EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/CHMP/585665/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivozall

International non-proprietary name: clofarabine

Procedure No. EMEA/H/C/005039/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ivozall
Applicant:	ORPHELIA Pharma 85 Boulevard Saint-Michel 75005 Paris FRANCE
Active substance:	CLOFARABINE
International non-proprietary name/Common name:	clofarabine
Pharmaco-therapeutic group (ATC Code):	antimetabolites, purine analogues (L01BB06)
Therapeutic indication(s):	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 section 5.1).
Pharmaceutical form(s):	Concentrate for solution for infusion
Strength(s):	1 mg/ml
Route(s) of administration:	Intravenous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

AAS: Atomic Absorption Spectrometry
ALL: Acute Lymphoblastic Leukemia
AML Acute Myeloid Leukemia
AP: Applicant's Part (or Open Part) of a ASMF
API: Active Pharmaceutical Ingredient
AR: Assessment Report
AS: Active Substance
ASM: Active Substance Manufacturer
ASMF: Active Substance Master File
ATC: Anatomical therapeutic chemical classification system
BCS: Biopharmaceutics classification system
BDL: Below the limit of detection
BE: Bioequivalence
BSE: Bovine spongiform encephalopathy
CEP: Certificate of Suitability of the Ph. Eur.
CFU: Colony-forming unit
CHMP: The Committee for Medicinal Products for Human Use
CoA: Certificate of analysis
CRS: Chemical Reference Substance (official standard)
CV: Captured volume
dNTP Deoxynucleotide triphosphate
DPM: Drug Product Manufacturer
DSC: Differential scanning calorimetry
EDQM: European Directorate for the Quality of Medicines
EMA: European Medicines Agency
EP: European Pharmacopoeia
ERA: Environmental Risk Assessment
EU: European Union
FP: Finished Product
GC Gas chromatography
GCP: Good Clinical Practice
GLP: Good Laboratory Practice
GMP: Good Manufacturing Practice
HDPE: High Density Polyethylene
HPLC: High Performance Liquid Chromatography
HT: Holding time
ICH: International Conference on Harmonisation
IPC: In-process controls
IR: Infra-Red Spectroscopy
LDPE: Low Density Polyethylene
LOA: Letter of Access
LOD: Limit of Detection
Log Kow: n-octanol/water partition coefficient
LOQ: Limit of Quantitation
LoQ: List of Questions
QbD: Quality by design
QTPP: Quality target product profile
MAH: Marketing Authorisation Holder
MS: Mass Spectrometry
ND: Not detected
NLT: Not Less Than
NMR: Nuclear Magnetic Resonance
NMT Not More Than
ODG: Office for Generic Drugs
OOS: Out of specification
PBT: Persistence Bioaccumulation Toxicity
PDE: Permitted Daily Exposure
PE: Polyethylene
Ph. Eur.: European Pharmacopoeia
PIL: Patient Information Leaflet

PP: Polypropylene
PVC: Poly vinyl chloride
PXRD: Powder X-ray diffraction
QOS: Quality Overall Summary
QP: Qualified Person
RH: Relative humidity
RLD: Reference Listed Drug
RP: Restricted Part (or Closed Part) of an ASMF
RPM: Rotation per minute
RRT: Relative retention time
RSD: Relative standard deviation
SS: Stainless steel
SmPC: Summary of Product Characteristics
TSE: Transmissible spongiform encephalopathy
TGA: Thermo-Gravimetric Analysis
USP: United States Pharmacopoeia
UV: Ultraviolet Spectroscopy
UPLC: Ultra Performance Liquid Chromatography
XRD: X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ORPHELIA Pharma submitted on 17 September 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Ivozall, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 April 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication: 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 section 5.1).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information and complete quality data.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Evoltra, 1mg/ml, concentrate for solution for infusion
- Marketing authorisation holder: Genzyme Europe B.V.
- Date of authorisation: 29-May-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/334/001-005

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Evoltra, 1mg/ml, concentrate for solution for infusion
- Marketing authorisation holder: Genzyme Europe B.V.
- Date of authorisation: 29-May-2006
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/06/334/001-005

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

N/A

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Simona Badoi

The application was received by the EMA on	17 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 January 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	24 May 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	1 July 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 July 2019
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 July 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2019
The Rapporteur circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	4 September 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ivozall on	19 September 2019

2. Scientific discussion

2.1. Introduction

This centralised procedure application is based on Article 10(1) for a generic product as defined in Article 10(2)(a) referring to a so-called reference medicinal product with a marketing authorisation granted in the Union. The active substance clofarabine has been in medicinal use for more than 10 years in the European Union. The reference medicinal product is Evoltra, 1mg/ml, concentrate for solution for infusion.

The product Ivozall is of the same indication, strength and route of administration as that of the reference medicinal product, having the same qualitative and quantitative composition in terms of active substance and is of the same pharmaceutical form as the originator product.

The proposed indication for Ivozall is for the treatment of acute lymphoblastic leukemia (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.

The active substance clofarabine is a purine nucleoside anti-metabolite. The mode of action of clofarabine in paediatric patients with acute lymphoblastic leukaemia (ALL) is believed to be due to 3 mechanisms:

- DNA polymerase α inhibition resulting in termination of DNA chain elongation and/or DNA synthesis/repair;

- Ribonucleotide reductase inhibition with reduction of cellular deoxynucleotide triphosphate (dNTP) pools;

- Disruption of mitochondrial membrane integrity with the release of cytochrome C and other proapoptotic factors leading to programmed cell death even in non-dividing lymphocytes.

Clofarabine must first diffuse or be transported into target cells where it is sequentially phosphorylated to the mono- and bi-phosphate by intracellular kinases, and then finally to the active conjugate, clofarabine 5'-triphosphate. Clofarabine has high affinity for one of the activating phosphorylating enzymes, deoxycytidine kinase, which exceeds that of the natural substrate, deoxycytidine.

In addition, clofarabine possesses greater resistance to cellular degradation by adenosine deaminase and decreased susceptibility to phosphorolytic cleavage than other active substances in its class whilst the affinity of clofarabine triphosphate for DNA polymerase α and ribonucleotide reductase is similar to or greater than that of deoxyadenosine triphosphate.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a concentrate for solution for infusion containing 1 mg/ml of clofarabine.

Other ingredients are sodium chloride and water for injection.

The product is available in type I glass vials with grey chlorobutyl fluoropolymer coated rubber stopper, polypropylene flip-off cap and aluminium overseal, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of clofarabine is (2*R*, 3*R*, 4*S*, 5*R*)-5-(6-amino-2-chloro-purin-9-yl)-4-fluoro-2-(hydroxymethyl)tetrahydrofuran-3-ol corresponding to the molecular formula $C_{10}H_{11}ClFN_5O_3$. It has a molecular weight of 303.68 g/mol and the following structure:

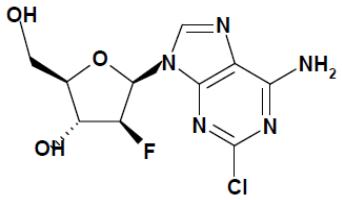

Figure 1: active substance structure

The chemical structure of the active substance was elucidated by a combination of IR, UV and NMR spectroscopy (both ^{1}H and ^{13}C NMR spectrum), mass spectrometry, elemental analysis and optical rotation. The solid state properties of the active substance were measured by DSC and XRPD analysis.

The active substance is a white to off white non-hygroscopic crystalline powder. It is slightly soluble in water, sparingly soluble in methanol and soluble in dimethyl sulfoxide.

Clofarabine shows potential isomerism at the anomeric carbon of the arabinofuranose ring. The desired anomer is a beta: due to this, the content of alpha anomer is controlled at the release by means of HPLC analysis.

Crystallization of clofarabine is described in the literature either from water or from methanol providing crystals with melting points of 225 – 227 °C and 237 °C respectively. According to the manufacturing process, clofarabine is consistently obtained in a well-defined crystalline form. The consistency of the polymorph is ensured by melting point analysis at the release and by melting point determination by DSC in the stability studies.

Stability of polymorphic form has been confirmed during accelerated and long-term stability studies by FT-IR analysis at the release and also by the melting point determination by DSC (test included also in the stability studies).

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Clofarabine is obtained from a single supplier.

Clofarabine is synthesized in three main steps using starting materials with acceptable specifications.

During the marketing authorisation application assessment, a major objection was raised by the CHMP on the proposed regulatory starting materials for the active substance synthesis. The ASMF holder showed that both starting materials used for the manufacture of clofarabine are commercially available and well-characterized materials with defined chemical properties justifying the starting materials. The discussion on the carry-over of potential impurities has shown that possible impurities in the starting materials are sufficiently controlled.

The applicant has provided sufficient discussion on the possibility to obtain impurities with different stereochemistry through the whole process. All the modifications which are performed on the molecule, beside final deprotection, involve the anomeric center C1. None of the described reactions has the possibility to alter the absolute configuration of any center other than the anomeric one. The absolute configuration of starting material 1 is proved by single crystal X-Ray analysis.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for: description (visual inspection), identity (HPLC, IR, melting point via capillary method), specific optical rotation (Ph. Eur.), sulfated ash (Ph. Eur.), pH value (Ph. Eur.), water content (KF), loss on drying (Ph. Eur.), residual solvents (GC), related substances (HPLC), assay (HPLC), bacterial endotoxins (Ph. Eur.), total aerobic microbial count (Ph. Eur.), and total yeast and mould count (Ph. Eur.).

The active substance is complying with ICH Q3D and there is no risk for potential elemental impurities. The risk assessment has been performed for Class 1 elements (Cd, Pb, As, Hg), Class 2A elements (Co, V, Ni), Class 3 elements (Li, Sb, Cu) used in the manufacturing process of the active substance. The ASMF holder performed an elemental impurities screening by ICP-OES on 3 consecutive batches of clofarabine and the results were found to be below 30 % of ICH Q3D limit. Therefore these impurities are not controlled in the release specification. Based on the risk assessment, the manufacturer revised the active substance specification to remove the test for heavy metal.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 4 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

So far, only two batches of the active substance have been used in the manufacture of industrial scale finished product batches. The Applicant committed to complete the batch analysis with the analytical results of a third batch of the active substance as soon as available and to provide the certificates of analyses in accordance with the active substance specification updated during the assessment procedure. This point is a quality recommendation by the CHMP.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Results on stress conditions: acid degradation (hydrochloric acid, phosphorous acid), basic degradation (sodium hydroxide), oxidative degradation (hydrogen peroxide, potassium permanganate), heat at 120°C for 1, 4, 7 and 15 days and light degradation under the lamp D65 were also provided.

The following parameters were tested: description, identification (melting point), pH, specific optical rotation, water content, assay, related substances, bacterial endotoxins, TAMC, TYMC and specified micro-organisms.

All tested parameters were within the specifications. There was no significant change in impurity profile and other properties of the active substance.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months stored in the proposed container at a mean temperature of 25 °C with allowed excursion at 15 – 30 °C.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Ivozall concentrate for solution for infusion is a sterile, clear (free from visible particles), colourless aqueous solution that is terminally sterilized. The finished product is intended for intravenous use and therefore must be diluted prior to use.

The product is available in one presentation of 20 mg/20 ml vial. The pH range of Ivozall concentrate for solution for infusion is 4.5 - 7.5. The osmolarity range of the product is 270 – 310 mOsm/l.

The aim of pharmaceutical development was to develop a stable one-to-one copy of the reference medicinal product Evoltra with acceptable physicochemical properties. The originator was characterised by performing deformulation studies, comparing laboratory batches of the finished product with Evoltra batches, examining the packaging of the originator and by literature search.

In order to obtain product and process understanding several parameters were studied during the formulation and process development.

The formulation development has been evaluated through the use of risk assessment. The proposed finished product formulation is the same as for the innovator. The product is composed of clofarabine 1 mg/ml and sodium chloride 9 mg/ml in aqueous solution for tonicity adjustment.

The active substance is fully solubilized and delivered as an infusion. Therefore, the particle size and the polymorphic form of the active substance have no impact on the bioavailability of the drug product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Compatibility of the excipients with the active substance was demonstrated through stability testing of the finished product.

The innovator samples of Evoltra were assessed with regards to composition, physical and chemical properties and the results showed that they could be considered identical to Ivozall. As Ivozall contains the same active substance as the originator, it is identical in strength and concentration and it has the same dosage form and route of administration as the originator, and since it is administered as an aqueous intravenous solution in the same concentration as in Evoltra, no bioequivalence study was needed.

As the finished product is intended for intravenous administration and it shows good stability, terminal sterilisation by heat was selected as the sterilisation method.

The primary packaging is Type I glass vial with grey chlorobutyl fluoropolymer coated rubber stopper, polypropylene flip-off cap and aluminium overseal. The flip-off seal does not come into contact with the

finished product. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is a solution that is prepared in a five-step manufacturing process consists of preparation of non-sterile bulk solution, pre-filtration, filling and sealing, terminal sterilisation of filled vials and inspection.

Major steps of the manufacturing process have been validated by a number of studies on three commercial batches consisting of three bulk solutions and three filling campaigns. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), clarity and degree of opalescence of liquids (Ph. Eur.), pH (Ph. Eur.), osmolarity (Ph. Eur.), extractable volume (Ph. Eur.), particulate matter – subvisible particles (Ph. Eur.), particulate matter – visible particles (Ph. Eur.), assay clofarabine (HPLC), related substances (HPLC), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). .

During the assessment the CHMP requested the applicant to tighten the proposed limits for pH (4.5 -7.5) since these were wider than those seen in batch analysis or stability studies. However these were justified based on the originator's values and the fact that only a limited amount of data is available to date since only four batches have been manufactured at industrial scale at the time of opinion. Therefore, the Applicant has committed to re-evaluate the pH acceptance criteria when a sufficient number of data has been collected (production of ten batches at industrial scale).

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the finished product specification. The analytical procedures are the same as used for release and are stability indicating.

All results remained within specifications and no significant changes have been observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of the photostability study demonstrate that the product is not sensitive to light.

The in-use stability data show that the infusion solution in both PVC and non-PVC of infusion bags and with both types of infusion solutions (0.9 % sodium chloride solution or 5 % glucose solution) is stable for seven days at room temperature and under refrigeration (2 °C - 8 °C). Although no specification limits are declared in the compatibility study, all tested parameters remained within limits of the shelf-life specification. The applicability of the generated data on the concentration ranges for administration and on the type of plastic bags to be used is acceptable. However, the compatibility study evaluated the stability of the clofarabine concentrate for solution for infusion diluted with 5% glucose infusion media only for 0.15 and 0.40 mg/ml diluted concentrations, while for the sodium chloride solution the investigated dilution concentrations were 0.15, 0.40 and 0.83 mg/ml, according to the compatibility study report. As concentration range (0.15-0.83 mg/ml) was not entirely covered, the dilution with 5% glucose infusion cannot be accepted without experimental data generated on 0.83 mg/ml concentration. Therefore, the applicant decided to delete the proposed dilution with 5% glucose from the SmPC.

Based on available stability data, the proposed shelf-life of 3 years and the finished product should not be frozen as stated in the SmPC (section 6.3) are acceptable.

Chemical and physical in-use stability has been demonstrated for seven days at room temperature and under refrigeration (2°C - 8°C) at a concentration range of 0.15 mg/ml to 0.83 mg/ml after dilution with sodium chloride 9 mg/ml (0.9%).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place under controlled and validated aseptic conditions.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

The product has been developed as a generic of Evoltra. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. to complete the batch analysis with the analytical results of a third batch of the active substance clofarabine as soon as available. Moreover, the new certificates of analysis should be in accordance with the API specification updated in March 2018.

2. to re-evaluate the finished product pH acceptance criteria when a sufficient number of data has been collected (production of at least 10 batches of medicinal product at industrial scale).

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Ivozall manufactured by ORPHELIA Pharma is considered unlikely to result in any significant increase in the combined sales volumes for all clofarabine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The overview justifies why the Applicant did not submit additional non-clinical pharmacology, pharmacokinetics and toxicology data. The CHMP agreed that no further non-clinical studies are required.

The non-clinical overview is considered acceptable based on the established pharmacological, pharmacokinetic and toxicological profile and the experience from therapeutic use of the active substance.

The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.3.4. Conclusion on the non-clinical aspects

The non-clinical aspects are considered adequate to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This is a generic centralised application for a medicinal product supplied as a concentrate for solution for infusion in glass vials for single use.

The applied indications, route of administration, dosage form and strength for Ivozall are the same as for the reference product Evoltra.

Exemption

No clinical bioequivalence studies have been submitted. The applicant applied for a waiver for bioequivalence studies/clinical studies on the basis that the proposed generic medicinal product has an identical qualitative and quantitative composition in the active substance and excipients compared to the approved reference medicinal product, Evoltra 1 mg/ml concentrate for solution for infusion, and the same pharmaceutical form and route of administration as a concentrate for solution for infusion for intravenous use.

According to the Appendix II of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **): "Bioequivalence studies are generally not required if the test product is to be administered as aqueous intravenous solution containing the same active substance as the currently approved product".

The applied product is to be administered as an aqueous solution for injection for intravenous administration containing the same active substance in the same concentration as the currently authorized originator product.

In addition, the test product contains the same excipients in identical amounts as the reference product and the excipients are not known to interact with the drug substance nor to otherwise affect the disposition of the drug substance.

Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were presented and no such studies are required for this application.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

This is a generic centralised application for a medicinal product supplied as a concentrate for solution for infusion in glass vials for single use.

No bioequivalence study has been submitted. The applicant has claimed a biowaiver on the basis that the proposed medicinal product has an identical qualitative and quantitative composition in the active substance and excipients compared to the approved reference medicinal product Evoltra 1 mg/ml and the same pharmaceutical form and route of administration as an aqueous solution for injection for intravenous use. That is acceptable from a pharmacokinetic point of view.

According to the *Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Appendix II)* no bioequivalence studies are required for intravenously administered aqueous solutions if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.

Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

A Clinical Overview based on published data was submitted. However, it is noted that the overview is based to a great extent on the information cited from Evoltra EPARs (2007 – 2018) and some (2016 – 2018) scientific literature. This is acceptable with respect to the well-known basic pharmacology and experience from the therapeutic use of the active substance.

2.4.6. Conclusions on clinical aspects

The biowaiver is considered acceptable.

The clinical aspects are considered adequate to support this application.

2.5. Risk management plan

Summary of the safety concerns

The applicant identified the following safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Bone marrow failure (myelosupresion) - Infection (septic shock, sepsis, bacteremia, pneumonia, herpes zoster, herpes simplex, Clostridium difficile colitis, oral candidiasis) - Hepatotoxicity - Veno-occlusive liver disease - Cardiotoxicity - Tumor lysis syndrome - Systemic inflammatory response syndrome and capillary leak syndrome - Stevens Johnson syndrome and toxic epidermal necrolysis - Pancreatitis - Rash - Enterocolitis, including neutropenic colitis, caecitis and C. difficile colitis - Hemorrhage, including cerebral, gastrointestinal and pulmonary hemorrhage - Hepatitis - Hepatic failure
Important potential risks	- Nephropathy toxic - Teratogenicity - Infertility - Off-label use in pediatric AML, in ALL patients with less than

Summary of safety concerns	
	two prior regimens, or in combination with other drugs
Missing information	- Safety of use for more than 3 cycles - Drug interactions with commonly used co-medications - Tolerability and pharmacokinetics in renal impairment - Tolerability and pharmacokinetics in hepatic impairment - Tolerability and pharmacokinetics in cardiac impairment - Pregnancy

Pharmacovigilance Plan

No additional risk minimisation activities were proposed.

Risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk Bone marrow failure (myelosuppression)	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Infection (septic shock, sepsis, bacteraemia, pneumonia, herpes zoster, herpes simplex, Clostridium difficile colitis, oral candidiasis)	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Hepatotoxicity	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4, 4.5 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk Veno-occlusive liver disease	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Cardiotoxicity	Routine risk minimisation measures SmPC section 4.2, 4.4, 4.5 and 4.8 PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Tumour lysis syndrome	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Systemic Inflammatory Response Syndrome and Capillary leak syndrome	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Stevens Johnson syndrome and toxic epidermal necrolysis	Routine risk minimisation measures: SmPC section 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Pancreatitis	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Rash	Routine risk minimisation measures: SmPC section 4.2, 4.4, 4.5 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Enterocolitis, including neutropenic colitis, caecitis, and Clostridium difficile colitis	Routine risk minimisation measures: SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Haemorrhage, including cerebral, gastrointestinal and	Routine risk minimisation measures:	Only routine pharmacovigilance activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
pulmonary haemorrhage	SmPC section 4.2, 4.4 and 4.8. PL section 2 and 4	
Important Identified Risk Hepatitis	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4, 4.5 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Identified Risk Hepatic failure	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4, 4.5 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Potential Risk Nephropathy toxic	Routine risk minimisation measures: SmPC section 4.2, 4.3, 4.4, 4.5 and 4.8. PL section 2 and 4	Only routine pharmacovigilance activities
Important Potential Risk Teratogenicity	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2	Only routine pharmacovigilance activities
Important Potential Risk Infertility	Routine risk minimisation measures: SmPC section 4.6 and 5.3 PL section 2	Only routine pharmacovigilance activities
Important Potential Risk Off-label use in paediatric AML, in ALL patients with less than two prior regimens, or in combination with other drugs	Routine risk minimisation measures: SmPC section 4.1 and 4.2 PL section 1	Only routine pharmacovigilance activities
Missing information Safety of use for more than 3 cycles	Routine risk minimisation measures: SmPC section 4.2 and 4.4	Only routine pharmacovigilance activities
Missing information Drug interaction with commonly used comedications	Routine risk minimisation measures: SmPC section 4.5 PL section 2	Only routine pharmacovigilance activities
Missing information	Routine risk minimisation	Only routine pharmacovigilance

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Tolerability and pharmacokinetics in renal impairment	measures: SmPC section 4.2, 4.3 and 4.4 PL section 2	activities
Missing information Tolerability and pharmacokinetics in hepatic impairment	Routine risk minimisation measures: SmPC section 4.2, 4.3 and 4.4 PL section 2	Only routine pharmacovigilance activities
Missing information Tolerability and pharmacokinetics in cardiac impairment	Routine risk minimisation measures: SmPC section 4.4 and 4.5 PL section 2	Only routine pharmacovigilance activities
Missing information Pregnancy	Routine risk minimisation measures: SmPC section 4.6 PL section 2	Only routine pharmacovigilance activities

Discussion

The summary of safety concerns is in line with the reference product. Having considered the data in the safety specification, the PRAC agrees that the safety concerns listed by the Applicant are appropriate.

The PRAC is of the opinion that no additional pharmacovigilance activities are necessary.

The originator has no additional risk minimisation activities. The safety information in the Product information is aligned to the safety information of the reference medicinal product. Consequently, the PRAC was of the opinion that, in line with the reference product, the proposed routine risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications and no additional risk minimisation measures are necessary.

Conclusion

The CHMP and PRAC considered that the risk management plan is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

As the innovator is under exceptional circumstances and under additional safety monitoring, generic products of clofarabine should submit annual PSURs, similarly to Evoltra, to ensure a harmonised assessment across all products.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Evoltra. The bridging report submitted by the applicant has been found acceptable.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, clofarabine is included in the additional monitoring list as the originator product Evoltra is approved under exceptional circumstances.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

This application concerns a generic version of clofarabine concentrate for solution for infusion. The reference product Evoltra 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The applicant did not submit clinical studies (pharmacokinetics and pharmacodynamics as well as the efficacy and safety studies). The applicant provided a clinical overview with clinical information from published literature and this was considered adequate. Furthermore, exemption from the need to conduct a bioequivalence study was considered adequately substantiated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

The originator product was authorised under exceptional circumstances, with the specific obligation of submitting yearly updates on any new information concerning efficacy and safety of the product in paediatric patients with acute lymphoblastic leukaemia 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.
The CHMP agreed that this specific obligation should not be imposed on this application for Ivozall but

annual PSURs (in which literature review will be provided) should be submitted for Ivozall, similarly to Evoltra. This would ensure a harmonised assessment across all products.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ivozall is not similar to Xaluprine, Iclusig, Blincyto, Besponsa and Kymriah within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ivozall is favourable in the following indication:

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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

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.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.