COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion (fludarabine phosphate)

NL/H/5179/001/DC

Date: 20 February 2023

This module reflects the scientific discussion for the approval of Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion. The procedure was finalised at 16 June 2008 in Germany (DE/H/0801/001/DC). After a transfer on 14 May 2020, the current RMS is the Netherlands. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion from Sandoz B.V.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Fludara, powder for solution for injection or infusion 50 mg/vial which has been registered in The Netherlands by Genzyme Europe B.V. since 26 September 1994.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Norway, The Netherlands, Poland, Portugal, Slovenia, Slovakia, Spain, Sweden and United Kingdom.

The difference between the reference product and the current product for registration is the change in pharmaceutical form. However, following reconstitution/solution, the composition of Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion is considered both qualitatively and quantitatively similar to the reference product.

II. QUALITY ASPECTS

II.1 Drug Substance

Fludarabine is a purine (adenine) nucleoside analogue and a member of the antimetabolite class of cytotoxic drugs. The dominant mechanism of action of F-ara-ATP is inhibition of DNA synthesis, although effects on RNA synthesis also contribute to inhibition of cell growth.

Pharmacological classification
ATC Code: L01B B05
Group: Antineoplastic agents, antimetabolite

Manufacturing process
The RMS 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.

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.

For the active substance a declaration from the Qualified Person of the manufacturer was provided which confirms in general that the active substance manufacturer operates in compliance with the detailed guidelines on good manufacturing practice for starting materials.

Statements of GMP compliance have been provided.

Quality control of drug substance
The drug substances from both manufacturers are sufficiently controlled for the most part. The specifications and the control tests are adequately drawn up.

Stability studies have been performed with the drug substances from both manufacturers. No significant changes in any parameters were observed. The proposed retest period of 48 months for fludarabine phosphate manufactured by one API supplier is justified. Moreover, a retest period of 60 months could be claimed according to the stability data provided. For fludarabine phosphate manufactured by the other API supplier a retest period of 36 months is considered to be justified. The drug substance has to be stored between 2°C and 8°C.

The chemical-pharmaceutical documentation and the expert report in relation to Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion are of appropriate quality in view of the present European regulatory requirements. It is recommended to grant marketing authorisation from the quality point of view.

II.2 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained.

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on four pilot batches. The batch analysis results show that the finished product meets the proposed specifications.

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up.
The stability data justify a shelf-life of 36 months if the drug product is stored between 2 and 8°C.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this application is a generic application referring to the originator product Fludara 50 mg powder for solution for injection or infusion, no new non-clinical studies on the pharmacology, pharmacokinetics and toxicology of fludarabine have been submitted. The non-clinical overview submitted by the applicant provides a sufficient outline on the available literature concerning the non-clinical pharmacology, pharmacokinetics and toxicology of fludarabine.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new data concerning clinical pharmacodynamics and pharmacokinetics were submitted by the applicant and none are required for a generic application.

IV.2 Pharmacokinetics

Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). Following reconstitution/solution, the composition of Fludarabine Sandoz is considered both qualitatively and quantitatively similar to the reference product. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

Fludarabine Sandoz 25 mg/ml, concentrate for solution for injection or infusion does actually not require additional risk minimisation measures beyond the Product Information and routine pharmacovigilance activities. The proposed Eu-SmPC reflects the known safety profile of fludarabine phosphate

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Fludara, powder for solution for injection or infusion 50 mg/vial which has been registered in The Netherlands by Genzyme Europe B.V. since 26 September 1994. Therefore, no new clinical studies on the pharmacology, efficacy and safety of fludarabine phosphate have been submitted and none are required.

There are no clinical concerns against the use of fludarabine phosphate in the claimed indications and at the recommended dosages. The subsumption of risks in the product information is adequate. The benefit: risk ratio is accepted to be favourable.

The application is approved. For intermediate amendments see current product information.

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/5179/001/IB/023	Update excipients in the labelling and package leaflet in line with the excipients guideline and to include editorial changes and small amendments to be in line with the current QRD template.	Yes	19-08-2020	Approved	N/A
NL/H/5179/001/IA/024	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient. Updated certificate from an already approved manufacturer.	No	03-05-2021	Approved	N/A
NL/H/5179/001/IA/025/G	Change in the name and/or address of the marketing authorisation holder	No	09-06-2021	Approved	N/A
NL/H/5179/001/IA/026/G	Finished product, manufacture, change batch release details or importer; Name/address of manufacturer, finished product, no batch release	No	05-10-2021	Partially approved	The proposed manufacturers were not listed correctly

NL/H/5179/001/IA/027/G	Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used)) Change that affects the product information	Yes	05-11-2021	Approved	N/A