivity in the body as a result of the injection of Steripet is very small and is passed out of the body in a few hours without the need for special precautions.

The active ingredient of Steripet 250 MBq/ml Solution for Injection, Fludeoxyglucose (^{18}F), is a sugar compound labelled with radioactive fluorine. It is taken up by cells in the body in the same way as glucose. It is used to determine how certain organs and tissues in the body are working by measuring glucose metabolism. It is mainly used to look at tumours, because cells in these tissues use more glucose than normal. Steripet 250 MBq/ml Solution for Injection may be useful in detecting and evaluating tumours in many parts of the body, including the digestive system, prostate, testes, ovaries, head and neck, lungs, bones and breast. Furthermore, Steripet 250 MBq/ml Solution for Injection is also used to check whether certain areas in the heart are still alive after a myocardial infarction. Finally, Steripet 250 MBq/ml Solution for Injection is also used to identify regions in the brain which have increased or decreased glucose metabolism, for example for the identification of the areas in the brain involved in epilepsy. Your doctor will explain which particular part of your body he believes a scan would give useful information about, and help decide on possible treatment.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Steripet 250 MBq/ml Solution for Injection outweighed the risks, hence a Marketing Authorisation has been approved.

TABLE OF CONTENTS

Module 1

Product Name	Steripet 250 MBq/ml Solution for Injection
Type of Application	Known Active Substance Initial application Bibliographic (Article 10a) Chemical substance Prescription only
Active Substance	Fludeoxyglucose (^{18}F)
Form	Solution for Injection/Infusion
Strength	250MBq/ml at activity reference time
MA Holder	GE Healthcare Limited, Amersham Place, Little Chalfont, Bucks, HP7 9NA
RMS	United Kingdom
CMS	Denmark, Italy, The Netherlands, Norway, Portugal, Spain
Procedure Number	UK/H/0814/001/MR
Timetable	Day 90: 5th December 2005

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Steripet 250 MBq/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 250 MBq Fludeoxyglucose (^{18}F) at the date and time of calibration.

The activity per vial ranges from 250 MBq to 2.5 GBq at the date and time of calibration.

Fluorine-18 decays to stable oxygen-18 with a half-life of 109.77 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

This medicinal product contains:
Sodium: 5.19 mg/ml. This needs to be taken into consideration for patients on a controlled sodium diet.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless or slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Fludeoxyglucose (^{18}F) is indicated for use with positron emission tomography (PET).

Oncology
Steripet is indicated for imaging in patients undergoing oncologic diagnostic procedures describing function or diseases where enhanced glucose influx of specific organs or tissues is the diagnostic target. The following indications are sufficiently documented (see also section 4.4):

Diagnosis:
- Characterisation of solitary pulmonary nodule
- Detection of cancer of unknown origin, revealed for example by cervical adenopathy, liver or bones metastases
- Characterisation of a pancreatic mass

Staging:
- Head and neck cancers including assistance in guiding biopsy
- Primary lung cancer
- Locally advanced breast cancer
- Oesophageal cancer
- Carcinoma of the pancreas
- Colorectal cancer particularly in restaging recurrences
- Malignant lymphoma
- Malignant melanoma, Breslow >1.5 mm or lymph node metastasis at first diagnosis

Monitoring of therapeutic response:
- Malignant lymphoma
- Head and neck cancers

Detection in case of reasonable suspicion of recurrences:
- Glioma with high grade of malignancy (III or IV)
- Head and neck cancers
- Thyroid cancer (non-medullary): patients with increased thyroglobulin serum levels and negative radioactive iodine whole body scintigraphy
- Primary lung cancer (see also section 4.4)

- Breast cancer
- Carcinoma of the pancreas
- Colorectal cancer
- Ovarian cancer
- Malignant lymphoma
- Malignant melanoma

Cardiology
In the cardiologic indication, the diagnostic target is viable myocardial tissue that takes up glucose but is hypo-perfused, as it must be assessed beforehand using appropriate blood-flow imaging techniques.

- Evaluation of myocardial viability in patients with severe impaired left ventricular function who are candidates for revascularisation when conventional imaging modalities are not contributive.

Neurology
In the neurologic indication, the interictal glucose hypometabolism is the diagnostic target.

- Localisation of epileptogenic foci in the presurgical evaluation of partial temporal epilepsy.

4.2 Posology and method of administration

Posology
The recommended activity for adults is 100 to 400 MBq (depending on the body weight of the patient and the type of camera used), administered by direct intravenous injection.

The experience in children is limited. Only few clinical data are available for patients aged under 18 years concerning safety and diagnostic efficacy of the product. Therefore, the use in oncologic paediatrics has to be carefully weighted.

The activity administered to children and to adolescents is a fraction of the activity recommended for adults.

This activity can be determined from the recommended activity for adults on the basis of body mass, using the following multiplying coefficient:

3 kg = 0.10	22 kg = 0.50	42 kg = 0.78
4 kg = 0.14	24 kg = 0.53	44 kg = 0.80
6 kg = 0.19	26 kg = 0.56	46 kg = 0.82
8 kg = 0.23	28 kg = 0.58	48 kg = 0.85
10 kg = 0.27	30 kg = 0.60	50 kg = 0.88
12 kg = 0.32	32 kg = 0.62	52-54 kg = 0.90
14 kg = 0.36	34 kg = 0.64	56-58 kg = 0.92
16 kg = 0.40	36 kg = 0.66	60-62 kg = 0.96
18 kg = 0.44	38 kg = 0.68	64-66 kg = 0.98
20 kg = 0.46	40 kg = 0.70	68 kg = 0.99

Administration of Steripet and PET examination
The activity of Fludeoxyglucose (^{18}F) has to be measured with a calibrator immediately prior to injection.

The injection must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

The emission scans are usually started 45 to 60 minutes after the injection of Fludeoxyglucose (^{18}F). Provided sufficient activity remains for adequate counting statistics, Fludeoxyglucose (^{18}F) PET can also be performed up to two or three hours after administration, thus reducing background activity.

If required, repeated examinations can be carried out at short notice.

For instructions for correct administration/use of Steripet, see Section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

This medicinal product contains a maximum of 51.9 mg sodium per dose. To be taken into consideration by patients on a controlled sodium diet.

Indication of the examination
For all patients, the radiation exposure must be justifiable by the expected diagnostic information achieved with the lowest possible radiation dose.

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

It should be taken into consideration that the effective dose per MBq is higher in children than in adults (see section 11).

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

In order to obtain images of best quality and to reduce the radiation exposure of the bladder patients should be encouraged to drink sufficient amounts and to empty prior to and after the PET examination.

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

The cerebral glucose metabolism depends on the brain activity. Thus, neurological examinations should be performed after a relaxation period in a darkened room and with less background noise.
A blood glucose test should be performed prior to administration since hyperglycaemia may result in a reduced sensitivity of Steripet, especially when glycaemia is greater than 8 mmol/l.
Similarly, Fludeoxyglucose (^{18}F)-PET should be avoided in subjects presenting uncontrolled diabetes.

Cardiology
Since glucose uptake in the myocardium is insulin-dependent, for a mycardial examination a glucose loading of 50 g approximately 1 hour prior to the administration of Steripet is recommended.
Alternatively, especially for patients with diabetes mellitus, the blood sugar level can be adjusted by a combined infusion of insulin and glucose (Insulin-Glucose-Clamp) if needed.

Interpretation of the FDG PET images
Infectious and/or inflammatory diseases as well as regenerative processes after surgery can result in a significant uptake of FDG and therefore lead to false positive results.

False positive or false negative Fludeoxyglucose (^{18}F)-PET results cannot be excluded after radiotherapy within the first 2-4 months. If the clinical indication is demanding an earlier diagnosis by Fludeoxyglucose (^{18}F)-PET, the reason for earlier Fludeoxyglucose (^{18}F)-PET examination must be reasonably documented.

A delay of at least 4-6 weeks after the last administration of chemotherapy is optimal, in particular to avoid false negative results. If the clinical indication is demanding an earlier diagnosis by Fludeoxyglucose (^{18}F)-PET, the reason for earlier Fludeoxyglucose (^{18}F)-PET examination must be reasonably documented. In case of chemotherapy regimen with cycles shorter than 4 weeks, the Fludeoxyglucose (^{18}F)-PET examination should be done just before re-starting a new cycle.

In low-grade lymphoma and suspicion of recurrence of ovarian recurrent cancer, only positive predictive values have to be considered because of a limited sensitivity of Fludeoxyglucose (^{18}F)-PET.

Fludeoxyglucose (^{18}F) is not effective in detecting brain metastases.

When applying a coincidence PET scanner system, sensitivity is reduced in comparison to dedicated PET, resulting in reduced detection of lesions smaller than 1 cm.

It is recommended that Fludeoxyglucose (^{18}F)-PET images shall be interpreted in relation to tomographic anatomical imaging modalities (e.g. CT, ultrasonography, MRI). Fusion of the functional Fludeoxyglucose (^{18}F)-PET images with morphologic images e.g. PET-CT can lead to an increased

sensitivity and specificity, and is recommended in pancreas, head and neck tumours, lymphoma, melanoma, lung cancers and recurrent colorectal cancers.

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

All medicinal products that modify blood glucose levels can affect the sensitivity of the examination (e.g. corticosteroids, valproate, carbamazepine, phenytoin, phenobarbital and catecholamines).

Under administration of colony-stimulating factors (CSFs), there is an increased uptake of Fludeoxyglucose(^{18}F) in the bone marrow and the spleen for several days. This must be taken into account during the interpretation of PET imaging. Separating CSF therapy from PET imaging by an interval of at least 5 days may diminish this interference.

The administration of glucose and insulin influences the influx of Fludeoxyglucose (18F) into the cells. In the case of high blood glucose levels as well as low plasma insulin levels, the influx of Fludeoxyglucose (^{18}F) into organs and tumours is reduced.

4.6 Pregnancy and lactation

There is no clinical experience with the use of Fludeoxyglucose (^{18}F) in pregnant women. When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques that do not involve ionising radiation have to be considered.

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

Administration of Steripet at activity of 400 MBq results in an absorbed dose to the uterus of 8.4 mGy.

In this dose range, lethal effects and the induction of malformations, growth retardations and functional disorders are not to be expected; however, the risk of the induction of cancer and hereditary defects may be increased.

Steripet should not be administered during pregnancy unless clearly necessary or when the benefit of the mother outweighs the risk to the foetus.

Fludeoxyglucose (^{18}F) is excreted into breast milk. Before administering Fludeoxyglucose (^{18}F) to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding. If administration during lactation is unavoidable, breast feeding has to be interrupted for at least 12 hours and the expressed milk has to be discarded. When appropriate, milk may be drawn off prior to administration of Steripet. Moreover, for radioprotection reasons, it is recommended to avoid close contact between the mother and the infant during the initial 12 hours following injection.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Undesirable effects after the administration of Fludeoxyglucose (18F) have not been observed to date. Since the administered substance quantity is very low, the major risk is caused by the radiation. Exposure to ionising radiation can lead to cancer or development of hereditary defects. Most examinations involving nuclear medicine involve levels of radiation (effective dose) less than 20 mSv. These effects can be expected with a low probability. After administration of the maximum recommended activity of this Fludeoxyglucose (18F) product, the effective dose is about 7.6 mSv.

4.9 Overdose

An overdose in the pharmacological sense is unlikely given the doses used for diagnostic purposes.

If an overdose of Fludeoxyglucose (18F) has been administered, the radiation dose delivered to the patient must be reduced by increasing as much as possible the elimination of the radionuclide, by forced diuresis and frequent mictions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, tumour detection, fludeoxyglucose (18F), ATC code: V09IX04

At the chemical concentrations used for diagnostic examinations, Fludeoxyglucose (18F) does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Fludeoxyglucose (18F) is a glucose analogue, which is accumulated in all cells using glucose as a primary energy source. Fludeoxyglucose (18F) is accumulated in tumours with a high glucose turnover.

Following intravenous injection, the pharmacokinetic profile of Fludeoxyglucose (18F) in the vascular compartment is biexponential. It has a distribution time of 1 minute and an elimination time of approximately 12 minutes.

The cellular uptake of Fludeoxyglucose (18F) is performed by tissue-specific carrier systems, which are partly insulin-dependent and, thus, can be influenced by eating, nutritional condition and the existence of diabetes mellitus. In patients with diabetes mellitus a reduced uptake of Fludeoxyglucose (18F) into the cells occurs due to a changed tissue distribution and glucose metabolism.

Fludeoxyglucose (18F) is transported via the cell membrane in similar fashion to glucose, but only undergoes the first step of glycolysis resulting in formation of Fludeoxyglucose (18F) -6-phosphate, which remains trapped within the tumour cells and is not further metabolised. Since the following dephosphorylation by intracellular phosphatases is slow, Fludeoxyglucose (18F) -6-phosphate is retained in the tissue over several hours (trapping-mechanism).

In healthy subjects, Fludeoxyglucose (18F) is widely distributed throughout the body, particularly in the brain and heart, and to a lesser degree in the lungs and liver.

Elimination of Fludeoxyglucose (18F) is chiefly renal, with 20% of activity being excreted in urine in the 2 hours following injection.

Binding to renal parenchyma is weak, but because of renal elimination of Fludeoxyglucose (18F), the entire urinary system, particularly the bladder, exhibits marked activity.

Fludeoxyglucose (18F) passes the blood-brain barrier. Approximately 7% of the injected dose is accumulated in the brain within 80-100 minutes after injection. Epileptogenic foci exhibit a reduced glucose metabolism in the seizure-free phases.

Approximately 3% of the injected activity is taken up by the myocardium within 40 minutes. The distribution of Fludeoxyglucose (18F) in normal heart is mainly homogenous, however, regional differences of up to 15% are described for the interventricular septum. During and after a reversible myocardial ischemia, an increased glucose uptake occurs into the myocardial cell. 0.3% and 0.9 - 2.4% of the injected activity are accumulated in the pancreas and lung respectively. Fludeoxyglucose (18F) is also bound to a lesser extent to ocular muscle, pharynx and intestine. Binding to muscle may be seen following recent exertion and in the event of muscular effort during the examination.

5.3 Preclinical safety data

In preclinical studies of acute toxicity the 50-fold human dose in dogs and the 1000-fold human dose in mice did not reveal any signs of toxicity.

Studies of chronic toxicity, of mutagenic potential as well as studies of reproduction toxicity and carcinogenic potential have not been performed because of the intended clinical use of the substance (usually a single intravenous application of the substance in the range of ng or µg).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Not more than 10 hours from the time of production.

6.4 Special precautions for storage

Store below 25°C, both before and after the vial is opened.

This product should be stored in accordance with national regulations concerning radioactive products.

6.5 Nature and contents of container

Steripet is supplied in Ph.Eur. Type I clear glass vials sealed with a chlorobutyl rubber closure and an aluminium overseal for multidose use. One vial contains between 1 and 10 ml of solution, corresponding to 250 MBq to 2.5 GBq at calibration time.

6.6 Special precautions for disposal

Radioactive waste must be disposed of in conformity with the relevant national and international regulations.

The administration of radiopharmaceuticals creates risks for other people from external radiation or contamination from spills of urine, vomit, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

The package must be checked before use and the activity measured using a calibrator.

Withdrawals should be performed under aseptic conditions.

The vials must not be opened after disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

The medicinal product may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

7 MARKETING AUTHORISATION HOLDER

GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 00221/0171

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 May 2005

10 DATE OF REVISION OF THE TEXT

18/03/2008

11 DOSIMETRY (IF APPLICABLE)

The table below shows the dosimetry as calculated according to Publication 80 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1998).

	Absorbed Dose Per Unit Activity Administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.012	0.015	0.024	0.038	0.072
Bladder	0.160	0.210	0.280	0.320	0.590
Bone surfaces	0.011	0.014	0.022	0.035	0.066
Brain	0.028	0.028	0.030	0.034	0.048
Breast	0.0086	0.011	0.018	0.029	0.056
Gall bladder	0.012	0.015	0.023	0.035	0.066
GI tract					
Stomach	0.011	0.014	0.022	0.036	0.068
Small intestine	0.013	0.017	0.027	0.041	0.077
Colon	0.013	0.017	0.027	0.040	0.074
ULI	0.012	0.016	0.025	0.039	0.072
LLI	0.015	0.019	0.029	0.042	0.076
Heart	0.062	0.081	0.120	0.200	0.350
Kidneys	0.021	0.025	0.036	0.054	0.096
Liver	0.011	0.014	0.022	0.037	0.070
Lungs	0.010	0.014	0.021	0.034	0.065
Muscles	0.011	0.014	0.021	0.034	0.065
Oesophagus	0.011	0.015	0.022	0.035	0.068
Ovaries	0.015	0.020	0.030	0.044	0.082
Pancreas	0.012	0.016	0.025	0.040	0.076
Red marrow	0.011	0.014	0.022	0.032	0.061
Skin	0.008	0.010	0.016	0.027	0.052
Spleen	0.011	0.014	0.022	0.036	0.069
Testes	0.012	0.016	0.026	0.038	0.073
Thymus	0.011	0.015	0.022	0.035	0.068
Thyroid	0.010	0.013	0.021	0.035	0.068
Uterus	0.021	0.026	0.039	0.055	0.100
Remaining organs	0.011	0.014	0.022	0.034	0.063
Effective dose (mSv/MBq)	0.019	0.025	0.036	0.050	0.095

For Steripet, the effective dose resulting from the administration of an activity of 400 MBq is about 7.6 mSv (for an individual weighing 70 kg).

For this activity of 400 MBq, the radiation doses delivered to the critical organs, bladder, heart and brain are respectively: 64 mGy, 25 mGy and 11 mGy.

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Any unused product or waste material should be disposed of in accordance with local requirements.

Module 3
Product Information Leaflet & Technical Leaflet

PACKAGE LEAFLET: INFORMATION FOR THE USER

Steripet 250 MBq/ml solution for injection
Fludeoxyglucose (^{18}F)

Read all of this leaflet carefully before you are given Steripet.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse.

In this leaflet:

1. What Steripet is and what it is used for

This medicine is used for diagnostic use only. It is used only to help identify illness.

Steripet is a 'radio-pharmaceutical' medicine. It is given before a scan and helps a special camera see inside a part of your body.

For position only

- It contains an active ingredient called 'fludeoxyglucose'.
- Once injected it can be seen from outside your body by a special camera used in the scan.
- The scan can help your doctor to detect or show changes in tumours in many parts of the body such as the brain, head and neck, thyroid, lungs, breast, pancreas, colon and rectum, ovaries, oesophagus, skin, liver and bones.
- The scan can help your doctor see how well the heart is working, or see damage to the heart after a heart attack.
- Some other people who have epilepsy or a similar illness are given this medicine to see affected areas of the brain.

Your doctor or nurse will explain which part of your body will be scanned.

2. Before you are given Steripet

You should not be given Steripet:

- If you are allergic (hypersensitive) to the active ingredient or any other ingredient. (Listed in Section 6).

Do not take Steripet if the above applies to you. If you are not sure talk to your doctor or nurse.

Take special care with Steripet
Check with your doctor or nurse before having Steripet:

- If you have diabetes or increased levels of sugar in your blood.
- If you are pregnant or think you might be pregnant.
- If you are on a low sodium diet.
- If you are having or have ever had radiotherapy or chemotherapy, because they may affect the results of your test with Steripet.

Taking other medicines
Please tell your doctor or nurse if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This includes herbal medicines. This is because some medicines can affect the way Steripet works.

Before your scan tell your doctor or nurse if you are taking any of the types of medicine below. This is because they may affect the results of your scan:

- Corticosteroids, such as prednisolone, deaxamethasone or hydrocortisone.
- Catecholamines such as adrenaline, noradrenaline or dopamine.
- Medicines used in the treatment of epilepsy, such as valproate, carbamazepine, phenytoin or phenobarbital.
- Glucose and insulin.
- Colony stimulating factors.

If you are not sure if any of the above apply to you, speak to your doctor or nurse before having Steripet.

Having Steripet with food and drink
In the time leading up to your scan:

- You should avoid drinking liquids containing a type of sugar called glucose.
- You will be given unlimited amounts of water or other liquids that do not contain glucose.
- You will have to stop eating for a period of time (at least 4 hours) before you have the injection.

Ask your doctor or nurse if you have any questions.

Pregnancy and breast-feeding
You must tell your doctor if you are pregnant or think you may be pregnant. Your doctor will only use this product if he considers that the benefit outweighs the risk.

Do not breast-feed if you are given Steripet. This is because small amounts of 'radioactivity' may pass into the mother's milk. If you are breast-feeding, your doctor may wait until you have finished breast-feeding before using Steripet. If it is not possible to wait your doctor may ask you to:

- stop breast-feeding for 12 hours, and
- use formula feed for your child, and
- express (remove) breast milk and throw away the milk.

Your doctor will let you know when you can start breast-feeding again.

Driving and using machines
Ask your doctor if you can drive or use machines after you have been given Steripet.

Test you may have before being given Steripet

- The amount of glucose in your blood may be checked before you are given Steripet.

Ask your doctor if you have any questions.

Important information about Steripet
When Steripet is used you are exposed to radioactivity.

- Your doctor will always consider the possible risks and benefits before you are given the medicine.
- You will be encouraged to pass water (urinate) after you have been given Steripet because this removes radioactivity from your body.
- The doctor will ask you to avoid close contact with young children for the first 12 hours following the use of Steripet.

Ask your doctor if you have any questions.

turn over ➤

3. How Steripet is given

Steripet will be given to you by a specially trained and qualified person.

- Steripet will always be used in a hospital or clinic.
- You may be asked to urinate after you have had your scan.
- You may be asked to relax and not read or speak. This is to reduce muscle tension before you have your scan.
- They will tell you anything you need to know for its safe use.

Your doctor will decide on the dose that is best for you.

The usual dose is:

- One single injection.

If you are given more Steripet than you should

Steripet is given in a hospital or clinic by a specially trained and qualified person. It is unlikely that you will be given too much.
If you have any concerns talk to your doctor or nurse.

4. Possible side effects

There have been no reports of any side effects after the use of Steripet. Although like all medicines, Steripet may cause side effects.

If you notice any side effects please tell your doctor or nurse.

5. How to store Steripet

The product label includes the correct storage conditions and the expiry date for the batch. Hospital staff will ensure that the product is stored correctly, including at the correct temperature (2 to 8°C). They will also ensure that the product is disposed of correctly and not used after the expiry date stated on the label.

6. Further information

What Steripet contains

- The active ingredient is fludeoxyglucose (^{18}F). Each ml of Steripet contains 250 MBq (Megabecquerel – the unit in which radioactivity is measured) of fludeoxyglucose at a fixed time.
- The other ingredients are sodium dihydrogen phosphate, sodium hydroxide and water for injections.

What Steripet looks like and contents of the pack

Steripet is supplied as a single colourless glass vial containing between 1 ml and 10 ml of a solution for injection.

Marketing Authorisation Holder

GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA
United Kingdom

Manufacturers

GE Healthcare S.r.l.
c/o Joint Research Centre
Unità BMS – Istituto I.H.C.P.
Cyclotron Building
21020 Ispra (Varese)
Italy

GE Healthcare B.V.
Den Dolech 2
5612 AZ, Eindhoven
The Netherlands

This leaflet was last approved in 07/2008.

Marketing Authorisations
UK: PL 00221/0171

Steripet is a trademark of GE Healthcare.

GE and the GE Monogram are trademarks of General Electric Company.

For position only

GE Healthcare

PATIENT INFORMATION

SteriPET (Fludeoxyglucose^{18}F)

250 MBq/ml solution for injection

Fludeoxyglucose (^{18}F)

FDG1P

1 1 1 1 1 1 1

P/0000/00

Steripet 250 MBq/ml Solution for Injection **FDG1P**

1. NAME OF THE MEDICINAL PRODUCT

Steripet 250 MBq/ml
Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution for injection contains 250 MBq Fludeoxyglucose (^{18}F) at the date and time of calibration.

The activity per vial ranges from 1 to 2.5GBq.

Fluorine-18 decays to stable oxygen-18 with a half-life of 109.77 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511keV.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless or slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.
Fludeoxyglucose (^{18}F) is indicated for use with positron emission tomography (PET).

Oncology

Steripet is indicated for imaging in patients undergoing oncologic diagnostic procedures describing function or diseases where enhanced glucose influx of specific organs or tissues is the diagnostic target. The following indications are sufficiently documented (see also section 4.4):

Diagnosis:
- Characterisation of solitary pulmonary nodule
- Detection of cancer of unknown origin, revealed for example by cervical adenopathy, liver or bone metastases.
- Characterisation of a pancreatic mass

Staging:
- Head and neck cancers including assistance in guiding biopsy
- Primary lung cancer
- Locally advanced breast cancer
- Oesophageal cancer
- Carcinoma of the pancreas
- Colorectal cancer particularly in restaging recurrences
- Malignant lymphoma
- Malignant melanoma, Breslow >1.5 mm or lymph node metastasis at first diagnosis

Monitoring of therapeutic response :
- Malignant lymphoma
- Head and neck cancers

Detection in case of reasonable suspicion of recurrences:
- Glioma with high grade of malignancy (III or IV)
- Head and neck cancers
- Thyroid cancer (non-medullary): patients with increased thyroglobulin serum levels and negative radioactive iodine whole body scintigraphy
- Primary lung cancer
- Breast cancer
- Carcinoma of the pancreas
- Colorectal cancer
- Ovarian cancer
- Malignant lymphoma
- Malignant melanoma

Cardiology

In the cardiologic indication, the diagnostic target is viable myocardial tissue that takes up glucose but is hypo-perfused, as it must be assessed beforehand using appropriate blood-flow imaging techniques.
- Evaluation of myocardial viability in patients with severe impaired left ventricular function who are candidates for revascularisation when conventional imaging modalities are not contributive.

Neurology

In the neurologic indication, the interictal glucose hypometabolism is the diagnostic target.
- Localisation of epileptogenic foci in the presurgical evaluation of partial temporal epilepsy.

4.2 Posology and method of administration

Posology

The recommended activity for adults is 100 to 400 MBq (depending on the body weight of the patient and the type of camera used), administered by direct intravenous injection.

The experience in children is limited. Only few clinical data are available for patients aged under 18 years concerning safety and diagnostic efficacy of the product. Therefore, the use in oncologic paediatrics has to be carefully weighted.

The activity administered to children and to adolescents is a fraction of the activity recommended for adults.

This activity can be determined from the recommended activity for adults on the basis of body mass, using the following multiplying coefficient.

3kg = 0.10	22kg = 0.50	42kg = 0.78
4kg = 0.14	24kg = 0.53	44kg = 0.80
6kg = 0.19	26kg = 0.56	46kg = 0.82
8kg = 0.23	28kg = 0.58	48kg = 0.85
10kg = 0.27	30kg = 0.62	50kg = 0.88
12kg = 0.32	32kg = 0.65	52-54kg = 0.90
14kg = 0.36	34kg = 0.68	56-58kg = 0.92
16kg = 0.40	36kg = 0.71	60-62kg = 0.96
18kg = 0.44	38kg = 0.73	64-66kg = 0.98
20kg = 0.46	40kg = 0.76	68kg = 0.99

Administration of Steripet and PET examination

The activity of Fludeoxyglucose (^{18}F) has to be measured with a calibrator immediately prior to injection.

The injection must be intravenous in order to avoid irradiation as a result of local extravasation, as well as imaging artefacts.

The emission scans are usually started 45 to 60 minutes after the injection of Fludeoxyglucose (^{18}F). Provided sufficient activity remains for adequate counting statistics, Fludeoxyglucose (^{18}F) PET can also be performed up to two or three hours after administration, thus reducing background activity. If required, repeated examinations can be carried out at short notice.

4.3 Contraindications

Steripet is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and special precautions for use

Indication of the examination

For all patients, the radiation exposure must be justifiable by the expected diagnostic information achieved with the lowest possible radiation dose.

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

It should be taken into consideration that the effective dose per MBq is higher in children than in adults (see 11 dosimetry).

Patient preparation

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

In order to obtain images of best quality and to reduce the radiation exposure of the bladder patients should be encouraged to drink sufficient amounts and to empty prior to and after the PET examination.

Oncology and neurology

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

The cerebral glucose metabolism depends on the brain activity. Thus neurological examinations should be performed after a relaxation period in a darkened room and with less background noise.

A blood glucose test should be performed prior to administration since hyperglycaemia may result in a reduced sensitivity of Steripet, especially when glycaemia is greater than 8 mmol/L.

Similarly, Fludeoxyglucose (^{18}F)- PET should be avoided in subjects presenting uncontrolled diabetes.

Cardiology

Since glucose uptake in the myocardium is insulin-dependent for a myocardial examination a glucose loading of 50g approximately 1 hour prior to the administration of Steripet is recommended. Alternatively, especially for patients with diabetes mellitus, the blood sugar level can be adjusted by a combined infusion of insulin and glucose (Insulin-Glucose-Clamp) if needed.

Interpretation of the FDG PET images

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

False positive or false negative FDG-PET results cannot be excluded after radiotherapy within the first 2-4 months. If the clinical indication is demanding an earlier diagnosis by FDG-PET, the reason for earlier FDG-PET examination must be reasonably documented.

A delay of at least 4-6 weeks after the last administration of chemotherapy is optimal, in particular to avoid false negative results. If the clinical indication is demanding an earlier diagnosis by FDG-PET, the reason for earlier FDG-PET examination must be reasonably documented. In case of chemotherapy regimen with cycles shorter than 4 weeks, the FDG-PET examination should be done just before re-starting a new cycle.

In low-grade lymphoma and suspicion of recurrence of ovarian recurrent cancer, only positive predictive values have to be considered because of a limited sensitivity of FDG-PET.

Fludeoxyglucose (^{18}F) is not effective in detecting brain metastases.

When applying a coincidence PET scanner system, sensitivity is reduced in comparison to dedicated PET, resulting in reduced detection of lesions smaller than 1 cm.

It is recommended that Fludeoxyglucose (^{18}F)-PET images shall be interpreted in relation with tomographic anatomical imaging modalities (e.g. CT, ultrasonography, MRI). Fusion of the functional fludeoxyglucose (^{18}F)-PET images with morphologic images e.g. PET-CT can lead to an increased sensitivity and specificity, and is recommended in pancreas, head and neck tumours, lymphoma, melanoma, lung cancers and recurrent colorectal cancers.

General Warnings

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

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

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

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

4.5. Interaction with other medicinal products and other forms of interaction

All medicinal products that modify blood glucose levels can affect the sensitivity of the examination (e.g. corticosteroids, valproate, carbamazepine, phenytoin, phenobarbital and catecholamines).

Under administration of colony-stimulating factors (CSFs), there is an increased uptake of Fludeoxyglucose (^{18}F) in the bone marrow and the spleen for several days. This must be taken into account for the interpretation of PET imaging. Separating CSF therapy from PET imaging by an interval of at least 5 days may diminish this interference.

The administration of glucose and insulin influences the influx of Fludeoxyglucose (^{18}F) into the cells. In the case of high blood glucose levels as well as low plasma insulin levels, the influx of Fludeoxyglucose (^{18}F) into organs and tumours is reduced.

4.6 Pregnancy and lactation

There is no clinical experience with the use of fludeoxyglucose (^{18}F) in pregnant women. When it is necessary to administer radioactive medicinal products to women of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists, it is important that radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques that do not involve ionising radiation have to be considered.

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

Administration of Steripet at activity of 400 MBq results in an absorbed dose to the uterus of 8.4 mGy.

In this dose range, lethal effects and the induction of malformations, growth retardations and functional disorders are not to be expected; however, the risk of the induction of cancer and hereditary defects may be increased.

Steripet should not be administered during pregnancy unless clearly necessary or when the benefit of the mother outweighs the risk of the foetus.

Fludeoxyglucose (^{18}F) is secreted into breast milk. Before administering Fludeoxyglucose (^{18}F) to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding. If administration during lactation is unavoidable, breast feeding has to be interrupted for at least 12 hours and the expressed milk has to be discarded. When appropriate, milk may be drawn off prior to administration of Steripet. Moreover, for radioprotection reasons, it is recommended to avoid close contact between the mother and the infant during the initial 12 hours following injection.

4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects
Undesirable effects after the administration of Fludeoxyglucose (18F) have not been observed to date. Since the administered substance quantity is very low, the major risk is caused by the radiation. Exposure to ionising radiation can lead to cancer or development of hereditary defects. Most examinations involving nuclear medicine involve levels of radiation (effective dose) less than 20 mSv. These effects can be expected with a low probability. After administration of the maximum recommended activity of this Fludeoxyglucose (18F) product, the effective dose is about 7.6 mSv.

4.9 Overdose
An overdose in the pharmacological sense is unlikely given the doses used for diagnostic purposes.

If an overdose of Fludeoxyglucose (18F) has been administered, the radiation dose delivered to the patient must be reduced by increasing as much as possible the elimination of the radionuclide, by forced diuresis and frequent mictions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group : diagnostic radiopharmaceuticals
ATC code: V09I X04

At the chemical concentrations used for diagnostic examinations, Fludeoxyglucose (18F) does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties
Fludeoxyglucose (18F) is a glucose analogue, which is accumulated in all cells using glucose as a primary energy source. Fludeoxyglucose (18F) is accumulated in tumours with a high glucose turnover.

Following intravenous injection, the pharmacokinetic profile of Fludeoxyglucose (18F) in the vascular compartment is biexponential. It has a distribution time of 1 minute and an elimination time of approximately 12 minutes.

The cellular uptake of Fludeoxyglucose (18F) is performed by tissue-specific carrier systems, which are partly insulin-dependent and, thus, can be influenced by eating, nutritional condition and the existence of a diabetes mellitus. In patients with a diabetes mellitus a reduced uptake of Fludeoxyglucose (18F) into the cells occurs due to a changed tissue distribution and glucose metabolism.

Fludeoxyglucose (18F) is transported via the cell membrane in similar fashion to glucose, but only undergoes the first step of glycolysis resulting in formation of Fludeoxyglucose (18F)-6-phosphate, which remains trapped within the tumour cells and is not further metabolised. Since the following dephosphorylation by intracellular phosphatases is slow, Fludeoxyglucose (18F)-6-phosphate is retained in the tissue over several hours (trapping-mechanism).

In healthy subjects, Fludeoxyglucose (18F) is widely distributed throughout the body, particularly in the brain and heart, and to a lesser degree in the lungs and liver. Elimination of Fludeoxyglucose (18F) is chiefly renal, with 20% of activity being excreted in urine in the 2 hours following injection.

Binding to renal parenchyma is weak, but because of renal elimination of Fludeoxyglucose (18F), the entire urinary system, particularly the bladder, exhibits marked activity.

Fludeoxyglucose (18F) passes the blood-brain barrier. Approximately 7% of the injected dose is accumulated in the brain within 80-100 minutes after injection. Epileptogenic foci exhibit a reduced glucose metabolism in the seizure-free phases.

Approximately 3% of the injected activity is taken up by the myocardium within 40 minutes. The distribution of Fludeoxyglucose (18F) in normal heart is mainly homogenous, however, regional differences of up to 15% are described for the interventricular septum. During and after a reversible myocardial ischemia, an increased glucose uptake occurs into the myocardial cell. 0.3% and 0.9 - 2.4% of the injected activity are accumulated in the pancreas and lung respectively. Fludeoxyglucose (18F) is also bound to a lesser extent to ocular muscle, pharynx and intestine. Binding to muscle may be seen following recent exertion and in the event of muscular effort during the examination.

5.3 Preclinical safety data
In preclinical studies of acute toxicity the 50 fold human dose in dogs and the 1000-fold human dose in mice did not reveal any signs of toxicity.
Studies of chronic toxicity, of mutagenic potential as well as studies of reproduction toxicity and carcinogenic potential have not been performed because of the intended clinical use of the substance (usually a single intravenous application of the substance in the range of ng or µg).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium dihydrogen phosphate
Sodium hydroxide
Water for injections

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life
The shelf life of the product is not more than 10 hours from the time of manufacture.

6.4 Special precautions for storage
Store below 25°C.

This product should be stored in accordance with national regulations concerning radioactive products.

6.5 Nature and contents of container
Steripet is supplied in Ph. Eur Type 1 clear glass vials sealed with a chlorobutyl rubber closure and an aluminium overseal for multidose use. One vial contains between 1 and 10 ml of solution, corresponding to 1 to 2.5GBq at calibration time.

6.6 Special precautions for disposal
Normal safety precautions for handling radioactive materials should be observed. After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

7. MARKETING AUTHORISATION HOLDER
GE Healthcare Limited
Amersham Place
Little Chalfont
Buckinghamshire
HP7 9NA
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
UK PL 00221/0171, Denmark DK.R 2233, Norway MTnr. 05-3635

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION
16 May 2005

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY

The table below shows the dosimetry as calculated according to Publication 80 of the ICRP (International Commission on Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press 1999).

Absorbed dose per Unit Activity Administered

Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.012	0.015	0.024	0.038	0.072
Bladder	0.160	0.210	0.280	0.320	0.590
Bone surfaces	0.011	0.014	0.022	0.035	0.066
Brain	0.028	0.028	0.030	0.034	0.048
Breast	0.0086	0.011	0.018	0.029	0.056
Gall bladder	0.012	0.015	0.023	0.035	0.066
GI tract					
Stomach	0.011	0.014	0.022	0.036	0.068
Small intestine	0.013	0.017	0.027	0.041	0.077
Colon	0.013	0.017	0.027	0.040	0.074
ULI	0.012	0.016	0.025	0.039	0.072
LLI	0.015	0.019	0.029	0.042	0.076
Heart	0.062	0.081	0.120	0.200	0.350
Kidneys	0.021	0.025	0.036	0.054	0.096
Liver	0.011	0.014	0.022	0.037	0.070
Lungs	0.010	0.014	0.021	0.034	0.065
Muscles	0.011	0.014	0.021	0.034	0.065
Oesophagus	0.011	0.015	0.022	0.035	0.068
Ovaries	0.015	0.020	0.030	0.044	0.082
Pancreas	0.012	0.016	0.025	0.040	0.076
Red marrow	0.011	0.014	0.022	0.032	0.061
Skin	0.008	0.010	0.016	0.027	0.052
Spleen	0.011	0.014	0.022	0.036	0.069
Testes	0.012	0.016	0.026	0.038	0.073
Thymus	0.011	0.015	0.022	0.035	0.068
Thyroid	0.010	0.013	0.021	0.035	0.068
Uterus	0.021	0.026	0.039	0.055	0.100
Remaining organs	0.011	0.014	0.022	0.034	0.063
Effective dose	0.019	0.025	0.036	0.050	0.095

For Steripet, the effective dose resulting from the administration of an activity of 400 MBq is about 7.6 mSv (for an individual weighing 70 kg).

For this activity of 400 MBq, the radiation doses delivered to the critical organs, bladder, heart and brain are respectively: 64 mGy, 25 mGy and 11 mGy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
The package must be checked before use and the activity measured using a calibrator.

The medicinal product may be diluted with sodium chloride 9 mg/ml (0.9%) solution for injection.

Withdrawals should be performed under aseptic conditions. The vials must not be opened after disinfecting the stopper; the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle.

The solution should be inspected visually prior to use. Only clear solutions, free of visible particles should be used.

This product should be stored in accordance with national regulations concerning radioactive products.

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences of the local competent official organisations (see section 6.6).

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken. The disposal of waste should be in accordance with the relevant national and international guidelines.

Any unused product or waste material should be disposed of in accordance with local requirements.

13. FURTHER INFORMATION
Manufacturers:
GE Healthcare S.r.l.
c/o Joint Research Centre
Unità BMS – Istituto I.H.C.P
Cyclotron Building
21020 Ispra (Varese)
Italy

GE Healthcare B.V.
Den Dolech 2
5612 AZ Eindhoven
The Netherlands

Steripet is a trademark of GE Healthcare

GE and the GE Monogram are trademarks of General Electric Company

GE Healthcare

TECHNICAL LEAFLET

SteriPET™ Fludeoxyglucose(18F)

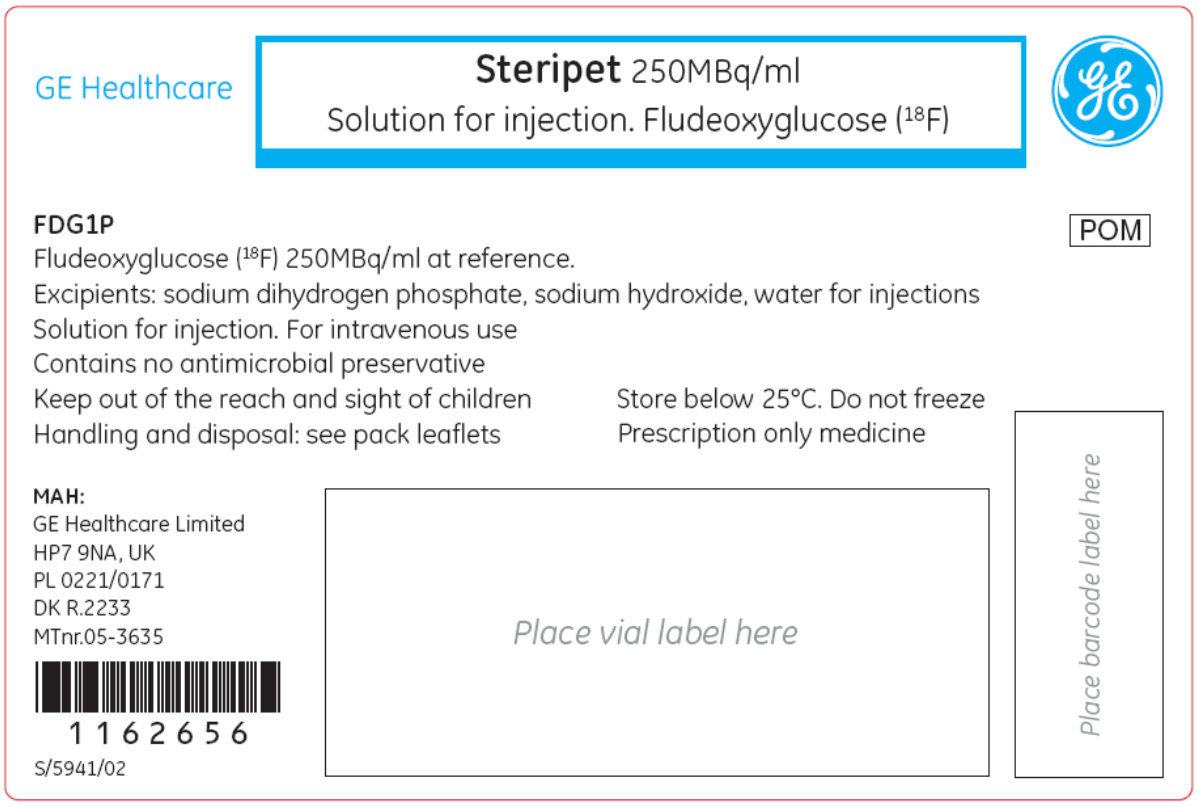
Steripet 250MBq/ml
Solution for Injection
Fludeoxyglucose (18F)

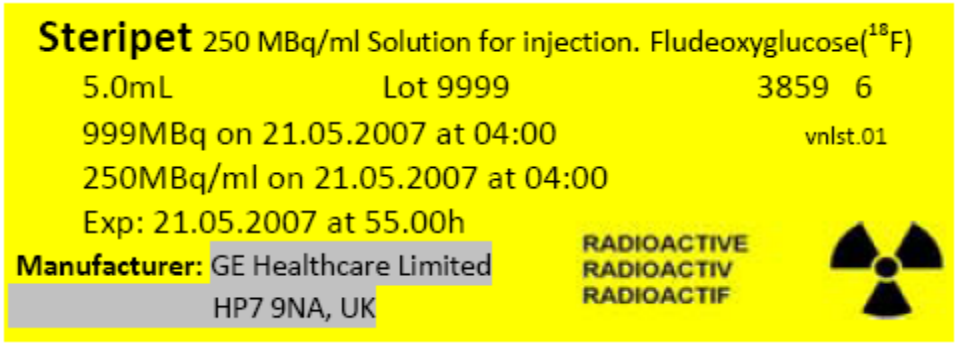
FDG1P

1 1 4 2 7 0 5

L/5637/02

Module 4
Labelling





Module 5
Scientific discussion during initial procedure

1. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Steripet 250 MBq/ml Solution for Injection could be approved. The product is a prescription-only medicine for diagnostic use only.

These are applications made under the mutual recognition procedure (MRP), according to Article 10a of Directive 2001/83 EC, as amended.

The active substance, Fludeoxyglucose (^{18}F), ([^{18}F]FDG), is a radiopharmaceutical which is used for diagnostic purposes in conjunction with Positron Emission Tomography (PET). [^{18}F]FDG competes with "normal" glucose to be incorporated into the cell by a membrane carrier-facilitated transport mechanism, by glucose transporters which are located in the cell membrane. It is phosphorylated within the cell to [^{18}F]FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated it cannot exit until it is dephosphorylated by glucose-6-phosphatase. The following points highlight [^{18}F]FDG clinical usefulness.

- [^{18}F]FDG will accumulate at higher rates in tumour cells than in non-neoplastic cells, and this is the basis for using [^{18}F]FDG as a tumour marker in oncology clinical practice.
- In the heart, under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidizing free fatty acids. However, under ischaemic conditions exogenous glucose becomes the preferred myocardial substrate. Under these conditions, phosphorylated [^{18}F]FDG accumulates in the myocyte and can be detected with PET imaging.
- In the brain, glucose metabolism provides approximately 95% of the ATP required for brain function. Under physiological conditions glucose metabolism is tightly connected to neuronal activity. Therefore, changes in neuronal activity induced by disease are reflected in an alteration of glucose metabolism.

Fludeoxyglucose (FDG) [^{18}F] has a well-established medicinal use as a diagnostic radiopharmaceutical agent. It has been used in research for more than 15 years and has a recognised clinical utility worldwide, including the EU.

The application of FDG [^{18}F] in the metabolic detection of malignant tumours has been shown to be a useful tool in oncology, as demonstrated by numerous published clinical studies. However, the technique appears to be complementary to morphological imaging and it should be used in clinical settings for which its usefulness has been demonstrated.

No new preclinical or clinical studies were conducted, which is acceptable given that the legal basis for this application is Article 10a, i.e. a bibliographic application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting authorisation.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

2. QUALITY ASPECTS

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

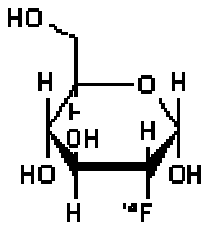
INN: Fludeoxyglucose ^{18}F

Other names: FDG, 2-Deoxy-2-fluoro-D-glucose

Chemical Name: 2-[^{18}F]fluoro-2-deoxy- D -glucopyranose (2-[^{18}F]fluoro-2-deoxy- D -glucose)

Molecular Formula: $C_6H_{11}{}^{18}FO_5$

Structure:



2 Deoxy 2 fluoro ^{18}F D glucopyranose

Molecular Mass: 181.15

Appearance: As the injection - A clear colourless or slightly yellow solution, free from particulates.

3.2.S.2 Manufacture

A detailed description of the manufacture of the active substance Fludeoxyglucose ^{18}F from its starting materials has been provided. Satisfactory certificates of analysis have been provided for all starting materials. Suitable in-process controls are present and a satisfactory process validation data have been provided from production-scale batches.

3.2.S.3 Characterisation

Suitable data concerning the elucidation of structure and other characteristics have been provided. A review of the potential impurities present in the active substance has been provided.

3.2.S.4 Control of Drug Substance

No drug substance specification has been provided as these tests are done as part of the finished product specification.

3.2.S.5 Reference Standards or Materials

See drug product below.

3.2.S.6 Container Closure System

See drug product below.

3.2.S.7 Stability

See drug product below.

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

The drug product is a sterile solution of 250MBq/ml (^{18}F) Fludeoxyglucose in water for injections. Other ingredients consist of the pharmaceutical excipients sodium dihydrogen phosphate and sodium hydroxide. It is available in a 10ml colourless Type I glass vial, with a Type I chlorobutyl rubber stopper and an aluminium overseal.

3.2.P.2 Pharmaceutical Development

The objective of the development programme was to formulate a stable, acceptable solution for injection, containing Fludeoxyglucose (^{18}F) that could be used for diagnostic purposes in conjunction with Positron Emission Tomography (PET).

Suitable pharmaceutical development data have been provided.

3.2.P.3 Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the finished product. The results appear satisfactory.

3.2.P.4 Control of Excipients

All excipients are controlled to their respective European Pharmacopoeia monograph. None of the excipients contain materials of animal or human origin. Satisfactory certificates of analysis have been provided for all excipients.

3.2.P.5 Control of Drug Product

The finished product specification is satisfactory. Test methods have been described and have been adequately validated as appropriate. Batch data have been provided and comply with the release specification.

3.2.P.6 Reference Standards or Materials

Certificate of analysis have been provided for all standards used.

3.2.P.7 Container Closure System

The product is packed in 10ml colourless Type I glass vial, with a Type I chlorobutyl rubber stopper and an aluminium overseal. One vial contains between 1 and 10 ml of solution, corresponding to 250 MBq to 2.5 GBq at calibration time.

Specifications are provided for all packaging. All primary packaging complies with current regulations concerning contact with products for parenteral use.

3.2.P.8 Stability

Stability data have been provided for batches of finished product, in accordance with ICH guidelines. The data support a shelf-life of 10 hours from the time of production, with storage conditions “Store below 25°C, both before and after the vial is opened” and “This product should be stored in accordance with national regulations concerning radioactive products.”

SPC, LABELS AND PACKAGE LEAFLET

The SPC, labels and leaflet supplied are pharmaceutically satisfactory.

PHARMACEUTICAL CONCLUSIONS

The grant of a product licence is recommended.

3. NON-CLINICAL ASPECTS

The marketing authorisation holder has submitted a suitable preclinical overview, which was written by an appropriately qualified person.

4. CLINICAL ASPECTS

CLINICAL PHARMACOLOGY

Pharmacodynamics

Fludeoxyglucose (^{18}F) is a glucose analogue that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. Fludeoxyglucose (^{18}F) is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to [^{18}F] FDG-6-phosphate by the enzyme hexokinase. Once phosphorylated, it cannot exit until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, the retention and clearance of Fludeoxyglucose (^{18}F) reflects a balance involving glucose transporter, hexokinase and glucose-6-phosphatase activities. When allowance is made for the kinetic differences between glucose and Fludeoxyglucose (^{18}F) transport and phosphorylation (expressed as the “lumped constant” ratio), Fludeoxyglucose (^{18}F) is used to assess glucose metabolism.

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

In cancer, the cells are generally characterised by enhanced glucose metabolism partially due to (1) an increase in the activity of glucose transporters, (2) an increased rate of phosphorylation activity, (3) a reduction of phosphatase activity or (4) a dynamic alteration in the balance among all these processes.

In the heart under normal aerobic conditions, the myocardium meets the bulk of its energy requirements by oxidising free fatty acids. Most of the exogenous glucose taken up by the myocyte is converted into glycogen. However, under ischaemic conditions, the oxidation of free fatty acids decreases, exogenous glucose becomes the preferred myocardial substrate, glycolysis is stimulated, and glucose taken up by the myocyte is metabolised immediately instead of being converted into glycogen. Under these conditions, phosphorylated Fludeoxyglucose (^{18}F) accumulates in the myocyte and can be detected with PET imaging.

In the brain, glucose metabolism provides approximately 95% of the adenosine triphosphate required for brain function. Under physiological conditions glucose metabolism is tightly connected to neuronal activity. Therefore, changes in neuronal activity induced by disease are reflected in an alteration of glucose metabolism. In epilepsy, the glucose metabolism varies. Generally during a seizure, glucose metabolism increases. Interictally, the seizure focus tends to be hypometabolic. In dementia changes in glucose metabolism occur, e.g. in Alzheimer’s hypometabolism occurs in the temporal-parietal lobes.

Pharmacokinetics

Following intravenous administration of Fludeoxyglucose (^{18}F), the arterial blood level profile for Fludeoxyglucose (^{18}F) was described as a triexponential decay curve. The effective half-life ranges of the three phases were 0.19±0.10 minutes, 4.21±1.09 minutes, and 50.08±14.62 minutes.

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

Steripet may contain the impurity 2-deoxy-2-chloro-D-glucose (ClDG). Biodistribution and metabolism of C1DG are presumed to be similar to [^{18}F] FDG and would be expected to result in intracellular formation of 2-deoxy-2-chloro-6-phospho-D-glucose (C1DG-6-phosphate) and 2-deoxy-2-chloro-6-phospho-D-mannose (ClDM-6-phosphate). The phosphorylated deoxyglucose compounds are dephosphorylated and the resulting compounds (FDG, FDM, ClDG, and ClDM) presumably leave cells by passive diffusion.

Fludeoxyglucose (^{18}F) and related compounds are cleared from non-cardiac tissues within 3 to 24 hours after administration. Clearance from the cardiac tissue may require more than 96 hours. Fludeoxyglucose (^{18}F) that is not involved in glucose metabolism in any tissue is excreted unchanged in the urine.

The pharmacokinetics of Fludeoxyglucose (^{18}F) in renally impaired patients have not been characterised. Fludeoxyglucose (^{18}F) is eliminated through the renal system. Care should be taken to prevent excessive and unnecessary radiation exposure to this organ system and adjacent tissues.

The effects of fasting, varying blood sugar levels, conditions of glucose intolerance, and diabetes mellitus on Fludeoxyglucose (^{18}F) distribution in humans have not been ascertained. Diabetic patients may need stabilisation of blood glucose levels the day before and on the day of the Fludeoxyglucose (^{18}F) study.

EFFICACY

The applicant has submitted a literature review and analysis covering many different cancer types. The following is a summary of the experience of the use of [^{18}F] FDG in cancer patients as reported in the literature in prospective trials.

Head and Neck Cancer

Lymph node (LN) staging is the most important prognostic factor. Computed tomography (CT) and MRI are anatomical imaging modalities used in the evaluation of the initial extension of the disease and may help identifying enlarged lymph nodes. However not all metastatic nodes will be enlarged, neither will all enlarged nodes be metastatic. When evaluating response to therapy (surgery, radiation or chemotherapy) CT and MRI have not been able to reliable differentiate between post treatment structural changes from recurrence or residual disease (Parker *et al.* 2000).

[^{18}F] FDG avidly accumulates in primary head and neck tumours (Wong *et al.* 1997). PET scanning of the head and neck area represents a reasonable alternative to panendoscopy but has a significant rate of false positives when the chest is included in the field of view (Keyes *et al.* 2000). However, [^{18}F] FDG has higher sensitivity and specificity than CT/MRI in detecting LN metastases in primary and recurrent cancer (Table 1).

Table 1 [^{18}F] FDGPET versus CT/MRI, U/S and neck palpation lymph node staging in patients with head and neck cancer (N=434).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	82 [67-91]	93[80-100]	79[48-94]	93 [82-99]	90 [79-96]
CT/MRI	74 [33-95]	72[25-97]	60 [20-86]	95 [78-98]	89 [57-93]
U/S	72	70	19	96	70
Palpation	61	97	72	95	93

References: Adams *et al.* 1998, Kau *et al.* 1999, McGuirt *et al.* 1998, Safa *et al.* 1999, Braams *et al.* 1995, Benchaou *et al.* 1996, Wong *et al.* 1997. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. Values are average; ranges are in "[ ]".

Characterising structural abnormalities after therapy has important implications in clinical management and [^{18}F] FDG has been shown to be able to detect early recurrence and residual disease, reducing the need for multiple random biopsies, a clearly uncomfortable test for the patients (Table 2).

Table 2 [^{18}F] FDGPET versus other modalities in the investigation of recurrent head and neck cancer (N=268).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	91[80-100]	89 [81-96]	70	94	90[85.7-97]
CT/MRI	61 [22-72]	89 [79-100]	N/R	N/R	65[64.3-66]
U/S	63	65	42	81	64

References: Goerres *et al.* 2000, Greven *et al.* 1997, Kao *et al.* 1998, Lapela *et al.* 1995, Lapela *et al. 2000*, *Li* et al. 2001, Lowe *et al*, 1999, Lowe *et al.* 2000. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. Values are average. Ranges are in "[ ]". N/R: Not reported.

Surveying the entire body with [^{18}F] FDG PET in search of a primary malignancy that debuts as metastatic LN in the head and neck area is also a valid alternative when the primary source has not been found (Braams *et al. 1997, Safa* et al. 1999). [$^{18F]}$ FDG can also detect early recurrence following failure of therapy in patients with head and neck cancer, allowing for an early change in patient therapy and avoiding the co-morbidities of an anti-cancer regimen with no obvious benefit to patients (Kitagawa *et al.* 1999, Lowe *et al.*1997).

Thyroid Cancer

Seven articles (from a total of 19) fulfilled the selection criteria, reporting the experience in a population of 367 patients. There is enough evidence that [^{18}F] FDG has several added advantages in the management of patients with DTC:

- [^{18}F] FDG can differentiate between benign and malignant nodules within the thyroid gland with an accuracy of 73% (Sasaki 1997).
- [^{18}F] FDG PET can yield additional information in the staging and can depict sites of tumour when ^{131} I whole body scintigraphy [WBS] images are negative in those patients with rising tumour markers and no evidence of disease, in 50-95% of the cases depending upon the series (Dietlin *et al.* 1998, Feine *et al.* 1996, Grundwald *et al.* 1996, 1997)

Lung Cancer, Including Single Pulmonary Nodule

A total of 33 out of 94 articles fulfilled the selection criteria. Total number of patients included in these series is 1,452. Differential uptake of [^{18}F] FDG by indeterminate pulmonary lesions (as shown by either simple visual or quantitative analyses) can help in the differentiation of benign from malignant disease (Gupta *et al. 1998,* Duhaylongsod *et al.* 1995). The accuracy of this radiopharmaceutical as shown by these series is higher than 90% (n=148). However sensitivity may decrease if small lesions (<1cm) are evaluated with conventional SPECT cameras equipped with high energy collimators instead of dedicated PET scanners (Mastin *et al.* 1999) and with hybrid cameras (Tatsumi *et al.* 1999*).*

Table 3 [^{18}F] FDGPET and CT in the evaluation of lymph node metastases in patients with lung cancer (N=208).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	84 [67-100]	87 [75-98]	74 [64-91]	93 [89-100]	75 [78-99]
CT	63 [52-72]	84 [79-89]	63 [60-67]	83[82-83]	51[67-78]

References: Higashi K *et al.* 1998a, Tatsumi *et al* 1999, Bury *et al.* 1996a, Chin *et al.* 1995, Scott *et al.* 1996, Nettelbladt *et al.* 1998, Magnani *et al.* 1999, Patz *et al.* 1995. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. Values are averages. Ranges are in "[ ]".

[^{18}F] FDG can complement information derived from structural imaging, mainly CT in the evaluation of lung malignancy (Albes *et al.* 1999, Magnani *et al.* 1999, Vansteenskiste *et al*. 1998) (n=123), and possible metastases to the adrenal glands (Erasmus *et al.* 1997*) (n=27).*

Patients undergoing therapy (surgery, chemo or radiation therapy) for lung cancer can benefit from the functional information obtained from an [^{18}F] FDG scan, since early detection of recurrent/residual disease is not dependent on the therapy induced structural changes (n=199) (Inoue *et al.* 1995, Bury *et al.* 1999, Vansteenskiste *et al.* 1998) as well as predicting response to therapy (n=30) (Ichiya *et al.* 1996).

Gupta *et al* found that abnormal [^{18}F] FDG uptake in radiographically indeterminate pulmonary nodules had 83% probability of being malignant, but those lesions without uptake only carried a 4.3% probability (n=63) (Gupta *et al.* 1996). The experience in 189 patients (Bury *et al.* 1996b, Lowe *et al.* 1998, Prauer *et al.* 1998) shows that [^{18}F] FDG can accurately predict malignancy in cases with indeterminate SPN by structural images, as shown in Table 4 below.

Table 4 [^{18}F] FDGPET and CT in the evaluation of SPN (N=189)

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	95 [90-100]	82 [69-90]	94	100	87
CT	100*	52	74	100	N/R

References: Bury *et al* 1996b, Lowe et al. 1998, Prauer *et al.* 1998. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy Values are averages. Ranges are in "[ ]". N/R: Not reported. *Sensitivity of CT for detecting SPN is considered to be 100 since this is a screening test and all patients were sent to [^{18}F] FDG PET imaging after being found to have SPN by CT

Breast Cancer

The following summarises the evidence extracted from 15 out of 48 articles that fulfilled the selection criteria. Clinical experience involves a total of 946 patients. [^{18}F] FDG has been evaluated in the differential diagnoses of breast lesions. The published series indicate that this radiopharmaceutical can differentiate benign from malignant tissue within the breast (n=124) with a sensitivity of 68-94% and a specificity of 84-97% (Avril *et al*. 1996, Avril *et al*. 1997). It can also aid in evaluating the extent of the primary cancer if the entire body is surveyed, having a higher accuracy than physical examination (n=57) (Scheidhauer *et al. 1996*, Noh *et al*. 1998), and detecting metastatic LN and other unsuspected sites of disease (n=51) (Avril *et al.* 1996). Imaging with [^{18}F] FDG also provides the additional advantage of not being affected by structural changes, i.e. those related with therapeutic or plastic surgery (Noh *et al.* 1998).

In the evaluation of the LN status in the axillae, [^{18}F] FDG has higher accuracy than physical exam (see table 5), although is not considered a replacement for axillary lymph node dissection (n=167) (Greco *et al.* 2001).

Table 5 [^{18}F] FDGPET versus physical examination (PE) in the evaluation of axillary LN metastases from breast cancer (N=620).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	89 [79-100]	85[66-97]	95	96[95-96]	87[77-94]
PE	57	90	80	74	76

References: Crippa *et al.* 1998, Utech *et al.* 1996. Adler *et al.* 1997, Crippa *et al.* 1997, Smith *et al.* 1998. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. PE: Physical examination. Values are averages. Ranges are in "[ ]".

Cancer of the Digestive System

These tumours account for one-fifth of all new visceral cancers. Their frequency and mortality will vary with the organ involved.

(a) Gastro-oesophageal Cancer

Experience in eight published trials that fulfilled the selection criteria (total number of 16) shows that oesophageal tumours are capable of concentrating [^{18}F] FDG at a higher rate than surrounding, normal tissues, allowing the differentiation between benign and malignant lesions (n=64) (Fukunaga *et al.* 1998, McAteer *et al.* 1999). However, due to the spatial resolution of the PET technique (compared with CT), isolation of disease-free wall and identification of surrounding LN is difficult (n=25) (Rankin *et al.* 1998.

(b) Liver Cancer

A total of four out of 12 articles fulfilled the selection criteria. The evidence indicates that evaluation of patients with primary liver tumours by means of [^{18}F] FDG can help in differentiating benign from malignant tumours and yields information regarding their histologic grade in a significant number of cases (n=127) (Torizuka *et al.* 1995, Delbeke *et al.* 1998). PET with [^{18}F] FDG can also improve staging in this group of patients by depicting metastases elsewhere (n=14) (Trojan *et al.* 1999) and monitor response to therapy (n=42) (Mantaka *et al.*1999). In the evaluation of suspected metastatic disease to the liver, [^{18}F] FDG can characterise these hepatic lesions (Delbeke *et al.* 1998) with a sensitivity of 89% (n=110).

(c) Pancreatic Cancer

The data from nine out of 26 papers show evidence that: a) that pancreatic cancer can effectively concentrate [^{18}F] FDG at a much higher rate than other benign conditions in the pancreas allowing for non-invasive detection of tumour (Friess *et al.* 1995, Kato *et al.* 1995, Keogan *et al.* 1998) (n=141), and b) this degree of uptake may be mediated by the expression of glucose transporters (GLUT-1) (n=35) (Higashi T *et al.* 1998). [^{18}F] FDG has higher diagnostic accuracy than ^{201}T1 SPECT (n=25)(Inokuma *et al.* 1995). Diagnostic accuracy is higher than conventional imaging modalities (CIM) as well (see table 6 below).

Table 6 [^{18}F] FDG PET versus (CT,U/S) in the differentiation of pancreatic carcinoma from chronic pancreatitis (N=167).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	95 [94-96]	91 [82-100]	96[94-100]	89[82-94]	91
U/S	93 [89-97]	55[45-64]	86[84-88]	72[56-88]	83[78-88]
CT	83 [80-89]	79[73-89]	87[80-91]	72[67-76]	85

References: Inokuma *et al.* 1995b, Stollfuss *et al.* 1995, Imdahl *et al.* 1999. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. CIM: conventional imaging modalities. Values are averages. Ranges are in "[ ]"

(d) Colorectal Cancer

Thirteen articles were selected from a total of 39. The following is a discussion of the evidence found in a population of 717 patients. [^{18}F] FDG PET has high sensitivity for depicting primary CRC, but remains suboptimal in detecting LN spread (which is also a drawback with CT imaging). However, [^{18}F] FDG PET also shows advantages over conventional imaging modalities, i.e. detection of liver metastases, early detection of local recurrence and assessing resectablility prior to surgery with curative intent (see Tables 7 and 8).

Table 7 [^{18}F] FDGPET versus CT in the detection of primary CRC and LN metastases (n=48).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)
Primary				
FDG-PET	100	43	90	100
CT	37	83	92	21
LN				

FDG-PET	29	96	80	72
CT	29	85	33	81

Reference: Abdel-Nabi et al. 1998. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value.

Table 8 [^{18}F] FDG PET versus CIM in the detection of liver metastases and local recurrence of CRC (n=349).

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
Liver					
FDG-PET	92 [88-95]	99[97-100]	99.7 [99-100]	83[71-97]	94[92-98]
CT	72[38-86]	78[58-97]	82[75-92]	66[41-86]	82[76-93]
CT port	97	7[5-9]	79[77-81]	42[33-50]	78[76-80]
Recurrence					
FDG-PET	89[79-97]	92[80-100]	N/R	N/R	95
CT	57[46-69]	94[90-98]	N/R	N/R	65

Refrences: Abdel-Nabi *et al.*1998, Lai *et al.* 1996, Delbeke *et al.* 1997, Vitola *et al.* 1996, Schiepers *et al. 1995*, Valk *et al*. 1999. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. CT port: CT portography. N/R: not reported. Values are averages. Ranges are in "[ ]".

Cancer of the genitourinary tract

(a) Ovarian Cancer

The evidence in three selected articles (total of 14) indicates that the addition of [^{18}F] FDG to U/S and MRI in the evaluation of asymptomatic adnexal masses improves the refinement of the differential diagnosis (n=101) (Grab *et* al. 2000). Furthermore, this holds true also for the staging of known ovarian cancer (n=64) (Schröder *et al.* 1999, Nakamoto *et al.* 2001).

(b) Uterine and Cervical Cancer

Experience drawn from four published reports that met the selection criteria (total of 8) shows that [^{18}F] FDG can accumulate in primary CC and metastatic lymph nodes (n=88) (Sugawara *et al.* Rose *et al.*1999, Reinhardt *et al.* 2001), as well as recurrent UC (n=13) (Umesaki *et al. I2000).* Interestingly tumour detection rates were slightly higher than those of MR1 (n=48) (Reindhardt *et al.* 2001, Umesaki *et al.* 2000).

Lymphoma

Evidence from 19 selected articles (total of 55) show that lymphomas accumulate [^{18}F] FDG at higher rates than non-lymphomatous lesions (n=22) (Lapela *et al.* 1995), enabling improved staging (Hoh *et al.* 1997, Moog *et al. 1997*, Bangerter et al. 1998, Jerusalem *et al.* 1999, Buchman *et al* 2000), for which [^{18}F] FDG exhibits higher diagnostic accuracy than CT (n=330). [^{18}F] FDG can also detect additional sites of disease not shown by conventional procedures and identify absence /presence of disease in sites suspected to be involved by structural imaging modalities (n=28) (Jerusalem *et al.* 2000).

Two studies have compared [^{18}F] FDG with [^{11}C]-Methionine in patients (n=42) with HD and NHL, finding no significant differences in detecting lymphomatous lesions by visual inspection (Rodriguez *et al.* 1995, Sutinen *et al.* 2000). Although both tracers appear then to be equally effective, it is worthy to mention that in clinical practice ^{11}C-labelled compounds are more cumbersome to manage than ^{18}F-labelled compounds due to the much shorter half life of the former compared with the latter.

Areas of abnormal [^{18}F] FDG uptake in the bone marrow have been correlated with suspected and unsuspected foci of lymphoma (n=184) (Moog *et al.* 1998, Moog *et al.* 1999, Carr *et al.* 1998). Evaluating residual masses with CT or MRI after therapy represents a diagnostic challenge, since these anatomical modalities cannot differentiate scar from residual tissue.

However, viable tumour accumulates [^{18}F] FDG (n=158) (Jerusalem *et al.* 1999, de Wit *et al. 1997*,Maisey *et al*. 2000, Dimitrakopoulos-Strauss *et al.* 1995) and this has therapeutic and prognostic implications (n=105) (Jerusalem *et al.* 2000, Cremerius *et al.* 2001, Bangerter *et al.* 1999).

Tumour of Unknown Origin

Surveying the whole-body in search of the source of UPT with [^{18}F] FDG has the advantage of no additional radiation dose to the patient (as opposed plain radiographs or CT examinations). Four articles (from a total of 13) that fulfilled the selection criteria report equivocal results in an inhomogenous population of patients with a wide variety of manifestations of UPT.

Experience in 39 patients shows a high sensitivity (>80%) but poorer specificity (<40%) (Lassen *et al*. 1999, Mukherji *et al*. 1996) when imaged with [^{18}F] FDG. The use of [^{18}F] FDG has been shown in sleeted cases to have utility (n=28) (Bohuslavizki *et al*. 1999), however, the literature is not in full agreement on this issue (Greven *et al.* 1999).

Musculoskeletal tumours

Evidence was collected from eight articles that fulfilled the selection criteria from a total of 17. PET scanning with [^{18}F] FDG has high accuracy in depicting primary soft tissue sarcomas, with a mean sensitivity of 95.75% (range, 91-100%), mean specificity of 74.5% (range, 66-82%) and accuracy of 86% (n=204 patients) (Kole *et al.* 1997, Lucas *et al.* 1999, Schulte *et al.* 1999, Schwarzbach *et al.* 1999). The degree of [^{18}F] FDG uptake is related with the tumour grade (n=70) (Eary *et al.* 1998) and has implications in patient management during monitoring of therapy (n=20) (Van Ginkel *et al.* 1996).

Malignant melanoma

Melanoma cells are very avid for [^{18}F] FDG. Experience in 226 patients (from 6 out 21 articles that fulfilled the selection criteria) shows that PET with [^{18}F] FDG has higher diagnostic accuracy in staging than CT, as shown in Table 9.

Table 9 [^{18}F] FDG PET versus CT in the staging of malignant melanoma (N=226)

Method	Sens (%)	Spec (%)	PPV(%)	NPV(%)	Acc(%)
FDG-PET	94.5 [92-100]	80.5[67-95]	94	57	92.5 [87-98]
CT	70[55-85]	71[58-84]	N/R	N/R	77

References: Boni *et al* 1995, Steinert, *et al* 1995, Holder *et al* 1998, Rinne *et al* 1998. Sens: sensitivity. Spec: specificity. PPV: positive predicted value. NPV: negative predictive value. Acc: accuracy. N/R: Not reported. Values are averages. Ranges are in "[ ]"

However, it seems that [^{18}F] FDG cannot replace sentinel node biopsy in the evaluation of local/regional LN spread (n=74) (Wagner *et al.* 1999) and may also miss small LN metastases in patients with primary lesions with <1.5mm thickness (n=23) (MacFarlane *et al.* 1998*).*

Assessor's Comment

The applicant has provided an extensive review and analysis of the literature in support of most of the oncological investigative and diagnostic procedures applied for as indications for use of the product. There appears to be a great deal of experience in many countries in Europe and worldwide regarding the use of [^{18}F] FDG in oncology. This is shown by the large number of published data which demonstrate its effectiveness that is comparable to the more established relevant procedures such as CT scanning and ultrasound.

SAFETY

No adverse events are reported in the published studies submitted for this application. The following is a summary of the safety review.

No randomised, blinded clinical trails assessing safety of [^{18}F] FDG injection were identified during the literature search. However, clinical experience is extensive. A prospective 4-year study was performed with 22 collaborating institutions in the USA using a questionnaire evaluating the number of PET procedures performed and the number of adverse events associated with PET radiopharmaceuticals, as well as with non-radioactive pharmaceuticals used for PET. As recorded by Silberstein, there were a total of 33,925 radiopharmaceutical doses. In addition, the total prospective number of administered doses recorded by the participants was 47,876, for a total number of positron emitting radiopharmaceutical administrations of 81,801. No adverse reactions were found from any PET radiopharmaceutical dose. The majority of the studies were performed with [^{18}F] FDG (Silberstein *et al.* 1998).

Another survey was performed in the EU with a total of 26 European PET centres participating. [^{18}F] FDG was by far the most used PET tracer with approximately 200 applications per week and not a single adverse reaction that could be related with any possible toxicological effect of [^{18}F] FDG was reported (Meyer *et al.*1995).

Assessor's Comment

It would appear the [^{18}F] FDG, when used as indicated, has been shown not to be toxic with no reported adverse reactions. The amount of activity injected is lower than most ^{99m}Tc-based radiopharmaceuticals used in clinical practice, and the radiation dose to the patient is also lower than most common nuclear as well as radiographic procedures commonly used in oncology.

EXPERT REPORT

A satisfactory and comprehensive clinical expert report has been submitted with appropriate CV.

SUMMARY OF PRODUCT CHARACTERISTICS

This is satisfactory.

PATIENT INFORMATION LEAFLET

This is satisfactory.

LABELLING

This is satisfactory.

DISCUSSION

The applicant has provided an extensive review and analysis of the literature in support of the oncological diagnostic procedures as indications for use of the product. There appears to be a great deal of experience in many countries in Europe and worldwide regarding the use of [^{18}F] FDG in oncology. This is shown by the large number of published data which demonstrate its effectiveness that is comparable to the more established diagnostic tools, such as CT scanning, MRI and ultrasound.

The presentation and discussions that support the different oncological indications are comprehensive with clear reviews of the different clinical settings.

In relation to the relevant oncological indications, overall, sufficient clinical information has been submitted. When used as indicated, [^{18}F] FDG has a favourable benefit-to-risk ratio. The hazard associated with [^{18}F] FDG appears to be low and acceptable when considered in relation to its therapeutic benefits.

CONCLUSIONS

A marketing authorisation may be granted on medical grounds.

5. OVERALL CONCLUSION

QUALITY

The important quality characteristics of Steripet 250 MBq/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

Suitable preclinical data were submitted for this application, based on relevant literature references.

EFFICACY

No new clinical data were submitted and none are required for an application of this type.

The summary of product characteristics, patient information leaflet and labelling are appropriate for a product of this type.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.

The bibliographic data provided have demonstrated Steripet 250 MBq/ml Solution for Injection to be an effective and safe medicinal product for diagnostic use.

Assessment of the benefits and risks for its use demonstrates a favourable benefit-risk profile.

Module 6

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome
01/04/2006	II	To update the SPC to extend the indications to neurology and cardiology, in line with the CMDh core SPC for Fludeoxyglucose, and to bring the SPC in line with the most recent QRD template.	Granted 22/11/2006
17/05/2006	IA	To register a new name and address of the Marketing Authorisation Holder in Spain from Amersham Health SA, Ronda de Poniente 12, Euronova, 28760 Tres Cantos, Madrid to GE Healthcare Bio-Sciences, S.A., Avda. de Europa, 22, Parque Empresarial "La Moraleja", E-28108 Alcobendas, Madrid.	Granted 30/06/2006
16/05/2006	IA	To register a new name and address of the Marketing Authorisation Holder in Italy from Amersham Health S.r.l., Via dei Giardini 7, 20121 Milano, Italia to GE Healthcare S.r.l, Via Galeno 36, 20126 Milano, Italia.	Granted 30/06/2006
30/06/2006	IA	To register a new name for the Marketing Authorisation Holder in The Netherlands from Amersham Health B.V. to GE Healthcare B.V. The address, Postbus 746, 5600 AS Eindhoven, Nederland, remains the same.	Granted 30/06/2006
19/06/2007	II	To update sections 2, 4.4, 5.1, 5.2, 6.1, 6.6, 7, 9, 11 of the SmPC with consequential changes to the leaflet for the healthcare professional and the patient information leaflet.	Granted 18/03/2008
27/07/2007	II	To provide the results of the PIL user testing. To also make some changes to the PIL including the conforming to the QRD templates.	Granted 29/08/2008