IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

ERtracER Solution for Injection
Fludeoxyglucose [18F]
PA1125/002/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

This application for ERtracER Fludeoxyglucose (^{18}F) solution for injection is submitted in accordance with Directive 2001/83/EC Article 10 (a) well-established use.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

Name of the product	ERtracER Solution for Injection
Name(s) of the active substance(s) (INN)	FLUDEOXYGLUCOSE (^{18}F) INJECTION
Pharmacotherapeutic classification (ATC code)	V09IX
Pharmaceutical form and strength(s)	Solution for injection, 10-130 GBq
Marketing Authorisation Number(s) in Ireland (PA)	PA1125/2/1
Marketing Authorisation Holder	M2i Limited
MRP/DCP No.	IE/H/0447/001/DC
Reference Member State	IE

II. QUALITY ASPECTS

II.1. Introduction

ERtracER (Fludeoxyglucose 18F Injection) is a diagnostic radiopharmaceutical drug product comprising 18F radiolabelled 2-fluoro-2-deoxy-D-glucose (18FDG), which contains the short-lived radionuclide 18Fluorine (half-life approximately 110 minutes) as the drug substance.

II.2 Drug substance

The active substance ^{18}F-fludeoxyglucose is formed as part of the finished product manufacturing process from two precursors; 18-fluorine and Tetra-o-acetyl-Mannose Triflate (TATM) as described in Ph Eur. monograph 1325. Both are adequately described. 18-fluorine is formed at the finished product manufacturing site immediately prior to the manufacturing process due to its short half-life. Acceptable specifications for both precursors are presented. Batch analytical data demonstrating compliance with these specifications has been provided.

II.3 Medicinal product

P.1 Composition and description

The product is an aqueous solution for injection of 110-10,000MBq/ml fludeoxyglucose (^{18}F). The active substance is fludeoxyglucose labelled with ^{18}F. The finished product is a radiopharmaceutical as described in the Ph. Eur. The active substance is formed at the finished product manufacturing site and eluted into a solution of sodium chloride and phosphate buffer.

Composition of the medicinal product

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites. The manufacturing process of the finished product is based on nucleophilic substitution of the starting material with [^{18}F]fluoride, as prescribed by the relevant Ph. Eur. monograph (1325). The product is sterile.

The process and its controls have been adequately described and are sufficient to ensure the quality of the finished product in conjunction with the finished product specification. The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/Ancillary Substances)

All ingredients comply with Ph. Eur. and are well known.

P.5 Control of Finished Product

The Finished Product Specification is based on the Ph. Eur. monograph for the finished product, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data. Batch analytical data for a number of batches from the proposed production sites have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with the relevant Ph. Eur. requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of ERtracER (Fludeoxyglucose ^{18}F Injection).

III. NON-CLINICAL ASPECTS

III.1 Introduction

ERtracER (Fludeoxyglucose ^{18}F Injection) is a diagnostic radiopharmaceutical drug product comprising ^{18}Fradiolabelled 2-fluoro-2-deoxy-D-glucose (^{18}FDG), which contains the shortlived radionuclide ^{18}Fluorine (half-life approximately 110 minutes). It is supplied as a "ready-to-use" (RTU) solution in a conventional glass vial with rubber stopper and aluminium crimp cap. The sealed vials are transported in suitable Type A protective packaging appropriate for radiopharmaceutical drug products.

The proposed drug product is the subject of an existing Marketing Authorisation (MA) in the Republic of Ireland (ROI). The information supporting the MA comprises a stand-alone bibliographic application, for which supporting references are provided. ^{18}FDG is indicated as a tracer for use in Positron Emission Tomography (PET) scanning for the diagnosis of a range of clinical conditions in conjunction with other diagnostic modalities, outlined in the product information. These include conditions affecting the brain and heart and a wide range of different cancers. ERtracER is intended for single dose intravenous injection. 2-fluoro-2-deoxy-D-glucose, also known as fludeoxyglucose or FDG, is an analogue of glucose and enters the glucose metabolic pathway. Within this metabolic pathway FDG can be phosphorylated to FDG-6-phosphate by hexokinase, but it cannot serve as a substrate for glycolysis or the synthesis of glycogen or to enter the pentosephosphate cycle. FDG has a

low membrane permeability and remains trapped within the cell until it is dephosphorylated by glucose-6-phosphatase and subsequently excreted into the urine.

The organs with the highest glucose-turnover are the brain and heart and therefore FDG is enriched in these organs. As might be expected, FDG also accumulates in tumours with a high turnover of glucose. In common with the brain and the heart, such tumours have high hexokinase and low glucose-6-phosphatase levels. In these tissues, the degree of concentration of FDG is a direct measure of hexokinase activity, and therefore, in principle, of the rate of glucose metabolism.

The HPRA has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology

The basic principle behind the use of Fludeoxyglucose ^{18}F Injection is that it provides a glucose analogue that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. It is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to ^{18}F FDG-6-phosphate by the enzyme hexokinase. Once it is phosphorylated it cannot leave the cell until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, because fludeoxyglucose ^{18}F can be imaged, the retention and clearance of fludeoxyglucose ^{18}F reflects a balance involving glucose transporter, hexokinase and glucose-6-phosphate activities. In contrast, regions of increased uptake of fludeoxyglucose ^{18}F reflect greater than normal rates of glucose metabolism. Cancer cells are generally characterized by enhanced glucose metabolism due to various factors. Despite this, uptake and distribution within tumors of various types can vary. However, despite these variations FDG has been demonstrated both in vitro and in vivo to be taken up and localized within tumor cells, primarily within the viable regions of the tumor, with uptake also correlating with young granulation tissue and infiltrating macrophages. Prenecrotic cells were also observed to uptake FDG but due to a lack of metabolic activity these cells fail to retain FDG. Hyperglycaemia can be a cause of false negative FDG uptake by tumour cells and studies in hyperglycaemic rats suggest that high serum glucose levels may substantially interfere with tumor imaging with FDG. The use of chemotherapeutic agents via their cytotoxic mechanism of action have been shown to cause a reduction in glucose metabolism which is reflected in FDG-PET images. Similarly irradiated tumors (20 Gy) have also shown a decrease in ^{18}FDG.

The tumour uptake of ^{18}FDG reached a peak by 30 minutes and remained relatively constant up to 60 minutes, with a very slow wash-out of ^{18}F activity from the tumour thereafter. Tumour-to-normal tissue and tumour-to blood ratios ranged from 2.1-9.2 and 2.6-17.8, respectively, depending on the type of tumour (27). In the heart under normal aerobic conditions, the myocardium meets the bulk of the energy requirement by oxidising free fatty acids. The myocardial uptake of ^{18}FDG was investigated in the rat under various feeding conditions. The uptake of FDG in the myocardium was rapid however the degree of uptake was greater under fed conditions than fasted conditions in the rat. Myocardial uptake by ^{18}FDG was relatively constant at glucose levels below 120 mg/100 ml and increased steeply at higher blood glucose levels. Insulin was also demonstrated to cause a marked increase in FDG myocardial uptake although blood glucose levels decrease.The suitability of ^{18}FDG for detection of alterations in local cerebral glucose metabolism was tested. It was demonstrated in the rat that there was a strong correlation between uptake of ^{18}FDG in the brain and blood glucose levels. Positron emission tomography (PET) with ^{18}F-2-deoxyglucose has become a valuable tool to identify the focus in temporal lobe epilepsy and to assist in the delineation of the focus in extratemporal lobe epilepsy.

III.3 Pharmacokinetics

Tissue distribution has been studied in mice, rats and dogs. It have been shown that FDG is rapidly distributed to all tissues but is predominately retained in the heart and brain, due to metabolic trapping, with rapid excretion (predominately unchanged) from the liver, lungs and kidney. [^{18}F] fludeoxyglucose is also bound to a lesser extent to ocular muscle, pharynx, intestine and bone marrow. Binding to muscle may be seen following recent exertion and in the event of muscular effort during PET scanning. The extent of binding to plasma proteins is unknown. The kinetics of FDG vary greatly among different tumour types. In malignant tumours, the maximum uptake is reached relatively late after FDG injection, up to six hours, while in inflammatory masses and benign tumours a plateau level is noted within 45 to 60 minutes (42, 43). This can be of value in differentiating malignant and benign lesions and help to increase the specificity of the test (13). FDG-PET imaging usually starts around 60 minutes after injection so that a satisfactory tumour to background activity ratio is achieved.

III.4 Toxicology

A full programme of conventional toxicology studies was not performed by the applicant. The present application only describes the effects of ^{18}FDG prepared by the nucleophilic substitution method. In terms of the approved drug product, a dose of 185 MBq ^{18}F equals 0.5 ng. From a toxicological point of view this amount is not significant. Doses of FDG administered

to mice and dogs were 14.3 mg/kg and 0.72 mg/kg iv respectively at weekly intervals for three weeks. Neither mice nor dogs that received FDG showed any gross or microscopic differences compared mg/kg at weekly intervals for 3 weeks. At the end of the study no gross or microscopic abnormalities were noticed in brain, spleen, liver, kidneys and lungs (29). The results obtained from these studies indicated that the anticipated initial dose of 1 mg (0.014 mg/kg) could be safety administered to human volunteers. The proposed initial human dose represented a factor of 150-times less than that administered i.v. to dogs and 3000-times less than that administered iv to mice, without any evidence of acute or chronic toxicity (44).

Although no reports are available, no risk is to be expected from the low amount of FDG to be used clinically. A risk may be associated with the exposure to ionising radiation by ^{18}F. This is not likely, because the equivalent for a single dose (400 – 700 MBq) is between 8 and 14 mSv. This is below the accepted limit of 20 mSv.

III.5 Ecotoxicity/environmental risk assessment

The product ERtracER is a radiopharmaceutical drug product. It is a radioactive material and is regulated by the following government agencies in the Republic of Ireland :

§ The Radiological Protection Institute of Ireland

No individual or organisation can receive, handle or use radioactive materials without the appropriate licence, registration or authorisation in place. A comprehensive risk assessment must be carried out and submitted to the relevant authorities as part of the licence application process, in compliance with IRR99 (Ionising Radiation Regulations 1999) and the Radioactive Substances Act (1993).

III.6 Discussion on the non-clinical aspects

The information provided by the applicant suggests that this product can be used safely in the licensed indications.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application for ERtracER Fludeoxyglucose (^{18}F) solution for injection is submitted in accordance with Directive 2001/83/EC Article 10 (a) well-established use and so all clinical data are presented on the basis of published information.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Following administration, ^{18}FDG is widely distributed throughout the body and is taken up in those tissues that are most actively involved in glucose metabolism. This feature of the drug product provides the basis of its efficacy as a radioactive tracer. The activity required is nearly always tailored to a particular patient's needs and physiological status, but is generally within the range 400 to 700 MBq. Alterations in administered activity based on whole body mass are required to achieve effective activity levels for scanning in children and adolescents.

IV.3 Pharmacodynamics

Specific clinical pharmacology studies have not been performed with ERtracER (^{18}FDG) because the drug product is a simple aqueous, "ready to use" (RTU) solution of ^{18}FDG and extensive data are already available within the published literature on the clinical pharmacology of the radioactive drug substance. Such studies are therefore not required. The clinical pharmacology of ^{18}FDG is very well established. The basic principle behind the use of ^{18}FDG is that it provides a glucose analogue that concentrates in cells that rely upon glucose as an energy source, or in cells whose dependence on glucose increases under pathophysiological conditions. It is transported through the cell membrane by facilitative glucose transporter proteins and is phosphorylated within the cell to ^{18}F FDG-6-phosphate by the enzyme hexokinase. Once it is phosphorylated it cannot leave the cell until it is dephosphorylated by glucose-6-phosphatase. Therefore, within a given tissue or pathophysiological process, because ^{18}FDG can be imaged, the retention and clearance of ^{18}FDG reflects a balance involving glucose transporter, hexokinase and glucose-6-phosphate activities. When allowance is made for the kinetic differences between glucose and fludeoxyglucose ^{18}F transport and phosphorylation (expressed as the "lumped constant ratio"), ^{18}FDG is used to assess glucose metabolism (6).

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

IV.4 Clinical Efficacy

FDG-PET is a very well established diagnostic method for the assessment of a wide range of different clinical diseases and conditions. A wealth of published information supports its widespread use in oncology, cardiology, neurology, and in the investigation of inflammation and infections of unknown origin. The common limiting factor, however, is often an economic one.

FDG-PET is nowadays commonly used with CT or MRI scanning to provide data and information to help construct a concise picture of the status or progression of a range of different diseases. Its use as a diagnostic tool is crucial in a wide range of disease areas. The MAH has produced an up to date thorough review of the current literature and has justified all changes to previously agreed SmPCs.

IV.5 Clinical Safety

The overall safety profile of intravenous ^{18}FDG is very well established and the drug product is well tolerated. The adverse event incidence for this drug product, when used in accordance with the proposed SmPC (product information), is expected to be very low. As outlined in the application dossier, the incidence rate for adverse reactions for radiopharmaceuticals is considerably lower than that reported for X-ray contrast media and for most drug products administered in a hospital setting. In a report by EB Silberstein (Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine) an incidence rate for radiopharmaceuticals was investigated during a five-year prospective study in 18 institutions was reported to be 2.3 adverse events per 100,000 administrations – many thousand times lower than that seen for X-ray contrast media.

Silberstein has retrospectively reviewed the incidence rate of adverse reactions generated from 33,925 PET procedures and confirmed that no adverse events were reported. A prospective 30-month study, including 22 centres and 42,458 PET procedures did not yield any adverse events that were related to FDG-PET in the 24-hour period following administration. Combining these results provided a potential
incidence rate (within 95% confidence limits) of 3.9 adverse events per 100,000. Vasovagal responses or injury from poor injection technique were not considered as adverse events.
In a 1999 review of the published literature, publicly available reference sources, and adverse drug reaction reporting systems indicated that adverse reactions have not been reported for ^{18}FDG.

The marketing authorisation holder (MAH) submitted a summary describing the Pharmacovigilance System, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU-QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

The Applicant 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 ERtracER Solution for Injection (Fludeoxyglucose (^{18}F) Injection)

Based on consideration of the identified risks, the potential risks and the need for additional information on the medicinal product, it is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

IV.6 Discussion on the clinical aspects

The information provided by the applicant suggests that this product can be used safely in the licensed indications.

V. OVERALL CONCLUSIONS

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for ERtracER Fludeoxyglucose (^{18}F) injection, solution for injection, for use with positive emission tomography in the diagnosis and/or investigation of the conditions listed in the SmPC, could be approved. A national marketing authorisation was granted on 21st

October 2005 and the original mutual recognition procedure was concluded on 4th February 2008. The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.