LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fludebro
(fludeoxyglucose (F-18))

Asp no: 2025-0926

This module reflects the scientific discussion for the approval of Fludebro. The procedure was finalised on 2026-05-29. For information on changes after this date please refer to the module 'Steps taken after the finalisation of the initial procedure - Summary'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Fludebro, 450-11000 MBq/ml, Solution for injection.

The active substance is fludeoxyglucose (F-18). A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 Rationale for the product

Fludeoxyglucose, 2-[^{18}F]fluoro-2-deoxy-D-glucose or FDG consists of “glucose” labelled with the positron emitting radionuclide 18F presented as a solution for injection. It is intended for diagnosis of diseased related to elevated metabolism of glucose (oncology, cardiology, neurology and inflammatory). FDG undergoes only the first step of glycolysis resulting in FDG-6-phosphate which remains trapped within the cell for several hours. ^{18}F decays by positron emission with a half life of 110 minutes. In the body the positron encounters an electron and annihilate resulting in two γ photons (511 keV) emitted at 180 degrees to each other. These γ photons are detected by a Positron Emission Scanner (PET Scanner) combined with x-ray Computed Tomography (CT), a PET-CT Scanner.

II.2 About the product

Fludeoxyglucose or FDG solution for injection for diagnosis has been manufactured by several Swedish university hospitals for more than 20 years under Manufacturing Authorizations by the Swedish drug inspectorate.

Fludeoxyglucose is a glucose analogue labelled with a short-lived positron emitting nuclide, F- 18 (half-life of 109.7 min). The radioactivity produced in the decay of the radionuclide will allow visualisation of FDG distribution using suitable camera equipment and the glucose analogue will mimic the distribution of glucose in the body. These properties make Fludeoxyglucose (FDG) a metabolic tracer to study, for example, cells with elevated glucose metabolism.

The indications are:

Detta läkemedel är endast avsett för diagnostik.
Fludeoxiglukos (18F) är avsett för användning vid positronemissionstomografi (PET) hos vuxna och pediatrisk population.

<u>Onkologi</u>
Fludebro är indicerat för avbildning inom funktionell onkologidiagnostik eller vid diagnos av sjukdomar där ökat glukosupptag i specifika organ eller vävnader är diagnoskriterium. Följande indikationer är tillräckligt dokumenterade (se även avsnitt 4.4):

Diagnos:
- *Karaktärisering av en solitär lungnodulus*
- *Upptäckt av cancer av okänt ursprung, t ex vid fall av förstorade lymfkörtlar på halsen, lever- eller skelettmetastaser.*
- *Karaktärisering av tumör i bukspottkörteln.*

Stadieindelning:

- *Cancer i huvud och hals inklusive som hjälpmedel för att vägleda biopsi*
- *Primär lungcancer*
- *Lokalt avancerad bröstcancer*
- *Matstrupscancer*
- *Cancer i bukspottkörteln*
- *Kolorektalcancer i synnerhet för stadieindelning vid återfall*
- *Malignt lymfom*
- *Malignt melanom, Breslow > 1,5 mm eller lymfkörtelmetastas vid första diagnosen*

Uppföljning av terapisvar:

- *Malignt lymfom*
- *Cancer i huvud och hals*

Detektion vid rimlig misstanke om recidiv:

- *Höggradigt gliom (grad III eller IV)*
- *Cancer i huvud och hals*
- *Sköldkörtelcancer (icke-medullär) hos patienter med förhöjd koncentration av tyreoglobulin i serum och inga avvikande upptag vid helkroppsscintigrafi med radioaktivt jod.*
- *Primär lungcancer*
- *Bröstcancer*
- *Cancer i bukspottkörteln*
- *Kolorektalcancer*
- *Ovarialcancer*
- *Malignt lymfom*
- *Malignt melanom*

<u>Kardiologi</u>
Den kardiologiska indikationen innebär detektion av viabel myokardvävnad som upptar glukos men har nedsatt perfusion. Denna måste bedömas i förväg med hjälp av lämpliga metoder för avbildning av blodflödet.

- *Bedömning av myokardviabilitet hos patienter med kraftigt nedsatt vänsterkammarfunktion, vilka har bedömts som lämpliga för revaskulariseringsingrepp då konventionella avbildningsmetoder inte givit konklusivt resultat.*

<u>Neurologi</u>

- *Lokalisering av epileptogena fokus vid preoperativ bedömning av partiell temporallobsepilepsi, där det diagnostiska målet är glukoshypometabolism inter ictum.*

<u>Infektiösa eller inflammatoriska sjukdomar</u>
För infektiösa eller inflammatoriska sjukdomar är diagnostikmålet vävnad eller strukturer med onormal koncentration av aktiverade vita blodkroppar.
För infektiösa eller inflammatoriska sjukdomar är följande indikationer tillräckligt dokumenterade:

<u>Lokalisering av onormala fokus som vägledning för den etiologiska diagnosen vid tillstånd med feber utan känd orsak</u>.

Diagnos av infektion gällande:

- *Misstänkt kronisk infektion i ben och/eller närliggande strukturer: osteomyelit, spondylit, diskit eller osteit även vid befintliga metallimplantat.*

- *Diabetiker med misstänkt Charcot´s neuroartropati i fot, osteomyelit och/eller infektion i mjukvävnad.*
- *Smärtande höftprotes*
- *Kärlprotes*
- *Febertillstånd hos patient med AIDS*
- *Detektion av septiskt metastatiska fokus vid bakteriemi eller endokardit.*

Registrering av inflammationens utbredning vid:
- *Sarkoidos*
- *Inflammatorisk tarmsjukdom*
- *Kärlinflammation som omfattar de stora kärlen*

Uppföljning av terapi:
- *Icke-resektabel alveolär echinococcos, vid sökande efter aktiv lokalisering av parasit under pågående medicinsk behandling samt när behandlingen avbrutits.*

II.3 General comments on the submitted dossier

The application for Fludebro, 450-11000 MBq/ml, Solution for solution for injection, is a Well-established use Art. 10a application submitted according to Directive 2001/83/EC. The applicant applies for a marketing authorisation in Sweden through a National Procedure.

For an application according to Article 10a, WEU, the applicant needs to demonstrate that the active substance of the medicinal product has been in well-established medicinal use for the claimed therapeutic indication within the Union for at least ten years, with recognised efficacy and an acceptable level of safety.

The active substance is not considered a new active substance.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The MPA has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product, except for the contract laboratory/laboratories where sterility testing is performed.

For manufacturing sites within the European Community, the MPA 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.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance is not isolated during the manufacturing of the drug product. However, the drug substance is controlled by the drug product specification.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

The Applicant has submitted a very sparse non-clinical overview. Several deficiencies have been identified, including few and not up to date references. However, FDG (18F) has been in clinical use for many years, and the pharmacological effects and safety concerns of the product are well known. Consequently, no additional references are requested. Considering that FDG (18F) is an isotope, it is considered to cause DNA damage and thus to be carcinogenic and reprotoxic.

EMA has published a core SmPC (EMA/CHMP/448228/2012) for fludeoxyglucose (18F). Importantly, warnings are stated in the submitted SmPC 4.6 to avoid use in lactating, pregnant and potentially pregnant women in line with the core SmPC. The SmPC also states that breastfeeding should be interrupted for 12 hours and the expressed feeds discarded and close contact with infants should also be restricted during the initial 12 hour following injection in line with the core SmPC and in line with all other approved fludeoxyglucose (18F) products on the Swedish market.

Environmental Risk Assessment (ERA)
The Applicant has presented an ERA concluding that FDG (18F) is unlikely to represent a risk to the environment. The product is a carbohydrate, 18F has a short half-life and the usage is restricted. The applicant´s view is agreed; the product is not expected to pose a risk to the environment.

III.3 Clinical aspects

Pharmacokinetics
The applicant has provided a brief summary of the pharmacokinetic (PK) information regarding Fludeoxyglucose (18F). Since Fludeoxyglucose (18F) is for diagnostic use only, will be administered in a clinical setting at a limited number of occasions, is dosed individually, based on both patient related factors and factors related to equipment, by trained health care personnel PK becomes

secondary and the lack of data is considered acceptable. Since the product and other Fludeoxyglucose (18F) products are aqueous solutions no BE-study is necessary to establish a bridge to the literature.

The proposed SmPC follow the core SmPC published by EMA regarding the pharmacokinetic information.

Clinical efficacy

This application is literature based, whereby no clinical studies have been performed by the Applicant.

It is acknowledged that the clinical uses of fludeoxyglucose(^{18}F) are at present well established in the scientific literature.

The applicant applied for the same indications that are included in the Guideline on core SmPC and package leaflet for fludeoxyglucose (^{18}F) published by EMA, (EMA/448228/2012). In support for this the applicant provided a total of 45 bibliographic references. It is noted that the core SmPC indications have all been previously approved in similar WEU applications and in the core SmPC the wording is given “The following indications are sufficiently documented (see also section 4.4):”.

Having considered the data, sufficient support for the core-SmPC indications is agreed.

Clinical safety

Pharmacological effects as well as radiation exposure are briefly discussed by the Applicant in the safety section. Limited pharmacological effects are agreed on. The reference to adherence to the ALARA principle as well as that Fludebro should only be administered when the expected benefit outweighs the risk are considered sufficiently communicated to prescribers in SmPC section 4.2, 4.4 and 4.6. The general safety profile of fludeoxyglucose (18F) is characterized as benign.

Pharmacovigilance system

Proposed MAH : Region Örebro län

The Applicant has submitted a revised signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the MPA considers the Summary acceptable.

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 Fludebro.

Part II Safety specification

Important identified risks	None
Important potential risks	None
Important missing information	None

Having considered the data in the safety specification an empty Safety concerns list is accepted.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic product, Flucorpus is found adequate. There are no objections to approval of Flucorpus, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available on the Swedish MPA website.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available on the Swedish MPA website.

V.4.2 Assessment of User Testing

Since the package leaflet is aligned with the core PL for fludeoxyglucose (18F) and follows the QRD template for package leaflets, no user testing of the content is deemed necessary. Moreover, since the PL will only be published (as a pdf document) on the MPA website, no user testing of the layout is deemed necessary.

In conclusion, exemption from the user testing requirement is granted.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-