Public Assessment Report

Scientific discussion

Clofarabine Synthon 1 mg/ml, concentrate for solution for infusion

(clofarabine)

NL/H/3786/001/DC

Date: 19 April 2018

This module reflects the scientific discussion for the approval of Clofarabine Synthon 1 mg/ml concentrate for solution for infusion. The procedure was finalised on 2 May 2017. 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
BP	British 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
EEA	European Economic Area
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
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Clofarabine Synthon 1 mg/ml, concentrate for solution for infusion from Synthon B.V.

The product is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤21 years old at initial diagnosis (see SmPC section 5.1).

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 Evoltra 1 mg/ml, concentrate for solution for infusion which has been registered in the EEA by Genzyme Europe B.V. through a centralised procedure (EU/H/C/000613) since 29 May 2006.

The concerned member states (CMS) involved in this procedure were Finland, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Similarity assessment in view of the orphan drug legislation
The MAH claims an indication for which an orphan designation has been granted, i.e. treatment of ALL. Currently five products are licensed as orphan drugs for treatment of ALL:

- Iclusig (ponatinib)
- Blincyto (blinatumomab)
- Sprycel (dasatinib)
- Xaluprine (mercaptopurine)
- Atriance (nelarabine)

These five products are authorised in the European Union through centralised procedure, after Evoltra had been authorised. Similarity has been assessed during the initial registration procedure. For all five products it was concluded that these products were not considered similar to Evoltra within the meaning of Article 3 of Commission Regulation (EC) No 847/2000. It is therefore concluded that the existence of any market exclusivity for the above mentioned products in the treatment ALL, does not prevent a marketing authorisation for a generic product of Evoltra.

CMDh discussion
It has been agreed with the MAH that additional monitoring does not apply for this generic application of Evoltra.

II. QUALITY ASPECTS

II.1 Introduction

Clofarabine Synthon is a clear, colourless solution, practically free from particles, with a pH of 4.5 to 7.5 and an osmolarity of 270 to 310 mOsm/l.

The solution is packed in a type I glass vial, closed with an uncoated bromobutyl rubber stopper and crimp cap with flip-off cap. The vials contain 20 ml concentrate for solution for infusion. Each ml of concentrate contains 1 mg of clofarabine.

The excipients are sodium chloride and water for injections.

II.2 Drug Substance

The active substance is clofarabine, an established active substance that is not described in the European, British or United States Pharmacopoeia (Ph.Eur.)(BP)(USP). Clofarabine is a white to off-white crystalline powder and exists in two polymorphic crystalline forms, form A and form B. The drug substance obtained from the drug substance manufacturers concerns form A. However, polymorphism is not considered as relevant since clofarabine is dissolved during manufacture of the drug product. Clofarabine is soluble in dimethyl sulfoxide and dimethyl formamide.

Both manufacturers use the Active Substance Master File (ASMF) procedure for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Clofarabine is synthesised in three steps. No class 1 solvents are used in the synthesis of clofarabine. Starting materials are accepted. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents, by both manufacturers.

Quality control of drug substance
The active substance specification is established in house and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches tested by the ASMF holders and two commercial scale batches tested by the drug product manufacturer.

Stability of drug substance
Stability data on the drug substance were provided by both suppliers for three production scaled batches. The stability studies (up to 24 months at 25°C/60% RH and six months at 40°C/75% RH) support a retest period of 36 months. Based on the data submitted, a retest period could be granted of 36 months when stored in the stated conditions.

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 MAH has shown that the drug substance source, the presence or absence of a coating of the stoppers, the presence or absence of nitrogen in the head space, the use of moulded or tubular glass, and storage of the vial in upright or inverted position does not affect the quality of the drug product. In addition, it was shown that the product at issue can be terminally sterilised. The MAH has also shown that the product at issue has the same in-use stability as the reference product. Pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process is sufficiently described and is regarded as a standard process. It includes preparation of the bulk solution, filtration, filling, and terminal sterilisation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of a medium commercial batch size in accordance with the relevant European guidelines. Acceptable process validation schemes were provided for a smaller and a larger batch size.

Control of excipients
All excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specification is adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, assay, related substances, pH,

extractable volume, particulate contamination, sterility, and bacterial endotoxins. The release and shelf life requirements differ with regard to the acceptance criteria for related substances. The drug product specification is acceptable. 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 four batches of the smallest commercial batch size from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for four batches of a medium commercial batch size stored at 25°C/60% RH (24 months (three batches) and 12 months (one batch)) and 40°C/75% RH (six months). Stability studies were carried out under ICH conditions. No significant changes were seen at any storage condition. On the basis of the data submitted, a shelf life was granted of 36 months. The labelled storage condition is “Do not freeze”. Photostability was shown.

The provided in-use stability data support the in-use shelf life of the diluted product of three days at 2-8°C and 25°C which is identical to that of the reference product

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 Clofarabine Synthon 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

The non-clinical overview is an adequate overview on available literature on pharmacology, pharmacokinetics and toxicology of clofarabine. These data show that clofarabine is a well-known medicinal substance with a well-known profile of safety and efficacy.

Clofarabine is a second-generation halogenated-adenosine analogue for the treatment of acute lymphoblastic leukaemia in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Based upon its mechanism of action as an inhibitor of both ribonucleotide reductase and DNA polymerase α, clofarabine is a member of the class of nucleoside analogue anti-metabolite anticancer agents that includes gemcitabine, fludarabine, and cladribine.

Impurities
The stability data of drug product show that a degradation product of clofarabine increases over time and exceeds the qualification threshold defined by ICH Q3B(R2) “*Impurities in New Drug Products*” (CPMP/ICH/2738/99). This limit has been justified on toxicological considerations.

Analyses with DEREK and SARAH point to a potential risk for mutagenicity of one specified impurity, based on the presence of an aromatic amine/amide. However, since this structural alert for mutagenicity is also present in clofarabine, the impurity is not expected to significantly add to the cancer risk of clofarabine itself.
The results of the *in vitro* study package for the qualification of the same impurity provided evidence that it is three to four orders of magnitude less potent as cytotoxic agent for five human bone marrow

cell lines and as inhibitor of the proliferation of erythroid and myeloid progenitor cells in a colony forming cell assay using human bone marrow *in vitro*, as compared to clofarabine.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Clofarabine Synthon 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.3 Discussion on the non-clinical aspects

This product is a generic formulation of Evoltra which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. A DEREK and SARAH analysis was performed on one potential degradation product to evaluate potential genotoxicity. No alert for mutagenicity was identified. The member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clofarabine 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.

IV.2 Pharmacokinetics

Clofarabine Synthon 1 mg/ml, concentrate for solution for 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 intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Clofarabine Synthon is entirely the same as the originator. 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

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 Clofarabine Synthon.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Capillary leak syndrome • Cardiotoxicity • Enterocolitis • Haemorrhage (including cerebral, gastrointestinal, and pulmonary haemorrhage) • Hepatotoxicity • Severe bone marrow suppression • Severe opportunistic infections • Severe skin reactions

	• Systemic inflammatory response syndrome • Tumour lysis syndrome
Important potential risks	• Effect on fertility • Use in patients with renal insufficiency
Missing information	• Exposure during pregnancy and lactation • Use for more than three treatment cycles • Use in infants (<1 year old) • Use in patients (>21 years old) • Use in patients with hepatic impairment

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Evoltra. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 Evoltra 1 mg/ml, concentrate for solution for infusion. The bridging report submitted by the MAH has been found acceptable; bridging is justified for the content of the leaflet. The format differences with the Evoltra PL are in line with a successful user tested PL (Eplerenone 25 mg and 50 mg film-coated tablets) previously performed by the MAH. The Clofarabine Synthon PL is considered readable and acceptable to the patient.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Clofarabine Synthon 1 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Evoltra 1 mg/ml, concentrate for solution for infusion. Evoltra is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

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 essential similarity has been demonstrated for Clofarabine Synthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 May 2017.

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)