CBG MEB

Public Assessment Report

Scientific discussion

Fludeoxyglucose (^{18}F) MCA 100 - 400 MBq, solution for injection in prefilled syringe

(fludeoxyglucose (^{18}F))

NL License RVG: 115336

Date: 17 April 2018

This module reflects the scientific discussion for the approval of Fludeoxyglucose (^{18}F) MCA 100 - 400 MBq. The marketing authorisation was granted on 16 April 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CHMP	Committee for Medicinal Products for Human Use
ERA	Environmental Risk Assessment
FDG	Fludeoxyglucose
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PET	Positron Emission Tomography
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Fludeoxyglucose (^{18}F) MCA 100 - 400 MBq, solution for injection in prefilled syringe from Stichting MCA Gemini Groep.

The product is indicated for diagnostic use only.
Fludeoxyglucose (^{18}F) is indicated as imaging agent in positron emission tomography (PET) in adults and children with oncological, cardiological and neurological diseases and for the detection of inflammatory sources in the body. The injection is administered directly (iv) into the patient.

The indications are further specified in section 4.1 of 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 drug substance is a well-known compound; it was synthesised for the first time over 40 years ago. Its structure and other characteristics have been elucidated since. In the Netherlands, four other radiopharmaceutical injections with the same drug substance are registered.

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

II. QUALITY ASPECTS

II.1 Introduction

Fludeoxyglucose (^{18}F) MCA is a colourless to slightly yellow clear solution, with pH 6.5. Osmolality is between 240 – 300 mOsmol/kg.

The solution is packed in 5 ml single dose polypropylene syringes, fitted with a polypropylene plunger. Onto the Luer-Lock tip an ABS plastic septum holder of synthetic polyisoprene is turned airtight. Each syringe contains 4.5 ml of solution, corresponding to 100 - 400 MBq fludeoxyglucose at calibration time. The radioactivity concentration range is between 22.2-88.9 MBq fludeoxyglucose (^{18}F)/ml at calibration time.

The excipients are: sodium chloride 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.). It is a colourless or nearly colourless solid. The molecule has four asymmetric centers. Like all similar radioactive substances, it is not isolated in solid form but is obtained as an aqueous solution.
Fludeoxyglucose (^{18}F) contains the nuclide fluorine-18. This nuclide 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 180º, each with an energy of 511 keV. Fluorine-18 has a half life of 110 minutes.

Manufacturing process
Manufacture of the drug substance involves production of the radioactive ^{18}F nuclide in a cyclotron, followed by a multistep synthesis of ^{18}F-FDG. The manufacturing process of the drug substance has been described in sufficient detail.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
There is no holding time in the production process and the drug substance solution is not tested. The drug substance cannot be stored. Therefore, applying a retest period (based on stability data) is not relevant.

II.3 Medicinal Product

Pharmaceutical development
The MAH has chosen a configuration of cyclotron, automated synthesis systems and hotcells which provided the best fit with the intended PET scan programs, required the least amount of labour to operate and would comply with GMP requirements. The dosage form which was considered the most convenient medium to administer the PET tracers was the prefilled syringe.
The radioactive concentration depends on the required dose for the patient and the planned time of administering the dose, in a prefilled syringe filled with 4.5 ml product solution. The product is administered only to patients of the hospital associated with the manufacturing site. Radioactive concentration of the product fluctuates within the ranges 100 - 400 MBq and is sufficiently limited.
Study results investigating extractable volume have been provided which show that the intended dose is extracted. Quality of the syringe, including functionality, has been sufficiently demonstrated.

Manufacturing process
The manufacturing process has been adequately described. The process is performed in a closed system. The sterilization and aseptic preparation complies to Ph. Eur. The syringe radiation method is according to Ph. Eur. The manufacturing process has been validated according to relevant European/ICH guidelines.

Control of excipients
The specifications of the excipients 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, identity, pH, chemical purity, radiochemical purity, radionuclidic purity, residual solvents, sterility and endotoxins. The specifications comply with the Ph. Eur. Monograph on Fludeoxyglucose (^{18}F) injection. The limits for residual solvents acetonitrile and ethanol are qualified. The sterility test (performed after complete nuclide decay) is according to the Ph. Eur. Satisfactory validation data for the analytical methods have been provided.
Batch analytical data from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Regarding stability of the drug product the MAH refers to 131 validation batches which included also a stability study. Stability results have also been provided of three additional, recent batches. The batches were stored during 8 hours at 18 - 24° C and 40 – 65% RH. Testing was performed at 0, 4 and 8 hours. Considering the nature of the product (radiopharmaceutical preparation), the design of the study is acceptable. The results of the three batches remained within the limits, which was also the case for the validation batches. The approved shelf life is 8 hours from production time, when stored below 25°C in a prefilled syringe.

Specific measures for 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 Fludeoxyglucose (^{18}F) MCA 100 - 400 MBq, solution for injection in prefilled syringe 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, pharmacokinetics and toxicology

For this bibliographic application a non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on scientific literature.

Fludeoxyglucose (^{18}F), ^{18}F-FDG, is a radiopharmaceutical used as diagnostic agent in PET. Its diagnostic strength is based on accumulation of ^{18}F-FDG after phosphorylation in cells exhibiting a higher glucose consumption than normal cells. Catching the radiation from radioactive decay of ^{18}F-FDG by PET visualizes the distribution of glucose uptake and phosphorylation by these cells in the body. During radioactive decay^{18}F-FDG-phosphate is transformed to ^{18}O-glucose-6-phosphate that is metabolized as normal glucose to non-radioactive end products. Although ^{18}F-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 ^{18}F-FDG nowadays is used for imaging tumours and for the assessment of glucose metabolism in heart, lungs and brain. The maximum administered quantity of 400 MBq represents a dosage of active substance of just over 1 nanogram. At such quantities for diagnostic studies, ^{18}F-FDG does not have any pharmacodynamic effects. The images obtained after administration of ^{18}F-FDG are formed by collecting the high energy photons (511 KeV) that result after collision of the emitted positrons with electrons in the tissue environment.

Although formal toxicological data are limited, there is extensive clinical experience of use without alerting reports on safety issues. Overall, efficacy and safety of the active substance in the proposed indications are sufficiently justified. No further non-clinical studies are required for this application.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The MAH has sufficiently justified that there is no environmental risk associated with the product. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Fludeoxyglucose (^{18}F) has a well-established medicinal use as a diagnostic radiopharmaceutical agent. It has a recognised clinical utility worldwide, including the EU. No new clinical studies were conducted, which is acceptable given that the legal basis for this application is Article 10a, i.e. a bibliographic application.

A core SmPC is available (EMA/CHMP/448228/2012), in which indication, posology and method of administration sections are laid down.

IV.2 Pharmacokinetics and pharmacodynamics

An overview of clinical pharmacology was provided in the dossier. In this section, reference is made to the a review by the FDA and a healthy volunteer study (Abouzied MM, 2005)[1].

The pharmacodynamics section mentions that a high baseline blood glucose level impacts on the biodistribution of ^{18}F-FDG. Special measures are recommended in cases of a blood glucose level of >10 mmol/l.
The SmPC mentions other interactions, which are not justified in the clinical overview: ‘All medicinal products that modify blood glucose levels can affect the sensitivity of the examination (e.g. corticosteroids, valproate, carbamazepine, phenytoin, phenobarbital and catecholamines)’ and ‘administration of colony-stimulating factors (CSFs)’.

[1] Abouzied MM, Crawford ES, Nabi HA. 18F-FDG Imaging: Pitfalls and Artifacts. J Nucl Med Technol 2005; 33: 145-155

The MAH did not identify pharmacodynamic interactions with other drugs in the literature. However, pharmacodynamic interactions with anti-diabetes drugs can be expected. Such interactions could be related to the underlying disease, glucose-lowering effects of treatment or specific interactions. Metformin is discussed in 18 publications on Pubmed and seems to change the distribution of FDG.

IV.3 Clinical efficacy

The following points highlight the clinical usefulness of ^{18}F-FDG:

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

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

IV.4 Clinical safety

The discussion of adverse reactions is primarily based on an operational definition by the Pharmacopeia Committee of the Society of Nuclear Medicine (SNM). This definition is much more restrictive than the definition in ICH-E2A, which among others includes extravasation and overdose. Reference is made to the publication of Silberstein (1998)[2].
Patient dosimetry for FDG radiation safety (6.23 mSv for 370 MBq) is comparable to diagnostic whole body CT imaging (7.2-25.9 mSv). It is agreed that the radiation dose that is delivered to patients when performing a PET or CT scan warrants a clinically justified indication for the procedure, and all measures must be taken to reduce radiation.
Although not required according to SmPC section 4.2, local practice in the MCA clinical facility includes a peripheral venous catheter for all patients to reduce the risk of extravasation.
The discussion of extravasation risks references Shapiro (1987)[3]. The article recommends informing the patient in case of local radiation doses > 20 Gy. In a worst case scenario, the radiation dose to the surrounding tissue would be 34 Gy according to the clinical overview. Practices like flushing the line significantly reduce such doses, but are not mandated by product information. This is agreed as it is in accordance with the core SmPC.

IV.5 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) MCA 100 - 400 MBq.
One important identified risk is included: 'radiation exposure with the potential to induce cancer and hereditary effects'. The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for this medicinal product.

IV.6 Discussion on the clinical aspects

Based on the presented literature and the report of experiences in the MCA department of Nuclear Medicine, the use of FDG is considered widespread in the community. The clinical overview clearly

[2] Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J. Nucl. Med. 39 (12), 2190–2192 (1998).)
[3] Shapiro, B., Pillay, M., & Cox, P. H. Dosimetric consequences of interstitial extravasation following i.v. administration of a radiopharmaceutical. Eur. J. Nucl. Med. 12 (10), 522–523 (1987)

documents the diagnostic benefits that may be obtained by using FDG-PET in the various proposed indications.

According to the core SmPC for FDG, exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. 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 clinical overview does not discuss (the calculation of) the radiation dose caused by the FDG-PET scanning procedure. As these data are always based on theoretical data, this omission can be accepted and standard methods can be used instead.

In clinical practice, there is an increase in the use of FDG-PET. This is mainly based on its great diagnostic sensitivity, which can guide further localised diagnostic modalities and disease management, especially in oncology. In these domains, the unfavourable effects are usually considered of minimal importance, as they occur only with low probability and after a long period of time. Risk management is adequately addressed.

V. USER CONSULTATION

The content of the package leaflet (PL) is in accordance with the Guideline on core SmPC and package leaflet for fludeoxyglucose (^{18}F) (EMA/CHMP/448228/2012). User testing of the PL is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Fludeoxyglucose (^{18}F) MCA 100 - 400 MBq, solution for injection in prefilled syringe has a proven chemical-pharmaceutical quality. The use of the active substance is considered well-established as imaging agent in PET in adults and children with oncological, cardiological and neurological diseases and for the detection of inflammatory sources in the body.

Fludeoxyglucose (^{18}F) MCA has a favourable efficacy and safety profile. Adequate non-clinical and clinical literature data have been provided.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that well-established use has been adequately demonstrated. Fludeoxyglucose (^{18}F) MCA 100 - 400 MBq was authorised in the Netherlands on 16 April 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached