COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

^{18}F-FDG Hoboken 250 MBq/ml, solution for injection

(fludeoxyglucose (^{18}F))

NL Licence RVG 121312

Date: 4 November 2019

This module reflects the scientific discussion for the approval of ^{18}F-FDG Hoboken 250 MBq/ml, solution for injection. The marketing authorisation was granted on 7 June 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CT	Computed Tomography
EANM	European Association of Nuclear Medicine
ED	Effective Dose
EEA	European Economic Area
EEG	Electroencephalography
ERA	Environmental Risk Assessment
FDM	2-fluoro-2-deoxy-D-mannose
ICH	International Conference of Harmonisation
LN	Lymph Node
MAH	Marketing Authorisation Holder
MIBI	methoxyisobutylisonitrile
PET	Positron Emission Tomography
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SNM	Society of Nuclear Medicine
SPECT	Single Photon Emission Computed Tomography
SPN	Single Pulmonary Nodule
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for ^{18}F-FDG Hoboken 250 MBq/ml, solution for injection from Cyclotron Rotterdam B.V.

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

Oncology
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 SmPC 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
- 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

Infectious or inflammatory diseases

In infectious or inflammatory diseases, the diagnostic target is tissue or structures with an abnormal content of activated white blood cells. In infectious or inflammatory diseases, the following indications are sufficiently documented:

<u>Localisation of abnormal foci guiding the aetiologic diagnosis in case of fever of unknown origin</u>

<u>Diagnosis of infection in case of:</u>

- Suspected chronic infection of bone and/or adjacent structures: osteomyelitis, spondilitis, diskitis or osteitis including when metallic implants are present
- Diabetic patient with a foot suspicious of Charcot's neuroarthropathy, osteomyelitis and/or soft tissue infection
- Painful hip prosthesis
- Vascular prosthesis
- Fever in an AIDS patient
- Detection of septic metastatic foci in case of bacteraemia or endocarditis

<u>Detection of the extension of inflammation in case of:</u>

- Sarcoidosis
- Inflammatory bowel disease
- Vasculitis involving the great vessels

<u>Therapy follow-up:</u>

Unresectable alveolar echinococcosis, in search for active localisations of the parasite during medical treatment and after treatment discontinuation.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a bibliographic application based on the well-established medicinal use of fludeoxyglucose (^{18}F). No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature.
The active substance has a long history of use in millions of patients over several decades. The numerous published clinical studies demonstrate the diagnostic benefits of ^{18}F-FDG in the various proposed indications. Furthermore, the provided literature shows that ^{18}F-FDG has been used in research for more than 15 years worldwide, including Europe, demonstrating the scientific interest of (^{18}F) FDG in the claimed indications.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

^{18}F-FDG Hoboken 250 MBq/ml is a clear, colourless or slightly yellow solution for injection, with pH between 4.5 - 8.5.

The solution for injection is packed in Ph.Eur. type I clear glass vials with a type I chlorobutyl rubber stopper and an aluminium seal. The multidose vials can contain 1 ml to 10 ml of solution.

One ml contains 250 MBq of 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}F) decays to stable oxygen (^{18}O) with a half-life of 110 minutes by emitting a positronic radiation of maximum energy of 634 keV, followed by photonic annihilation radiations of 511 keV.

The excipients are: sodium citrate dibasic, trisodium citrate, sodium chloride, hydrochloric acid and water for injections.

II.2 Drug Substance

The active substance is fludeoxyglucose (^{18}F), an established active substance described in the European Pharmacopoeia (Ph.Eur.). This radionuclide decays by positron emission followed by annihilation of the β+ particle when it collides with an electron. Annihilation results in the emission of two γ-photons at an angle of ^{18}0°, each with an energy of 511 keV. The oxygen-^{18} daughter is stable.
Full information on the active substance and its manufacturing process has been included in the dossier.

Manufacturing process
The manufacturing process of the drug substance has been sufficiently described. Additional information has been provided on the precursor. Manufacture of the drug substance and drug product is a continuous process due to the short half life of ^{18}F of approximately 110 minutes.

Quality control of drug substance
It is agreed that no specification has been defined for the drug substance, as the manufacture of the drug substance and drug product is a continuous process.

Stability of drug substance
It is agreed that no stability data have been generated for the drug substance, as the manufacture of the drug substance and drug product is a continuous process.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. A common synthetic route has been chosen. The primary packaging is sterilised and depyrogenated by standard methods. The risk for microbiological contamination appears low. The product does not contain any formulation differences that can influence efficacy and safety, compared to the products in the literature referred to.

Manufacturing process
The manufacturing process of the drug product includes dilution to the nominal radioactive concentration (250 MBq/ml at reference time and date), and dispensing of the final product into sealed, evacuated vials. This is done aseptically and by using a computer controlled semi-automatic dispensing unit.
At dispensing, the formulated bulk product is filtered. Dispensing takes place in a grade A hot cell. The dispensing/dilution step is described in detail. Process validation was performed following the described process.

Control of excipients
Sodium chloride 0.9% solution is the only excipient which is used during manufacture of the drug product. The other excipients are used during manufacture of the drug substance. An acceptable specification has been laid down.

Quality control of drug product
The product complies with the Ph. Eur. monograph for "Fludeoxyglucose [^{18}F] injection" and the specification includes tests for appearance, pH, identification by gamma-ray spectrometry photon energy, half life, retention time, F-^{18} radioactivity concentration per ml, F-^{18} radioactivity (% of declared value), content of 2-fluoro-2-deoxy-D-glucose, content of aminopolyether (Cryptand 222), residual solvents, sterility, bacterial endotoxins, radionuclidic purity and radiochemical purity. The release and shelf-life requirements are identical. Analytical methods were adequately described and validated.

Batch analytical data from the proposed production site have been provided on single and dual run batches. Overall, the data demonstrate compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full-scale single run and dual run batches. The drug product was shown to be stable for at least ten hours. Based on the provided results, the claimed shelf life of 12 hours after the time of manufacture when stored below 25°C in its commercial packaging is acceptable.

The product is packed in multidose vials to allow withdrawals for multiple patients. In-use stability studies are, however, not deemed necessary in view of the maximum expected in-use period of 4 hours and the fact that withdrawals take place under aseptic conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that ^{18}F-FDG Hoboken 250 MBq/ml, solution for injection has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

The general metabolic rates of tissues in intact organisms can be imaged and quantified using the glucose analogue 2-fluoro-2-deoxy-D-glucose (FDG) that acts as a substrate for the "hexokinase reaction", resulting in intracellular accumulation of FDG-6-phosphate.

The use of the 2-deoxy analogues of glucose such as ^{18}F-FDG is based on having similar kinetics and biochemical properties as glucose. ^{18}F-FDG is transported across the cell membrane into the cytosol by the same carrier mechanism as glucose. Five structurally related proteins (the family of glucose transporters GLUT1 to GLUT5) mediate the transport of ^{18}F-FDG across cell membranes.

Once inside the cell, ^{18}F-FDG is phosphorylated to ^{18}F-FDG-6-phosphate by the enzyme hexokinase. The low Km of hexokinase for ^{18}F-FDG ensures both rapid phosphorylation and conversion at low ^{18}F-FDG concentrations. ^{18}F-FDG can be used as a surrogate to track glucose utilisation. This will work best in tissues where glucose is the major substrate for metabolism, where there is minimal phosphatase activity, and where glycogen synthesis from glucose is extremely low.

Biodistribution studies have demonstrated that ^{18}F-FDG is well-distributed into the major organs in the body.

III.2 Pharmacokinetics

It was shown that intravenous administration of ^{18}F-FDG to mice resulted in a rapid distribution to heart, brain, kidneys, lungs, liver, small and intestine, followed by a rapid elimination of radioactivity from these organs with the exception of the heart and brain. In these two organs, significant amounts of radioactivity relative to initial distribution remained two hours post-injection: the heart-to-lung ratio was 12:1, and heart-to-liver ratio was 32:1.
FDG is converted through phosphorylated intermediates to 2-fluoro-2-deoxy-D-mannose (FDM). Two fluorinated compounds, FDG and FDM, were identified, suggesting bioisomerisation of FDG to FDM or FDM-6-P in organs. In the brain, nuclear magnetic resonance signals were detected as early as 5 minutes post dose, with signal intensity decreasing with time and becoming undetectable at 48 hours. The blood profile was similar to the brain profile. In contrast, accumulation was slower in the heart with total signal intensity increasing up to 24 hours and decreasing thereafter. Fluorinated compounds were still detectable in cardiac tissues up to 96 hours after administration of FDG, raising the possibility that halogenated deoxyglucose compounds may be retained in cardiac tissues for several days following administration of FDG.
^{18}F-FDG is largely excreted unchanged in urine. The appearance of ^{18}F-FDG in urine signifies an important difference between the renal handling of glucose and FDG, apparently due to lack of tubular reabsorption of FDG. Under normal physiological conditions, glucose is reabsorbed by the renal proximal tubules by a carrier mediated active transport mechanism. In pig liver ^{18}F-FDG is not only metabolised to ^{18}F-FDG-6-P, but is also significantly metabolised to the subsequent oxidation products, 2-[^{18}F]-fluoro-2-deoxy-6-phospho-D-gluconolactone ([^{18}F]FD-PGL) and 2-[^{18}F]-fluoro-2-deoxy-6-phospho-D-gluconate ([^{18}F]FD-PG1). These metabolites started to appear in the liver 45 minutes after the ^{18}F-FDG injection and reached a level of 40% of the total metabolites after ^{18}0 minutes.

III.3 Toxicology

No significant adverse findings were observed in mouse (up to 1000x human dose in mg/kg) nor in dog (50x human dose in mg/kg). The LD50 in mice and rat was 600 mg/kg for single dose and 200 mg/kg/day for five subsequent daily doses. The maximum recommended clinical dose is 11 µg/kg. FDG was cytotoxic at 1 mg/ml in mouse lymphoma (L5178Y) cells.

There are no literature reports of studies performed to evaluate the carcinogenicity, immunotoxicity or mutagenicity of ^{18}F-FDG, or its effects on reproduction. Since animal reproduction studies have not been conducted, it is not known whether ^{18}F-FDG can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity.

A risk assessment for the impurities introduced by using the FASTlab 2 and FDG Duo process for drug substance manufacture has been performed. As the FDG Duo cassette allows producing two batches of FDG, this risk assessment has been performed on both solutions.

Based on the available data, none of the impurities assessed, at the concentrations observed, constitute a risk to human health at administration volumes of 10 ml or less.

The following impurities were reported at concentrations well within internationally accepted specifications for medicinal products:

- Ethanol, acetone, acetonitrile and 2-propanol were within the European Pharmacopoeia specifications for residual solvents
- Aminopolyether (Kryptofix) was within the specifications set by the European Pharmacopoeia monograph on Fludeoxyglucose (^{18}F) Injection
- Trace amounts (<0.1 µg/ml) of Oleamide and Erucamide were detected. These are approved plastic additives and the FASTlab cassette components comply with the European Pharmacopoeial specifications for contact materials for a primary container closure.

A number of volatile compounds were also detected which could not be identified due to their low individual concentrations. These were estimated by performing a sum of all the unknown peaks presents, resulting in a total of less than 0.2 µg/ml. This total would give a maximum exposure of approximately 2 µg per patient, if the 10 ml of fludeoxyglucose (^{18}F) injection preparation is administered. The fact that FDG Duo cassette uses ICH class 3 solvents, combined with the low levels reported, means these unknown compounds are not considered to constitute a risk to human health.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since this well established use application will lead to substitution of an existing market share, the approval of ^{18}F-FDG Hoboken 250 MBq/ml will not lead to increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion on the non-clinical aspects

For this well-established use application, the MAH submitted a non-clinical overview on the pharmacology, pharmacokinetics and toxicology, which is based on up-to-date and adequate scientific literature. According to the MAH, effects of fludeoxyglucose (^{18}F) on reproduction were not available in literature. However, possible adverse effects of radiation on the fetus are well known. This is adequately stated in section 4.6 of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview was initially written in 2005. At the time of writing the clinical overview, the indications were in line with those published by the Society of Nuclear Medicine (SNM) and the European Association of Nuclear Medicine (EANM). Since then, a

core SPC for (^{18}F)-FDG has been published in 2010 in which an additional indication was proposed, namely infectious or inflammatory diseases. In order to bring the clinical overview up to date an addendum to the clinical overview was written in 2013. Finally, in order to bridge the period between the update to the clinical overview and the date of dossier submission, a clinical expert overview is provided that summarized the efficacy, safety, and new uses of fludeoxyglucose with reference to the main publications and guidelines that have been published between 2010 and 2016.

IV.2 Pharmacokinetics

Fludeoxyglucose (^{18}F) is used as a diagonistic agent and therefore expected to be used as a single administration. Based on this and the provided pharmacokinetics section, no pharmacokinetic interactions are expected to be relevant.
Bioequivalence studies may be waived for this application. Bridging with the available literature based on quality attributes is appropriate.

IV.3 Pharmacodynamics

Fludeoxyglucose (^{18}F)-Hoboken is a radiopharmaceutical agent containing a glucose analogue labelled with fluorine-^{18}, which is used for diagnostic purposes in conjunction with Positron Emission Tomography (PET).
Fluorine-^{18} is a positron emitter. When injected, the positron particles emitted during decay collide with electrons in the patient's body and are thus annihilated while at the same time two gamma photons are emitted, at an angle of ^{18}0°, both having an energy of 511 keV. These 511 photons are detected by the PET camera.
^{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. Once inside the cell, FDG is phosphorylated into FDG-6-phosphate by hexokinase. The presence of fluorine instead of the 2-hydroxyl group in glucose blocks further metabolism of FDG, leaving FDG-6P trapped in the cell 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 due to a higher glucose turnover, which 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.

- Increased ^{18}F-FDG uptake is detected in certain cell types of the immune system, such as macrophages when they are activated. Hence the use of ^{18}F-FDG for the diagnosis of infectious or inflammatory/autoimmune disease.

IV.4 Clinical efficacy

Clinical applications of fludeoxyglucose (^{18}F) in oncology

Central nervous system
An overview of 10 clinical studies (dated 1998-2000) has been provided to compare the usefulness of ^{18}F-FDG-PET with other imaging modalities such as MRI CT and other radiopharmaceuticals in detecting and staging primary as well as recurrent malignancies, monitoring response to therapy and evaluating prognosis in patients with intracranial tumours. These studies showed that ^{18}F-FDG can differentiate between malignant and benign tissues in cases where recurrence or residual brain tumour is suspected. Additionally, ^{18}F-FDG showed positive correlation with histology grade. Finally, ^{18}F-FDG could also provide prognostic information since those patients with residual abnormal uptake after therapy interventions seem to have significantly worse survival rates than those where it is absent.

Head and neck cancer
An overview of 25 clinical studies (dated 1995-2000) has been provided to support the usefulness of ^{18}F-FDG in detection of head and neck cancer. The studies showed that ^{18}F-FDG has higher sensitivity and specificity than CT/MRI in detecting lymph node (LN) metastases in primary and recurrent cancer. Furthermore, ^{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. Additionally, according to the MAH the degree of uptake can yield prognostic information since this is the result of the aggressiveness of the tumour, which is an advantage over structural imaging modalities.

Thyroid cancer
An overview of 7 clinical studies (dated 1996-2000) has been provided to report the experience of ^{18}F-FDG in 367 patients with differentiated thyroid carcinoma. These studies reported that ^{18}F-FDG can differentiate between benign and malignant nodules within the thyroid gland with an accuracy of 73%. Furthermore, ^{18}F-FDG- PET can yield additional information in the staging and can depict sites of tumour when ^{131}I whole body scintigraphy 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.

Lung Cancer, including Single Pulmonary Nodule (SPN)
An overview of 33 clinical studies (dated 1995-2002) has been provided to support the usefulness of ^{18}F-FDG in the differentiation between benign and malignant masses in the lung. The studies reported that the accuracy of ^{18}F-FDG is higher than 90%, although the sensitivity may decrease if small lesions (<1cm) are evaluated with conventional SPECT cameras equipped with high energy collimators instead of dedicated PET scanners. When compared with other radiopharmaceuticals ^{18}F-FDG has higher uptake in primary lung cancer

and metastatic LN than ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin, leading to a better diagnostic accuracy of the former (n=73). FDG (^{18}F) also performs better than other conventional oncological radiopharmaceuticals such as ^{201}Tl in smaller lesions. Furthermore, in the assessment of possible mediastinal involvement from lung cancer, ^{18}F-FDG exhibits higher accuracy than CT. Finally, in a large series with 105 patients, ^{18}F-FDG was able to change patient treatment options in 62 cases by accurately either upstaging or downstaging patients and directing delivery of radiation therapy, which led to better patient management.

Breast Cancer
An overview of 15 clinical studies (dated 1996-2001) has been provided to evaluate the use of ^{18}F-FDG in the differential diagnosis of breast lesions. The studies indicate that ^{18}F-FDG can differentiate benign from malignant tissue within the breast with a sensitivity of 68-94% and a specificity of 84-97%. Staging primary and recurrent breast cancer can also benefit from combining structural information from conventional imaging modalities with functional information from ^{18}F-FDG whole-body PET scans. ^{18}F-FDG was also shown to be effective in monitoring response to therapy.

Cancer of the digestive system
An overview of 34 clinical studies (dated 1995-2001), has been provided to support the usefulness of ^{18}F-FDG-PET for detection of gastro-oesophageal-, liver-, pancreas-, and colorectal cancer. From these studies, the MAH concluded that ^{18}F-FDG can help in the differentiation between benign and malignant lesions and yield information regarding their histologic grade in a significant number of cases. Additionally, ^{18}F-FDG can provide prognostic information and depict early response to therapy before any structural changes occur.

Ovarian Cancer
An overview of 3 clinical studies (dated 1999-2001) has been provided to support the usefulness of ^{18}F-FDG for detection of (recurrent) ovarian cancer. From the studies the MAH concluded 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. Furthermore, ^{18}F-FDG also appears effective in the staging of known ovarian cancer.

Lymphoma
An overview of 19 clinical studies (dated 1995-2001) shows that lymphomas accumulate ^{18}F-FDG at higher rates than non-lymphomatous lesions, enabling improved staging for which ^{18}F-FDG exhibits higher diagnostic accuracy than CT. ^{18}F-FDG was also suggested to 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.

Tumour of Unknown Origin
An overview of 4 clinical studies (dated 1996-2000) showed a high sensitivity (>80%) but poorer specificity of ^{18}F-FDG in detection of unknown primary tumours. The use of ^{18}F-FDG has been shown in selected cases to have utility (n=28), although the literature is not in full

agreement on this issue. The MAH concluded that there is some evidence that ^{18}F-FDG may help in selected cases, but there is not enough support to recommend the regular use in this filed at the moment.

Malignant melanoma
226 patients from 6 clinical studies (dated 1995-1999) showed that PET with ^{18}F-FDG has higher diagnostic accuracy in staging than CT. However, it seems that ^{18}F-FDG cannot replace sentinel node biopsy in the evaluation of local/regional LN spread and may also miss small LN metastases in patients with primary lesions with < 1.5mm thickness.

Clinical applications of fludeoxyglucose (^{18}F) in Neurology
Epilepsy
An overview of 7 clinical studies (dated 1996-1998) has been provided to support the usefulness of ^{18}F-FDG to localise the anatomical origin of an epileptic seizure. These studies reported that ^{18}F-FDG PET scanning yielded prognostic information regarding improvement of control seizure after surgery and appeared to be as useful as invasive EEG and ictal SPECT.

Clinical applications of fludeoxyglucose (^{18}F) in Cardiology
An overview of 5 clinical studies on the usefulness of ^{18}F-FDG in the evaluation of myocardial viability has been provided (dated 1995-1997). Experience in ^{18}0 patients shows that a flow-metabolism mismatch (decrease flow with preserved or increased ^{18}F-FDG uptake) is a highly accurate predictor of functional recovery after re-vascularisation procedures. Comparison with conventional radiopharmaceuticals shows that ^{18}F-FDG has higher positive predictive value and negative predictive value than ^{99m}Tc-MIBI in detecting myocardial viability.

Clinical applications of fludeoxyglucose (^{18}F) in Infectious or inflammatory diseases
Fever of unknown origin
One review of Ergul et al. (2011[1]) has been provided by the MAH in which prospective and retrospective studies demonstrated that the contributions of ^{18}F-FDG to the final diagnosis range from 16% to 69% in patients in patients with fever of unknown origin by FDG-PET or 42% to 89% by PET/CT.

Diagnosis of Infection
An overview of 17 clinical studies (dated 1995-2008) has been provided on the usefulness of ^{18}F-FDG-PET to detect osteomyelitis (related to diabetic foot), spondylitis, diskitis, osteitis, infected prosthesis and metallic implants, fever in an AIDS patients. Overall, the MAH concluded that ^{18}F-FDG-PET is a highly effective imaging procedure and could be recommended for diagnosing of different types of infections.

[1] Ergul, N., & Cermic, F. T. (2011), FDG-PET or PET/CT in Fever of Unknown Origin: The Diagnostic Role of Underlying Primary Disease. International Journal of Molecular Imaging, 1-9.

Detection of Septic Metastatic Foci in Case of Bacteraemia
One study of Vos et al. (2010[2]) has been provided which reported that ^{18}F-FDG PET/CT is a valuable technique in detecting infectious foci that results in lower mortality rates. The sensitivity, specificity, negative predictive value and positive predictive value of ^{18}F-FDG PET/CT were 100%, 87%, 100% and 89%, respectively.

Detection of the Extension of Inflammation in case of Sarcoidosis, Inflammatory bowel disease, or Vasculitis involving the great vessels
An overview of 7 clinical studies (dated 2002-2011) on the usefulness of ^{18}F-FDG-PET/CT in diagnosing and evaluating therapy in sarcoidosis, inflammatory bowel disease and vasculitis has been provided. It was concluded from the studies that ^{18}F-FDG-PET is a highly sensitive imaging technique for the detection of inflammation with sensitivity and specificity values in the range of 85%-98% and 89%-100%.

Therapy Follow-Up
Five clinical studies (dated 2007-2010) on metabolic activity in alveolar echinococcosis during medical treatment and after treatment discontinuation demonstrated that ^{18}F-FDG–PET is generally considered useful for the therapeutic follow-up of unresectable alveolar echinococcosis.

IV.5 Clinical safety

Adverse events relating to the non-radioactive moiety
The amount of non-radioactive material that is administered in diagnostic nuclear medicine procedures is extremely small when compared with radiographic contrast media, indicating that the risk of associated adverse events is likely to be insignificant.

Safety of administering a source of ionising radiation
Any procedure that involves radiation exposure to the patient must be carefully evaluated and should always follow the ALARA (As Low As Reasonably Achievable) criteria to ensure that the highest quality information will be obtained with a minimal dose to the patient.
When evaluating the potential harmful effect of ionising radiation to the human body two effect types should be considered, deterministic and stochastic effects. Those effects which are dose related (deterministic) will only appear after a certain threshold is surpassed and are the result of cell death at the tissue/organ level (e.g. low white blood cell counts leading to opportunistic infections). No radiopharmaceutical is administered in such a dose that would reach near this level in any of the diagnostic procedures in nuclear medicine. Stochastic effects are related with the late development of cancer and genetic defects, and safety in this regard is evaluated in terms of risk. There is no threshold level for these late-appearing effects, but higher doses carry higher risk for developing stochastic effects. International agreement is to use Effective Dose (ED, international units are Sieverts [Sv]) to allow comparison amongst different techniques.

[2] Vos FJ, Bleeker-Rovers CP, Sturm PD, Krabbe PFM, van Dijk APJ, Cuijpers MLH, Adang EMM, Wanten GJA, Kullberg B-J and Oyen WJG. 18F-FDG PET/CT for Detection of Metastatic Infection in Gram-Positive Bacteremia. J Nucl Med August 1, 2010 vol. 51 no. 8 1234-1240

In terms of ED, ^{18}F-FDG compares favourably with other radiopharmaceuticals and radiographic techniques.

Safety from clinical experience

No randomised, blinded clinical trials assessing safety of ^{18}F-FDG injection were identified during the literature search. However clinical experience is extensive. A prospective four-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 (Silberstein et al., 1998[3]). 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.

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[4]).

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to ^{18}F-FDG Hoboken 250 MBq/ml, solution for injection.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	Radiation exposure, including the risk on carcinogenicity and mutagenicity
Important potential risks	--
Missing information	--

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

[3] Silberstein, E. B., and the Pharmacopeia Committee of the Society of Nuclear Medicine, Prevalence of Adverse Reactions to Positron Emitting Radiopharmaceuticals in Nuclear Medicine, J Nuc Med, 1998, 39:2190-2192.
[4] Meyer, G. J. et al., PET Radiopharmaceuticals in Europe: Current Use and Data Relevant for the Formulation of Summaries of Product Characteristics (SPCs), European Journal of Nuclear Medicine, 22:1420-1432, 1995.

IV.7 Discussion on the clinical aspects

Benefit-risk balance

Benefits

The MAH has provided an extensive review of published clinical studies (n= 199, dated 1995-2010) in support of the use of ^{18}F-FDG in the various proposed indications. The numerous published clinical studies demonstrate the diagnostic benefits of ^{18}F-FDG in the various indications, although detailed information on the design of the studies and method of diagnostic imaging/testing has not been provided for most of the studies. However, considering that the proposed set of indications is similar to the indications in the core SmPC of FDG, an extensive efficacy assessment of each specific indication is not required and, therefore, this omission can be accepted. Furthermore, the provided literature shows that ^{18}F-FDG has been used in research for more than 15 years worldwide, including Europe, demonstrating the scientific interest of ^{18}F-FDG in the claimed indications. Although data on the amount of cases of each type of cancer has been provided by the MAH, data on the extensive use of ^{18}F-FDG in PET imaging in these cases has not been provided. However, several other ^{18}F-FDG medicinal products are currently registered in the Netherlands for more than 10 years for the same indications indicating that the use of ^{18}F-FDG in the various proposed indications can be considered well-established. Additionally patient information documents of different Dutch hospital centers including the Antoni van Leeuwenhoek, Bavis hospital and Jeroen Bosch hospital, reported the use of ^{18}F-FDG for PET imaging. Furthermore, different guidelines including that of the Society of Nuclear Medicine and Molecular Imaging also recommended the use of ^{18}F-FDG for PET imaging.

Risks

- Unfavourable effects

Considering that the medicinal product applied for concerns (^{18}F-labeld) glucose, adverse events due to administration of glucose are not expected. This is confirmed by two articles on the clinical experience of ^{18}F-FDG where no adverse reactions were found from ^{18}F-FDG administration.

- Uncertainty in the knowledge about the unfavourable effects

With respect to the potential harmful effect of ionising radiation, it is acknowledged that the analysis of the risks associated with the use of ionising radiation is difficult. According to the core SmPC for FDG, exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary effects. As the effective dose is 7.6 mSv when the maximal recommended activity of 400 MBq is administered these adverse reactions are expected to occur with a low probability. The risks associated with the use of ^{18}F-FDG are minimal.

Balance

Based on above, the MEB considered that the provided published literature is sufficient to support that ^{18}F-FDG has been used in the various proposed indications for more than 10 years worldwide, including the EU, with recognised efficacy and an acceptable level of

safety. The benefit-risk balance of ^{18}F-FDG Hoboken 250 MBq/ml, solution for injection is positive.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Steripet (NL/H/3528/001/MR). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

^{18}F-FDG Hoboken 250 MBq/ml, solution for injection has a proven chemical-pharmaceutical quality. Fludeoxyglucose (^{18}F) is an effective drug, and its use is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that well-established use has been demonstrated for this medicinal product, and has therefore granted a marketing authorisation. ^{18}F-FDG Hoboken 250 MBq/ml, solution for injection was registered in the Netherlands on 7 June 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse
Change in shape or dimensions of the container or closure (immediate packaging). Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flipoff caps, colour code rings on ampoules, change of needle shield (different plastic used)). Change in supplier of packaging components or devices (when mentioned in the dossier).	IB/G	N	13-6-2019	Approval	--