CBG MEB

Public Assessment Report

Scientific discussion

Steripet 250 MBq/ml, solution for injection

(fludeoxyglucose (^{18}F))

NL/H/3528/001/MR

Date: 20 February 2018

This module reflects the scientific discussion for the approval of Steripet 250 MBq/ml, solution for injection. The procedure was finalised on 29 June 2006. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. 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), (FDG (^{18}F)), is a radiopharmaceutical which is used for diagnostic purposes in conjunction with Positron Emission Tomography (PET). FDG (^{18}F) 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.

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

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.

II. QUALITY ASPECTS

II.1 Introduction

Drug substance:

- 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: $C_6H_{11}{}^{18}FO_5$
- Molecular Mass: 181.15
- Appearance: As the injection - A clear colourless or slightly yellow solution, free from particulates.

The drug product is a sterile solution of 250 MBq/ml (^{18}F) FDG in water for injections. Other ingredients consist of the pharmaceutical excipients sodium dihydrogen phosphate and sodium hydroxide. It is available in a 10 ml 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.

II.2 Drug Substance

Manufacturing process
A detailed description of the manufacture of the active substance FDG (^{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.

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.

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

Stability of drug substance
See drug product below.

II.3 Medicinal Product

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

Suitable pharmaceutical development data have been provided.

Manufacturing process
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.

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.

Quality 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.

Stability of drug product
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.”

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Steripet has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Steripet is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

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

IV. CLINICAL ASPECTS

IV.1 Pharmacodynamics

FDG (^{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. FDG (^{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 FDG (^{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 FDG (^{18}F) transport and phosphorylation (expressed as the “lumped constant” ratio), FDG (^{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 FDG (^{18}F) reflect the decrease or absence of glucose metabolism. Regions of increased uptake of FDG (^{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 FDG (^{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.

IV.2 Pharmacokinetics

Following intravenous administration of FDG (^{18}F), the arterial blood level profile for FDG (^{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.

FDG (^{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.

FDG (^{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. FDG (^{18}F) that is not involved in glucose metabolism in any tissue is excreted unchanged in the urine.

The pharmacokinetics of FDG (^{18}F) in renally impaired patients have not been characterised. FDG (^{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 FDG (^{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 FDG (^{18}F) study.

IV.3 Clinical 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). [^{18}F] 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 (<1 cm) 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 201T1 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 recur

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

References: 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 <1.5 mm thickness (n=23) (MacFarlane *et al.* 1998*).*

Assessor's Comment
The MAH 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 [18F] 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.

IV.4 Clinical 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 ^{99}mTc-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.

IV.5 Discussion on the clinical aspects

The MAH 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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3528/IA/060/G	• Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)* • Deletion of a supplier.		8-3-2016	Approval	
NL/H/3528/001/R/001	Renewal		10-6-2016	Approval	
NL/H/3528/1/IA/061	Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)*		6-7-2016	Approval	
NL/H/3528/1/IB/062	The main change is that the QRD statements regarding ADR reporting have been added to the SmPC and PIL. In addition a word that was omitted from the SmPC in error has been included and minor text changes to improve readability of the PIL have been made.		15-9-2016	Approval	
NL/H/3528/1/IA/065	The activities for which the manufacturer/importer is responsible include batch release		21-9-2016	Approval	
NL/H/3528/IB/063/G	• Change of name for one testing - deletion of the sterility testing facility • The detailed description of the pH test method is being reduced and cross-reference is made to Ph Eur monograph 2.2.3 (Variation B.II.d.2.f). • Approval is sought to update the specification and		24-9-2016	Approval	

	testing methods for Fludeoxyglucose (18F) Injection in line with the current Ph Eur monograph 1325.				
NL/H/3528/1/IB/064	Approval is sought to add a batch control testing site (sterility testing). Normally this would be classified as a Type IA variation, but this submission has been upgraded to a Type IB variation to reflect the fact that this change is a correction.		11-10-2016	Approval	
NL/H/3528/IB/063/G	• Change of name for one testing facility • Deletion of the sterility testing facility. • The detailed description of the pH test method is being reduced and cross-reference is made to Ph Eur monograph 2.2.3 (Variation B.II.d.2.f). • Approval is sought to update the specification and testing methods for Fludeoxyglucose (18F) Injection in line with the current Ph Eur monograph 1325.		24-9-2016	Approval	
NL/H/3528/IA/066/G	• To remove irrelevant cyclotron parameters from the dossier. • To delete a manufacturing site for active substance and to delete a manufacturing site for finished product. • To add an alternative sterility testing site.		24-5-2017	Partially approved	