COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Fludeoxyglucose ($^{18}$F) RTM 200 MBq/ml, solution for injection

# (fludeoxyglucose ($^{18}$F))

# NL/H/4034/001/DC

# Date: 15 August 2019

**This module reflects the scientific discussion for the approval of Fludeoxyglucose ($^{18}$F) RTM 200 MBq/ml, solution for injection. The procedure was finalised at 17 July 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

| | |
|---|---|
| ASMF | Active Substance Master File |
| 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 |
| IBD | Inflammatory Bowel Disease |
| 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 quality, safety and efficacy data, the Member States have granted a marketing authorisation for Fludeoxyglucose ($^{18}$F) RTM 200 MBq/ml, solution for injection from Radboud Translational Medicine B.V.

***Indication***
This medicinal product is for diagnostic use only.
Fludeoxyglucose ($^{18}$F) RTM 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:

- Localisation of abnormal foci guiding the aetiologic diagnosis in case of fever of unknown origin
- Diagnosis of infection in case of
    - 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 (see also SmPC section 4.4)
- Detection of the extension of inflammation in case of
    - Sarcoidosis
    - Inflammatory bowel disease
    - Vasculitis involving the great vessels
- Therapy follow-up
    - 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.

***Well-established use***

Fludeoxyglucose $^{18}$F 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, although detailed information on the design of the studies and method of diagnostic imaging/testing have not been provided for most of the studies. However, considering that the proposed set of indications is in line with the indications in the core SmPC of FDG, an extensive efficacy assessment of each specific indication is not required. 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 substance is authorised in the Netherlands in the following similar products, for the same indication:

- Fludeoxyglucose ($^{18}$F) MCA 100 - 400 MBq, solution for injection in prefilled syringe (NL Licence RVG 115336; authorised in 2015)
- Fludeoxyglucose ($^{18}$F) IBA 185 MBq/ml, solution for injection (NL Licence RVG 29834; authorised in 2004)
- EFDEGE 1,0 GBq/ml, solution for injection (NL Licence RVG 30417; authorised in 2005)
- Glucotrace, solution for injection 185 MBq/ml (NL Licence RVG 30437; authorised in 2004)
- Steripet 250 MBq/ml, solution for injection (NL Licence RVG 33033; authorised in 2006)
- 18F-FDG Hoboken 250 MBq/ml, solution for injection (NL Licence RVG 121312; authorised in 2018)

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

The concerned member states (CMS) involved in this procedure were Belgium and Germany.

# II. QUALITY ASPECTS

## II.1 Introduction

Fludeoxyglucose ($^{18}$F) RTM is a clear, colourless or slightly yellow solution for injection, with pH between 4.5 - 8.5 and osmolarity between 300 - 360 mOsm/kg.

One ml contains 200 MBq of fludeoxyglucose ($^{18}$F) at the date and time of calibration. The activity per vial ranges from 100 MBq to 2000 MBq 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 solution is packed in a 10 ml, colourless, type I glass vial with a Teflon chlorobutyl stopper and an aluminum seal. The multidose vials can contain 0.5 ml to 10 ml of solution, depending on the number of patients involved, the time of administration, the dose, and the permitted dose to be carried.

The excipients are:
- sodium chloride 9 mg/ml
- sodium citrate dibasic sesquihydrate
- trisodium citrate dihydrate
- hydrochloric acid
- 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.). In the active substance, the 2-hydroxyl group of glucose is substituted with $^{18}$F. 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 180°, each with an energy of 511 keV. The oxygen-18 daughter is stable. The half life of $^{18}$F is approximately 110 minutes.

Manufacturing process
Overall, the manufacturing process of the drug substance has been sufficiently described. Additional information has been provided on the precursor, in the form of a complete Active Substance Master File (ASMF). Manufacture of the drug substance and drug product is a continuous process due to the short half life of $^{18}$F.

Quality control of drug substance
No specification has been defined for the drug substance as the manufacture of the drug substance and drug product is a continuous process. This is accepted.

Stability of drug substance
No stability data have been generated for the drug substance as the manufacture of the drug substance and drug product is a continuous process. This is accepted.

## II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main goal was to develop a product that complies with the Ph.Eur. monograph on fludeoxyglucose ($^{18}$F) injection. A common synthetic route has been chosen. The MAH has gained experience with 50 batches of the drug product which show that the manufacturing process is robust and reproducible. The

risk for microbiological contamination is low. The sterilisation of the hold tank, dispensing set, and container closure system is adequate.
As it concerns a well-established use application, information on the composition of the product described in the supporting literature and bridging of these data for the product at issue has been addressed.

Manufacturing process
The manufacturing process of the drug product includes sterile filtration of the purified active substance solution, determination of the volume and radioactivity, dilution to the desired radioactive concentration (MBq/ml), mixing under nitrogen, sterile filtration and filling of the product vials. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

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 included for the sodium chloride 0.9% solution. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, pH, identification by gamma-ray spectrometry - photon energy, half life, and retention time, F-18 radioactivity concentration per ml, F-18 radioactivity (% of declared value), content, residual solvents, sterility, bacterial endotoxins, radionuclidic purity, and radiochemical purity. The release and shelf life requirements are identical. The specification is in accordance with the Ph.Eur. monograph on Fludeoxyglucose ($^{18}$F) injection. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 50 full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three full scale batches. The lowest (0.5 ml) and highest (10 ml) volume of a batch was stored in the production area (17-24°C and 40-65% RH) and at accelerated condition in the commercial packaging in inverted position. The drug product was shown to be stable for at least ten hours.

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 member states consider that Fludeoxyglucose ($^{18}$F) RTM 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

Fludeoxyglucose ($^{18}$F), 18F-FDG, is a radiopharmaceutical used in PET. Its diagnostic strength is based on accumulation of 18F-FDG after phosphorylation in cells exhibiting a higher glucose consumption than normal cells. Catching the radiation from radioactive decay of 18F-FDG by PET visualises the distribution of glucose uptake and phosphorylation by these cells in the body.
During radioactive decay 18F-FDG-phosphate is transformed to $^{18}$O-glucose-6- phosphate that is metabolised as normal glucose to non-radioactive end products. Although 18F-FDG was initially developed for imaging brain metabolism, early studies showed that it was also concentrated in animal tumours due to enhanced glycolysis in cancer cells. In PET 18F-FDG nowadays is used for imaging tumours and for the assessment of glucose metabolism in heart, lungs and brain.

The biochemical basis of the use of 2-deoxy analogues of glucose such as FDG rests on the basic assumption that they have similar kinetics and biochemical properties as glucose. 18F-FDG is transported through the cell membrane by facilitative glucose transporter proteins (GLUTs). Within the cell, 18F-FDG is phosphorylated to 18F-FDG-6-phosphate by the enzyme hexokinase. *In vitro* incubation of 14C-FDG with purified yeast hexokinase and ATP resulted in the formation of 14C-FDG-phosphate. The hexokinase has a low Km for 18F-FDG and this ensures that phosphorylation occurs rapidly and at low concentrations of 18F-FDG. Because the action of hexokinase is not reversible and because 18F-FDG-6-phosphate is a poor substrate for enzymes such as glucose-6-phosphate isomerase or glucose-6-phosphate dehydrogenase, subsequent steps in glucose metabolism are essentially blocked. As the cell membrane is largely impermeable to charged molecules, the 18F-FDG-6-phosphate is trapped inside the cell. 18F-FDG concentrates in normal cells using glucose as energy source, and in cells which have become increasingly dependent upon glucose due to pathophysiologic changes, such as in tumour cells. During a PET scan with 18F-FDG, regions with reduced glucose metabolism show a parallel reduction in 18F-FDG uptake compared to their environment, while regions with increased glucose metabolism exhibit increased uptake. Initially, (cold $^{19}$F) FDG had been labelled with 14C to study local glucose metabolisation in the brain but later synthesis methods were developed to replace the $^{19}$F atom with $^{18}$F in order to map brain metabolism with PET.

Accretion of 18F-FDG into a wide variety of human tumour xenografts was evaluated in nude mice and compared with the targeting ability of monoclonal antibodies. In the xenograft human tumours the uptake of 18F-FDG was very much higher than that of the monoclonal antibodies. These preclinical data strongly suggested that tumour imaging with 18F-FDG was possible in man.

There is some evidence to suggest that 18F-FDG may act as a non reversible inhibitor of glucose phosphorylation, but it is not very likely that glucose metabolism in any type of cells will be influenced by the compound given the extremely low concentrations reached in the body. Due to the very high specific radioactivity of 18F-FDG (in the proposed product), patients will receive at the usual dose levels a quantity of 18F-FDG in the order of magnitude of 1 ng.

## III.2 Pharmacokinetics

*Absorption and Distribution*
In mice 18F-FDG distributes to the kidneys, heart, brain, lungs and liver. It is cleared rapidly from these organs except the heart and the brain, where significant amounts remain two hours after injection. The heart and the brain showed high rates of phosphorylation, whereas in the lungs, liver and kidney the unmetabolised 18F-FDG predominates in the early stages followed by increasing concentration of 18F-FDG-6-phosphate with time. Clearance of mostly unchanged 18F-FDG from the lungs, liver and kidneys is attributable to the lower hexokinase and/or glucose-6-phospohatase activity in these organs. The retention of 18F-FDG in the heart and brain is the result of metabolic trapping within these organs and is reflective of endogenous glucose utilization.
In dogs, the organs showing the highest F-18 activity 60 minutes after i.v. administration were the heart, brain, liver and lungs, with the heart containing 2.8-4.1% (two dogs) and the brain 2.14% of total administered radioactivity. At 135 minutes these values were 2.4% and 2.1-3.5% respectively. After 135 minutes, the urine contained 42-57% of the injected activity, most probably as unchanged 18F-FDG as negligible amounts of free $^{18}F^-$ could be traced.
In tumour-bearing rats it was shown that not only the heart and the brain can retain 18F-FDG but also tumor tissue. In contrast with liver and kidney these tissues effectively phosphorylate 18F-FDG to 18F-FDG-6-phosphate, reflecting their dependency on glucose as energy source.
18F-FDG is excreted in the urine mostly as the unchanged 18F-FDG thereby reducing the body background radioactivity rapidly.

*Metabolism and Excretion*
18F-FDG is metabolised via phosphorylation in tissues to 18F-FDG-6-phosphate by hexokinase. 18F-FDG remains in the cell as the phosphate until it is dephosphorylated by glucose-6-phosphatase; it leaves the cell by passive diffusion.
18F-FDG that is not involved in glucose metabolism in any tissue is excreted unchanged in the urine. The fluorine-18 decays to oxygen-18 resulting in the formation of 18O-glucose and presumably some 18O-mannose. The metabolic fate of these compounds has not been

confirmed but it is safe to assume that these are metabolised like glucose.
18F-FDG is cleared from most tissues within 24 hours and can be eliminated from the body unchanged into the urine. Approximately 20% of an administered dose is excreted in the urine within two hours after injection. After 24 hours 18F-FDG has been fully cleared from non-cardiac tissue; clearance from cardiac tissue may require 96 hours or more.

## III.3 Toxicology

*General toxicity*
Toxicological studies with 18F-FDG have been performed over 30 years ago, in a time where synthesis methods were not yet capable of delivering product with a very high radiochemical purity. The most common syntheses in these days used electrophilic substitution leading to product containing predominantly 19F-FDG.
Unavoidably, toxicological studies had to focus on the effects of the cold analogue. For instance, in one study the authors refer to a specific radioactivity of their product of 1-29.4 mCi/mg, or 37-1100 MBq/mg.
Although the mass quantity of FDG is still very low at a dose level of 150 MBq, this figure compares very unfavourably with the specific radioactivity of 18F-FDG. As mentioned in several other sections of the dossier, this product has a specific activity of 3.49*108 MBq/mg, a factor 300,000 higher.
The toxicity of low radioactive doses such as used for 18F-FDG cannot be measured, either acute or long term. If any signs of toxicity are noticed therefore, these are attributable to other compounds present in the formulation, in the form of either cold FDG, FDM or by-products in other syntheses, such as 2-chloro-deoxyglucose. To put the matter in perspective: at the average dose level of 275 MBq, a patient will receive a mass quantity of approximately 0.8 nanograms of active FDG, while, depending on the time elapsed since filling, the mass of decayed 'FDG' (18O-glucose) will be ten times this quantity - negligible compared to the amount of ordinary glucose present in the product as a result of hydrolysis of the precursor.
Having said this, it should be noted that cold FDG is devoid of toxicity according to the study mentioned above. Mice given 14.3 mg/kg of FDG on three occasions did not show any immediate or long term effects, either by routine observation or by gross and histopathological investigation of internal organs. Similarly, no abnormalities were found in dogs given 0.72 mg/kg on three occasions.
In one study, dating from 1973, mention is made of an LD50. Given that the figure of 400 mg/kg is roughly 400 million times the dose administered routinely to humans, the relevance of such data is questionable.

*Mutagenic and carcinogenic potential*
Although no reports are available no risk is to be expected from the low amount of 18F-FDG to be used clinically. A risk may be associated with the exposure to ionizing radiation by $^{18}F$. However, this risk is minimal because the effective dose equivalent for a single dose of 370 MBq is 7,6 mSv, which is well below the accepted limit of 20 mSv.

### III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Fludeoxyglucose ($^{18}$F) RTM 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.5 Discussion on the non-clinical aspects

Pharmacological, pharmacokinetic and toxicological characteristics of Fludeoxyglucose ($^{18}$F) RTM as presented in the non-clinical overview are based on literature review and the non-clinical overview is considered appropriate. The non-clinical overview has addressed the pharmacological and toxicological literature. There are no issues relating to the pharmacology or toxicology and formulation of Fludeoxyglucose ($^{18}$F) RTM. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

18F-FDG is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

This application is literature-based only. To justify the use of 18F-FDG in conjunction with PET in the various proposed diagnostic indications the MAH referred to 230 scientific publications (dated 1981-2013).

### IV.2 Pharmacokinetics

Absorption
This formulation is i.v. administered, thus this section is not considered to be relevant. The influence of food is expected not to be relevant, since 18F-FDG is given to sufficiently hydrated patients under fasting conditions of minimal four hours.

Distribution
After i.v. administration 18F-FDG is rapidly cleared from blood to all organs of the body with peak tissue concentrations usually occurring in 30 minutes. Clearance from blood follows a 3$^{rd}$ order exponential process, with an effective t½ of the early phase of about 20 seconds, of 10-13 minutes for a second phase and a terminal phase of 80-95 minutes. This pattern is largely similar to that observed in dog experiments. 18F-FDG readily passes the blood brain

barrier and achieves relatively high concentrations in brain tissue, with around 4 % of the dose accumulating in brain in 30 minutes, slowly increasing till 80-100 minutes after injection and then stabilizing until about 180 minutes after injection. Uptake in the heart is also rapid and amounts to 1-4% of the administered dose. Because hibernating cardiac tissues is characterized by an increased dependency on glucose as energy source, 18F-FDG uptake in these myocardial cells is also increased. Relatively high concentrations of 18F-FDG are also found in spleen, pancreas and liver. Cancer cells usually exhibit increased glucose metabolism; however, accumulation of 18F-FDG is dependent on tumour type, stage and location. In many tumour types the concentration of 18F-FDG progressively builds up in 3-4 hours. Because 18F-FDG is not reabsorbed by the renal tubuli like glucose, its concentration also rapidly builds up in the bladder to be excreted renally.

Metabolism

18F-FDG is metabolised via phosphorylation in tissues to 18F-FDG-6-phosphate by hexokinase. 18F-FDG remains in the cell as the phosphate until it is dephosphorylated by glucose-6-phosphatase; it leaves the cell by passive diffusion. 18F-FDG that is not involved in glucose metabolism in any tissue is excreted unchanged in the urine. The fluorine-18 decays to oxygen-18 resulting in the formation of 18O-glucose and presumably some 18O-mannose. The metabolic fate of these compounds has not been confirmed but it is safe to assume that these are metabolized like glucose.

Excretion

18F-FDG is cleared from most tissues within 24 hours and can be eliminated from the body unchanged into the urine. In the study with the four healthy volunteers referred to above, a mean of 3.9% of the administered dose was measured in the urine within 33 minutes after injection. Approximately 20% of an administered dose is excreted in the urine within two hours after injection. After 24 hours 18F-FDG has been fully cleared from non-cardiac tissue; clearance from cardiac tissue may require 96 hours or more.

## IV.3 Pharmacodynamics

Fludeoxyglucose ($^{18}$F) RTM is a radiopharmaceutical agent containing a glucose analogue labelled with fluorine-18, which is used for diagnostic purposes in conjunction with 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 180°, both having an energy of 511 keV. These 511 photons are detected by the PET camera.

18F-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 18F-FDG clinical usefulness.

- 18F-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 18F-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 oxidising free fatty acids. However, under ischaemic conditions exogenous glucose becomes the preferred myocardial substrate. Under these conditions, phosphorylated 18F-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 18F-FDG uptake is detected in certain cell types of the immune system, such as macrophages when they are activated. Hence the use of 18F-FDG for the diagnosis of infectious or inflammatory/autoimmune disease.

## IV.4 Clinical efficacy

**Infection and inflammation**

***($^{18}$F)FDG-PET or PET/CT in fever of unknown origin***

*Adults*

An overview of 15 clinical studies on the use of ($^{18}$F)FDG-PET or PET/CT in the evaluation of fever of unknown origin (FUO) in adults was provided by the MAH (dated 2000-2013). The percentage of ($^{18}$F)FDG-PET scans helpful in the diagnostic process in patients with FUO varied between 35% and 98%. Sensitivity, specificity, positive predicted value (PPV), and negative predicted value (NPV) reported in the clinical studies were 0.5-0.97, 0.33-0.97, 0.30-0.98, and 0.50-1.0, respectively. Table 1 presents the diagnostic performance parameters of the different studies.

**Table 1 Literature overview on the diagnostic performance of (18F) FDG-PET(/CT) in fever of unknown origin**

| Author (year) | Number of Patients | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|
| Lorenzen (2001)[11] | 16 | - | - | - | - |
| Bleeker-Rovers (2004)[1] | 35 | 0.93 | 0.90 | 0.87 | 0.95 |
| Buysschaert (2004)[6] | 74 | - | - | - | - |
| Kjaer (2004)[17] | 19 | 0.50 | 0.46 | 0.30 | 0.67 |
| Bleeker-Rovers (2007)[4] | 70 | 0.88 | 0.77 | 0.70 | 0.92 |
| Meller (2007)[2] | 18 | 0.81 | 0.86 | 0.92 | 0.75 |
| Keidar (2008)[9] | 48 | 1.00 | 0.81 | 0.81 | 1.00 |
| Balink (2009)[8] | 68 | - | - | - | - |
| Federici (2010)[10] | 14 | - | - | - | - |
| Ferda (2010)[12] | 48 | 0.97 | 0.75 | - | - |
| Sheng (2011)[5] | 48 | 0.89 | 0.33 | 0.80 | 0.50 |
| Kim (2012)[13] | 109 | - | - | - | - |
| Manohar (2013)[14] | 103 | 0.90 | 0.97 | 0.98 | 0.83 |

*Children*

One clinical study on the use of ($^{18}$F)FDG-PET or PET/CT in the evaluation of FUO in children was provided by the MAH (Jasper *et al.* 2009). The percentage of ($^{18}$F)FDG-PET scans helpful in the diagnostic process in patients with FUO was 45%.

Overall, the MAH concluded that ($^{18}$F)FDG-PET is considered a valuable diagnostic tool for the detection of unexplained signs of inflammation.

***($^{18}$F)FDG-PET in fever of unknown in patients with HIV-infection***

An overview of four clinical studies on the use of ($^{18}$F)FDG-PET or PET/CT in the evaluation of FUO in HIV-positive patients was provided by the MAH (dated 1997-2013). One study (Martin et al. 2013) provided the percentage of ($^{18}$F)FDG-PET scans helpful in the diagnostic process, *i.e*. 80%. Two clinical studies presented the diagnostic parameters, i.e. 0.63 and 0.92 for sensitivity and 0.75 and 0.94 for specificity. The MAH concluded that ($^{18}$F)FDG-PET/CT is a valuable tool in patients with HIV-associated FUO. Due to a high sensitivity and specificity for lesions causing the fever, FDG PET/CT directs to the origin of the fever in the majority of patients. The addition of anatomical landmarks by means of CT to the PET findings allows an accurate and easy localisation of the sites to be punctured.

***Role of ($^{18}$F)FDG-PET in inflammatory bowel disease***

An overview of one review and ten clinical studies on the usefulness of ($^{18}$F)FDG-PET or PET/CT for the identification of inflammatory areas of the bowel in patients with

inflammatory bowel disease (IBD) was provided by the MAH (dated 2002-2011). Sensitivity and specificity reported in the clinical studies varied between 0.82-0.98 and 0.50-0.97, respectively. In general, the studies suggested that the major advantage of the use of ($^{18}$F)FDG-PET or PET/CT in IBD is accurately and noninvasively quantifying disease activity.

***($^{18}$F)FDG-PET/CT in osteomyelitis, spondylodiscitis and prosthetic bone and joint infections***

*Chronic osteomyelitis of peripheral skeleton:*

An overview of six clinical studies on the usefulness of ($^{18}$F)FDG-PET or PET/CT to detect osteomyelitis was provided by the MAH (dated 1998-2005). Sensitivity, specificity and accuracy reported in the studies were 1.0, 0.83-0.99 and 0.91-0.96, respectively. Additionally, ($^{18}$F)FDG-PET/CT appears to have a superior diagnostic accuracy for confirming or excluding chronic osteomyelitis compared with MRI and scintigraphy (Termaat *et al*. 2005).

*Spondylodiscitis:*

An overview of three clinical studies on the usefulness of ($^{18}$F)FDG-PET or PET/CT to detect spondylodiscitis was provided by the MAH (dated 2002-2010). Stumpe *et al.* (2002) reported that
($^{18}$F)FDG-PET is superior to MRI in the differentiation of degenerative and infectious endplate abnormalities of lumbar spine, reporting sensitivity and specificity of ($^{18}$F)FDG-PET in detecting disc space infection of 1.00 and 1.00, respectively.

*Infected prosthesis and metallic implants:*

An overview of four clinical studies on the usefulness of ($^{18}$F)FDG-PET or PET/CT to detect metallic implant-associated infections was provided by the MAH (dated 2003-2009). In these studies, the reported sensitivity, specificity, and accuracy varied between 0.83-1.0, 0.75-1.0 and 0.83-1.0, respectively.

*Diabetic patient with a foot suspicious of Charcot's neuroarthropathy, osteomyelitis and/or soft tissue infection:*

An overview of nine clinical studies on the usefulness of ($^{18}$F)FDG-PET or PET/CT in differentiating between osteomyelitis, Charcot neuroarthropathy and soft tissue infections in patients with a diabetic foot was provided by the MAH (dated 2004-2013). In these studies, the reported sensitivity, specificity, and accuracy of ($^{18}$F)FDG-PET/CT for the diagnosis of osteomyelitis in the diabetic foot were 0.29-1.0, 0.92-0.93, and 0.79-0.95, respectively.

Overall, it was concluded that ($^{18}$F)FDG-PET is a highly effective imaging procedure and could be recommended for diagnosing of complications of hip and knee arthroplasty and other metallic implants without reservation. If MRI is contraindicated of equivocal, ($^{18}$F)FDG-PET/CT could be a useful alternative for diagnostic work-up of patients with suspected spinal osteomyelitis and spondylodiscitis and for the diagnosis of osteomyelitis related to diabetic foot.

***($^{18}$F)FDG-PET and PET/CT in vasculitis***

An overview of 19 clinical studies on the usefulness of ($^{18}$F)FDG-PET/CT in diagnosing and evaluating therapy in vasculitis was provided by the MAH (dated 2003-2012). The sensitivity and specificity reported in these studies were 0.77-0.92 and 0.89-1.00, respectively. In general, the provided studies demonstrated that ($^{18}$F)FDG-PET is suitable to detect vasculitis of large arteries.
Additionally, combined guidelines from the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) recently stated that based on cumulated sensitivity of 0.80, specificity of 0.89 and accuracy of 0.85, primary evaluation of vasculitis belongs to the major evidence based indications for the use of ($^{18}$F)FDG-PET/CT.

***($^{18}$F)FDG-PET in prosthetic graft infection***
An overview of seven clinical studies on the use of ($^{18}$F)FDG-PET/CT in detection of infected grafts was provided by the MAH (dated 2000-2013). The sensitivity, specificity, PPV, and NPV reported in these studies were 0.85-1.00, 0.64-0.91, 0.82-0.97, and 0.88-0.96, respectively. The studies demonstrated that combining PET with CT has significantly improved the specificity and diagnostic accuracy of this non-invasive imaging modality, particularly by decreasing the rate of false-positive cases.

***Role of (18F)FDG-PET in sarcoidosis***
An overview of seven clinical studies on the use of ($^{18}$F)FDG-PET/CT in detection of cardiac and extra- cardiac sarcoidosis has been provided by the MAH (dated 2004-2013). In the detection of cardiac sarcoidosis, the sensitivity, specificity, and accuracy of ($^{18}$F)FDG-PET were 0.85-1.00, 0.39-0.97, and 0.87, respectively. Diagnostic parameters concerning extra-cardiac sarcoidosis have not been provided by the MAH. In general, the MAH concluded that ($^{18}$F)FDG-PET has been shown to be a sensitive technique to assess the inflammatory activity in sarcoidosis by detecting and quantifying the level of inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body.

**Oncology**

***($^{18}$F)FDG-PET in differentiating benign from malignant lesions***
An overview of 12 clinical studies (dated 1991-2013), including six meta analysis, has been provided to support the usefulness of ($^{18}$F)FDG-PET(/CT) in the differentiation between benign and malignant masses in lung and, although less definitive, in masses of the adrenals, pancreas, and soft tissue. The pooled sensitivity and specificity of ($^{18}$F)FDG-PET(/CT) reported in these studies were between 0.88-1.0 and 0.68-0.91. The MAH's conclusion from these studies was that ($^{18}$F)FDG-PET(/CT) is an accurate non invasive imaging test for differentiating benign versus malignant masses in lung, adrenal, pancreas and soft tissue. As such, ($^{18}$F)FDG-PET may prevent unnecessary (complex) biopsies or may help to prevent false negative biopsy results in the diagnostic work-up of such masses.

***($^{18}$F)FDG-PET in the detection of an unknown or suspected primary tumour***
Five clinical studies to support the use of ($^{18}$F)FDG-PET or PET/CT in the detection of an unknown or suspected primary tumour were provided by the MAH (dated 2003-2013). The

sensitivity and specificity reported in these studies were 0.78-0.87 and 0.79-0.71 for ($^{18}$F)FDG-PET and 0.81-1.00 and 0.83-0.90 for ($^{18}$F)FDG-PET/CT, respectively. Overall, the MAH concluded that ($^{18}$F)FDG-PET/CT for the detection of an unknown primary tumour is a useful technique when the initial presentation of a malignancy is presence of a metastasis.

***($^{18}$F)FDG-PET for staging of cancer***

An overview of 49 clinical studies on the use of ($^{18}$F)FDG-PET/CT for staging of cancer has been provided by the MAH (dated 1998-2013). Diagnostic parameters of these studies are presented in Table 2**.**

Overall, the MAH concluded that the additional value of ($^{18}$F)FDG-PET/CT comparing to conventional anatomical imaging is well determined in various types of malignant lymphomas, lung-, breast-, head and neck-, oesophageal-, and colorectal cancer and mesothelioma. The role of ($^{18}$F)FDG-PET/CT still has to be further established in melanoma, multiple myeloma and genitourinary male and female cancers. There is a limited additional value of this technique in staging of thyroid, prostate and testicular cancer.

Of note, scientific evidence confirming superiority of ($^{18}$F)FDG-PET/CT comparing to conventional imaging modalities has grown exponentially during the past decade. This information is unfortunately not always reflected in the currently available (Dutch) guidelines.

**Table 2 ($^{18}$F)FDG-PET/CT in staging of malignancies**

| Tumour | Primary tumour | Lymph node metastases | Distant metastases | Conventional imaging | Guidelines |
|---|---|---|---|---|---|
| Malignant lymphoma[2,160-163,165,166,209] | HL: +++<br>NHL (DLBCL): +++<br>Indolent NHL +/- | | Bone marrow localizations:<br>HL: +++<br>NHL (DLBCL): ++<br>Indolent NHL +/- | ++ | The International Harmonization Project (IHP) recommends: baseline ($^{18}$F)FDG-PET scan for HL and DLBCL because of their consistent ($^{18}$F)FDG-avidity and potential curability.<br>For other subtypes, ($^{18}$F)FDG-PET imaging is recommended for clinical trials, particularly, when response rate is the primary objective.<br><br>The current National Comprehensive Cancer Network guidelines (NCCN) recommend baseline ($^{18}$F)FDG-PET imaging as an essential test in HL, DLBCL, AIDS related B-cell lymphomas and as a useful test in selected cases in FL, MZL, MZL, MCL, but does not recommend it in CLL. |
| Multiple myeloma[167,168,170] | +++ | | | +++ | The International Myeloma Working Group recommends WBXR for global myeloma care as the golden standard, ($^{18}$F)FDG-PET/CT and MRI on indication |

| Tumour | Primary tumour | Lymph node metastases | Distant metastases | Conventional imaging | Guidelines |
|---|---|---|---|---|---|
| Lung cancer[169,171,173,174] | Nodules >1 cm<br>+++ | Pooled per-patient data :<br>Se ++<br>Sp/NPV +++ | Pooled data<br>+++ | Pooled data on distant metastases<br>+/- | Primary tumour SUV measurement has a prognostic value in NSCLC<br>Se and Sp is low in GGO<br><br>Correct nodal staging is essential: if N3 nodes are involved, nodal surgery is not recommended. |
| Malignant mesothelioma[172,173,175,176] | ++ | N2 staging<br>++/+ | +++ | Pooled data on distant metastases<br>+/- | ESMO clinical practice guidelines recommend ($^{18}$F)FDG-PET/CT to rule out distant metastases. Role of FDG Pet is still under investigation, but current data is promising. |
| Oesophageal cancer[173,177,178] | + | + | Pooled data<br>+++ | Pooled data on distant metastases<br>+/- | According to Dutch guidelines, ($^{18}$F)FDG-PET is indicated in T3 tumours to exclude distant metastases. |
| Gastric cancer[173,179] | - | Se –<br>Sp +++<br>Acc + | | Pooled data on distant metastases<br>+/- | Dutch guidelines do not recommend ($^{18}$F)FDG-PET or PET/CT for pre-operative staging of gastric cancer |
| Colorectal cancer[173,181,182] | Brush<br>- | - | | Pooled data on distant metastases<br>+/- | Dutch guidelines do not recommend ($^{18}$F)FDG-PET/CT for staging of primary colon carcinoma |
| Pancreatic cancer[139,173] | ++ | ++ | | Pooled data on distant metastases<br>+/- | Dutch guidelines advice to be cautious when using ($^{18}$F)FDG-PET/CT for diagnostics and staging of pancreatic cancer. |
| Gallbladder cancer[173,183] | +++ | ++ | | Pooled data on distant metastases<br>+/- | IKNL guidelines and Dutch guidelines do not advise ($^{18}$F)FDG-PET/CT as routine diagnostic and staging tool in gallbladder cancer and cholangiocarcinoma<br><br>A number of studies published in 2013 indicate major influence of PET/CT on clinical decision making in primary biliary malignancies, helping triage patients to the most appropriate treatment. These data could influence future guidelines. |
| Cholangiocarcinoma[61,173,184,185] | No data available | Se -<br>Sp ++ | | Pooled data on distant metastases<br>+/- | |
| Ovarian cancer[186-189] | ++ | ++/+++ | +++ | MRI/CT<br>+++/++ | Dutch guidelines do not address the role of ($^{18}$F)FDG-PET/CT in staging of ovarian cancer |
| Cervical cancer[189,210-213] | Se +<br>Sp +++<br><br>NB limited resolution for detection of parametrial involvement | Se-<br>Sp +++ | +++ | MRI /CT<br>T +++/+<br>N ++/++<br>M +/- | Dutch guidelines advise ($^{18}$F)FDG-PET/CT use on indication, if regional lymph node metastases are suspected on CT or MRI |
| Endometrial cancer[214,215] | ++ | Se +<br>Sp +++ | +++ | MRI<br>Se +<br>Sp +++<br>CT<br>Se-<br>Sp++ | Dutch guidelines state that MRI is the best technique for staging of endometrial carcinoma |
| Vulvar cancer[190] | There is no validated data for diagnostic impact of PET/CT in staging of vulvar cancer | | | Not applicable | Dutch guidelines do not address the role of ($^{18}$F)FDG-PET/CT in staging of vulvar carcinoma |

| Tumour | Primary tumour | Lymph node metastases | Distant metastases | Conventional imaging | Guidelines |
|---|---|---|---|---|---|
| Vaginal cancer[190] | There is no validated data for diagnostic impact of PET/CT in staging of vaginal cancer | | | Not applicable | Dutch national guidelines do not address the role of ($^{18}$F)FDG-PET/CT in staging vaginal cancer |
| Gestational trophoblastic tumours[216,217] | There is no validated data for diagnostic impact of PET/CT in staging of gestational trophoblastic tumours.<br>Several small studies report additional value of PET/CT in high-risk disease. | | | Not applicable | Dutch guidelines do not address the role of ($^{18}$F)FDG-PET/CT in staging of gestational trophoblastic tumours |
| Renal cell carcinoma[191] | Se:+<br>Sp:+++ | Se:++<br>Sp:+++ | | | Dutch guidelines see no additional value for ($^{18}$F)FDG-PET/CT in staging of renal cell carcinoma |
| Adrenal cortical carcinoma | There is no validated data for diagnostic impact of PET/CT in staging of adrenocortical cancer. | | | Not applicable | No Dutch guideline available |
| Bladder cancer1 [192-194] | Se*: +++<br>Sp: +++<br>* delayed pelvic imaging after diuretics | Se: +<br>Sp:+++<br>Acc:++ | Limited data for diagnostic impact of PET/CT in evaluation of distant metastases in bladder cancer. | MRI, lymph node staging:<br>Se:-<br>Sp++ | Dutch guidelines (2009) do not discuss the value of ($^{18}$F)FDG-PET/CT in bladder cancer. |
| Urethral cancer | There is no validated data for diagnostic impact of PET/CT in staging of urethral cancer. | | | Not applicable | No Dutch guideline available |
| Prostate cancer[195,196] | ($^{18}$F)FDG-PET/CT has limited use in staging of prostate cancer.<br>Several studies report additional value in high-risk patients. | | | Not applicable | Dutch guidelines (2004) do not see of ($^{18}$F)FDG-PET/CT in staging of prostate cancer. |
| Testicular cancer[218,219] | ($^{18}$F)FDG-PET/CT has no use in staging of testicular cancer | | | Not applicable | Dutch guidelines do not see of ($^{18}$F)FDG-PET/CT in staging of testicular cancer. |
| Penile cancer[197,198] | No data available | Inguinal node involvement: +++ | No data available | Not applicable | Dutch guidelines do not see of ($^{18}$F)FDG-PET/CT in staging of penile cancer. |
| Head and neck cancer[173,199-201] | No data available | Se ++<br>Sp +++ | +++ | MRI: +++<br>CT: ++ | Dutch guidelines (2010) recognize additional value of ($^{18}$F)FDG-PET/CT in staging of head and neck malignancies, but do not advice it as a routine method, though state that it could be used for evaluation of the second primary tumours and distant metastases. |
| Carcinoma of the thyroid gland[64,202,203] | No role in staging of differentiated thyroid cancer.<br>Additional value in aggressive forms of thyroid cancer (Hurtle cell).<br>Additional value in characterization of FDG avid thyroid nodes<br>Se: +++ ; Sp - ; Acc + | | | Not applicable | Dutch guidelines to not recommend ($^{18}$F)FDG-PET/CT for staging of differentiated thyroid cancer |
| Breast cancer[173,204,205] | No role for primary tumour staging. | Se: +<br>Sp: +++ | +++ | Not applicable | Dutch guidelines recommend ($^{18}$F)FDG-PET/CT for staging of stage III breast cancer and could be performed in stage II if neo-adjuvant chemotherapy is planned. |
| Primary bone tumours and soft-tissue sarcoma[206] | There is only limited data for diagnostic impact of PET/CT in staging of primary bone tumours and soft tissue sarcoma. | | | No data available | Dutch guidelines recommend ($^{18}$F)FDG-PET/CT use to exclude distant metastases in bone tumours. PET/CT is not indicated in soft tissue sarcoma's |
| Malignant melanoma[207,208] | No role for primary tumour staging. | Se:-<br>Sp: +++ | Se: ++<br>Sp: +++ | Pooled data for regional lymph node staging<br>CT: ++<br>US: +<br>Se: +<br>Sp: +++ | Dutch guidelines see no additional value of ($^{18}$F)FDG-PET/CT in staging of low stages of melanoma (stage I-IIIA). It could be used in stage IIIB on individual basis to exclude distant metastases. |

+++ *sensitivity, specificity and/or accuracy > 80%*
++ *sensitivity, specificity and/or accuracy > 70%*
+ *sensitivity, specificity and/or accuracy > 60%*
+/- *sensitivity, specificity and/or accuracy > 50%*
- *sensitivity, specificity and/or accuracy < 50%*

*Sensitivity, specificity and/or accuracy are stated separately if differ for more than 10%.*

*Table is based on meta-analyses, systematic reviews and trial data published throughout the past decade.*

***($^{18}$F)FDG-PET/CT for restaging/recurrence of malignancies***

An overview of 19 clinical studies (dated 2002-2013) has been provided to support the usefulness of ($^{18}$F)FDG-PET(/CT) for detection of recurrent various types of malignant lymphomas and lung-, head and neck-, colon-, ovarian-, breast-, and thyroid cancer.
The MAH concluded that ($^{18}$F)FDG-PET/CT has been confirmed as a good and effective test for the diagnosis of cancer recurrence and for the estimation of tumour extent.

***($^{18}$F)FDG-PET for therapeutic monitoring in oncology***

An overview of 35 clinical studies on the use of ($^{18}$F)FDG-PET(/CT) for treatment monitoring in oncology has been provided by the MAH (dated 2000-2011). An overview of these studies are presented in Table 3 and Table 4. The MAH concluded that there is strong evidence for successful ($^{18}$F)FDG-PET-based treatment monitoring, however, future validation of ($^{18}$F)FDG-PET/CT for monitoring tumour responses will be required especially for certain tumour types.

**Table 3 Overview of studies regarding early evaluation of therapy response with ($^{18}$F)FDG-PET(/CT)**

| Tumour | First Author | Year | N | Criteria | Time Point | Responders | Non-responders | *P* Value | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Lymphoma | Haioun[256] | 2005 | 90 | Visual | 2 cycles | 90% | 61% | 0.006 | 2-year estimates of overall survival* |
| | Hutchings[257] | 2006 | 77 | Visual | 2 cycles | 96% | 0% | <0.001 | 2-year progression-free survival† |
| | Cashen[258] | 2011 | 50 | Visual | 2-3 cycles | 85% | 63% | 0.031 | 2-year event-free survival |
| | Markova[259] | 2011 | 69 | Visual | 4 cycles | 96% | 78% | 0.016 | 4-year progression-free survival |
| Lung | Weber[248] | 2003 | 57 | −20% | 2 weeks | 9 | 5 | 0.005 | Median survival‡ |
| | Hoekstra[260] | 2005 | 56 | −35% | 2 weeks | 43 | 18 | 0.04 | Median survival‡ |
| | Decoster[261] | 2008 | 31 | Visual | 3 weeks | >49 | 14 | 0.004 | Median survival‡ |
| | Tanvetyanon[262] | 2008 | 89 | Visual | 7 weeks | >48 | 36 | 0.93 | Median survival‡ |
| | Hua-Qi[263] | 2011 | 46 | -50% | 3 weeks | 73% | 69% | 0.001 | 1-year overall survival |
| Oesophagus | Weber[264] | 2001 | 37 | −35% | 2 weeks | >48 | 20 | 0.04 | Median survival‡ |
| | Wieder[265] | 2004 | 22 | −30% | 2 weeks | >38 | 18 | 0.011 | Median survival‡ |
| | Ott[266] | 2006 | 65 | −35% | 2 weeks | >42 | 18 | 0.01 | Median survival‡ |
| | Lordick[267] | 2007 | 110 | −35% | 2 weeks | >36 | 26 | 0.015 | Median survival‡ |
| | Malik[268] | 2010 | 37 | -26% | 2 weeks | 21 | 24 | 0.68 | Median Survival‡ |
| Gastric | Ott[269] | 2003 | 35 | −35% | 2 weeks | >48 | 17 | 0.001 | Median survival‡ |
| | Ott[270] | 2008 | 71 | −35% | 2 weeks | >35 | 24 | 0.037 | Median survival‡ |
| Colorectal | Cascini[271] | 2006 | 33 | −52% | 12 days | 100% | 100% | NA | Histopathologic response prediction§ |
| | Rosenberg[252] | 2008 | 29 | −35% | 2 weeks | 74% | 70% | NA | Histopathologic response prediction§ |

| Tumour | First Author | Year | N | Criteria | Time Point | Responders | Non-responders | *P* Value | Comment |
|---|---|---|---|---|---|---|---|---|---|
| Colorectal *(cont'd)* | Lambrecht[272] | 2010 | 22 | -40% | 2 weeks | 100% | 75% | NA | Histopathologic response prediction§ |
| | Janssen[273] | 2010 | 30 | -43% | 15 days | 77% | 93% | NA | Histopathologic response prediction§ |
| | Guerra[274] | 2009 | 31 | -49% | 1-3 weeks | 63% | 56% | NA | Histopathologic response prediction§ |
| Breast | Schelling[275] | 2000 | 22 | −55% | 2 weeks | 100% | 85% | NA | Histopathologic response prediction§ |
| | Smith[276] | 2000 | 30 | −20% | 2 weeks | 90% | 74% | NA | Histopathologic response prediction§ |
| | Dose Schwarz¶[277] | 2005 | 11 | Visual | 3 weeks | 19.2 | 8.8 | NS | Overall survival‡ |
| | Dose Schwarz[278] | 2008 | 104 | -45% | 1 cycle | 73% | 63% | NA | Histopathologic response prediction§ |
| | Martoni[279] | 2010 | 34 | -50% | 2 cycles | 100% | 30% | NA | Histopathologic response prediction§ |
| | Keam[280] | 2011 | 78 | -50% | 2 cycles | 86% | 61% | NA | Histopathologic response prediction§ |
| Ovarian | Avril[281] | 2005 | 33 | −20% | 2 weeks | 38 | 23 | 0.008 | Median survival‡ |
| Melanoma | Strobel[282] | 2008 | 25 | −30% | 3 cycles | 80% | 40% | 0.048 | 1-year overall survival ǀ |
| Head and neck | Brun[283] | 2002 | 47 | Median | 5 to 10 days | >120 | 40 | 0.004 | Median survival‡ |
| GIST | Stroobants[284] | 2003 | 17 | −25% | 8 days | 92% | 12% | 0.001 | 1-year progression-free survival** |
| | Goerres[285] | 2004 | 28 | Visual | 19 days | >48 | 22 | 0.001 | Median survival‡ |
| | Holdsworth[286] | 2007 | 63 | −40% | 1 month | 26 | 3 | 0.002 | Time to treatment failure‡ |
| | Choi[287] | 2007 | 40 | −70% | 2 months | 70% | 30% | 0.01 | 2-years progression-free survival† |
| | Prior[288] | 2009 | 23 | SUV<8 | 4 weeks | 17 | 6 | 0.004 | Overall survival |

*NS, not significant; NA, not available; * Percentage of patients with 2-year overall survival;† Percentage of patients with 2-year progression-free; ‡ Survival in months; § Sensitivity and specificity for prediction of histopathologic response;¶ Metastatic disease; ǀ Percentage of patients with 1-year overall survival;** Percentage of patients showing 1-year progression-free survival*

**Table 4 Overview of studies regarding late evaluation of therapy response with ($^{18}$F)FDG-PET(/CT)**

| Tumour | First Author | Year | N | Criteria | Responders | Non-responders | *P* Value | Comment |
|---|---|---|---|---|---|---|---|---|
| Lymphoma | Spaepen*[289] | 2001 | 54 | Visual | 31 | 10 | <0.001 | Median progression-free survival† |
| | Juweid‡[290] | 2005 | 60 | Visual | >48 | 12 | 0.003 | Progression-free survival† |
| Lung | MacManus[247] | 2003 | 73 | Visual | >36 | 12 | <0.0001 | Median survival† |
| | Hellwig[291] | 2004 | 47 | SUV > 4 | 56 | 19 | <0.001 | Median survival† |
| | Pottgen[292] | 2006 | 37 | Visual | >24 | 15 | 0.03 | Progression-free survival† |
| Oesophagus | Brucher[293] | 2001 | 27 | −52% | 23 | 9 | <0.0001 | Median survival† |
| | Flamen[294] | 2002 | 36 | Visual | >34 | 8 | 0.005 | Median survival† |
| | Downey[295] | 2003 | 17 | −60% | 63% | 38% | 0.055 | 2-year disease-free survival rate§ |
| | Kim[296] | 2007 | 62 | −80% | 31 | 17 | 0.025 | Disease-free survival† |
| | Port[297] | 2007 | 62 | −50% | 36 | 18 | 0.03 | Disease-free survival† |
| | Swisher[298] | 2004 | 103 | SUV > 4 | >24 | 15 | 0.01 | Median survival† |
| Colorectal | Calvo[299] | 2004 | 21 | SUV > 2.5 | 86% | 80% | NS | 3-year survival rate¶ |
| | Guillem[300] | 2004 | 15 | −62.5% | >55 | 39 | 0.02 | Recurrence-free survival† |
| | Capirci[301] | 2007 | 45 | −66.2% | 81% | 79% | NA | Histopathologic response prediction‖ |
| | Rosenberg[252] | 2008 | 29 | −57.5% | 79% | 70% | NA | Histopathologic response prediction‖ |
| Cervix | Grigsby[302] | 2004 | 152 | Visual | >60 | 30 | <0.001 | Median survival† |
| | Nishiyama**[303] | 2007 | 21 | −65% | 90% | 82% | NA | Histopathologic response prediction‖ |
| Head and neck | Kunkel[304] | 2003 | 35 | SUV > 4 | >60 | 18 | 0.046 | Median survival† |
| | Connell[305] | 2007 | 30 | Visual | †† | †† | 0.037 | Overall survival† |
| Sarcoma | Schuetze[306] | 2005 | 46 | −40% | >100 | 40 | 0.02 | Median survival† |
| | Hawkins[307] | 2005 | 36 | SUV > 2.5 | 72% | 27% | 0.01 | 4-year progression-free survival‡‡ |
| | Evilevitch[308] | 2008 | 42 | −60% | 100% | 71% | NA | Histopathologic response prediction‖ |

*NS, not significant; NA, not available;* * *Hodgkin's disease;* † *Survival in months;* ‡ *NHL;* § *Percentage of patients with 2-year disease-free survival;* ¶ *Percentage of patients with 3-year survival;* ‖ *Sensitivity and specificity for prediction of histopathologic response;* ** *Ovarian and uterine cancer;* †† *Not given;* ‡‡ *Percentage of patients with 4-year progression-free survival*

## Other applications of ($^{18}$F)FDG-PET

### *($^{18}$F)FDG-PET in myocardial viability evaluation*

An overview of 15 clinical studies on the usefulness of ($^{18}$F)FDG-PET in the evaluation of myocardial viability has been provided (dated 1981-2011). Several studies demonstrated that patients who were evaluated for myocardial viability using ($^{18}$F)FDG-PET had improved survival after revascularisation, indicating the prognostic importance of assessing myocardial. Furthermore, based on several studies, the sensitivity and specificity of ($^{18}$F)FDG to predict improvement of regional myocardial function after revascularisation was 0.89 and 0.57, respectively.

From the studies, the MAH concluded that the use of ($^{18}$F)FDG-PET in the evaluation of myocardial viability has advantages over other imaging modalities and displays a favourable sensitivity, specificity, PPV and NPV.

### *($^{18}$F)FDG-PET in localisation of epileptogenic foci*

An overview of ten clinical studies on the usefulness of ($^{18}$F)FDG-PET in localisation of epileptogenic foci has been provided (dated 1980-2013). These studies demonstrated the ability of ($^{18}$F)FDG-PET to detect the reduced glucose metabolism reflecting the

epileptogenic lesions of the temporal lobe. Pooled results from several studies showed a sensitivity of 0.84 in the temporal lobe.
The MAH concluded that ($^{18}$F)FDG-PET provides important insights into the functional integrity and activity of neural systems, and is a sensitive, minimally invasive method for measuring brain metabolism and is useful in localising epileptogenic areas and establishing surgical margins in patients with temporal lobe epilepsy.

## IV.5 Clinical safety

The MAH shortly discussed potential adverse events related with injection site reactions, injection errors, exposure to ionising radiation and radioactive contamination.

Injection site reactions: there is no evidence of any hypersensitivity reactions in the scientific literature, therefore other than the standard injection site reactions cannot be expected.

Injection errors: medication errors concerning the injection are possible.
Administrations can only be performed within hospitals and by health care professionals. Risk of above medication errors is therefore minimal.

Exposure to ionising radiation: radiation exposure may lead to the development of cancer and hereditary effects. After administration of the maximum recommended activity (400 MBq) of fludeoxyglucose ($^{18}$F), the effective dose is about 7.6 mSv. The probability of the occurrence of cancer and hereditary defects is therefore small.

Radioactive contamination: radiopharmaceuticals adhere to radiation protection precautions in accordance with national regulations and should only be used by authorised persons in designated clinical settings. Nuclear departments have measures in place to prevent radioactive contamination. They have protocols to minimise avoidable radiation burden which take into consideration the shorter half-life of 18F-FDG. Such protocols are available in the “Procedure Guidelines Nuclear Medicine” issued by the Dutch Society for Nuclear Medicine in 2016, which describes in detail the use of many common radiopharmaceuticals in nuclear departments. Nuclear departments are expected to be aware of radiation protection issues and the prescribing Information mandates adherence to national regulations for radiation protection.

## 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 Fludeoxyglucose ($^{18}$F) RTM.

**Table 5. Summary table of safety concerns as approved in RMP**

| | |
|---|---|
| Important identified risks | -- |

| | |
|---|---|
| Important potential risks | • Radiation Exposure, including the risk on carcinogenicity and mutagenicity |
| Missing information | -- |

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

### IV.7 Discussion on the clinical aspects

Fludeoxyglucose ($^{18}$F) RTM is considered widely established. The MAH has provided an extensive review of published clinical studies (n=230, dated 1980-2013) in support of the efficacy and well-established use of 18F-FDG in the various proposed indications. The numerous published clinical studies demonstrate the diagnostic benefits of 18F-FDG in the various proposed indications, although detailed information on the design of the studies and method of diagnostic imaging/testing have not been provided for most of the studies. This omission can be acceptable, considering that the proposed set of indications is similar to the indications in the core SmPC of FDG and that, therefore, an extensive efficacy assessment of each specific indication is not required. Furthermore, the provided literature shows that 18F-FDG has been used in research for more than 15 years worldwide, including Europe, demonstrating the scientific interest of 18F-FDG in the claimed indications (one of the criteria of a WEU application). Data on extensive use of 18F-FDG in PET imaging has not been provided by the MAH. However, several other 18F-FDG medicinal products are currently registered amongst others in the Netherlands for more than ten years for the same indications, indicating that the use of 18F-FDG in the various proposed indications can be considered well-established. Additionally patient information documents of different Dutch hospital centres including the Antoni van Leeuwenhoek, Bavis hospital, Jeroen Bosch hospital, reported the use of 18F-FDG for PET imaging. Furthermore, different guidelines including the Society of Nuclear Medicine and Molecular Imaging also recommended the use of 18F-FDG for PET imaging. Based on above, it is considered that the extensive use of 18F-FDG in PET imaging has been demonstrated.
No data has been submitted to bridge the product applied for to literature data, which is considered acceptable considering that the product applied for concerns a solution for i.v. injection.
The MAH discussed potential adverse events related with injection site reactions, injection errors, exposure to ionising radiation and radioactive contamination. The risk of injection side reactions or medication errors is minimal and therefore acceptable.

## 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 (UK/H/0814/001/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

Fludeoxyglucose ($^{18}$F) RTM 200 MBq/ml, solution for injection has a proven chemical-pharmaceutical quality. Fludeoxyglucose ($^{18}$F) RTM is an effective drug, which is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Fludeoxyglucose ($^{18}$F) RTM with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 July 2018.

## 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/4034 /1/IB/001 | The dispensing set of the active substance has been renewed by the manufacturer. | -- | 22-5-2019 | Approval | -- |