13 October 2022
EMA/889120/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Plerixafor Accord

International non-proprietary name: plerixafor

Procedure No. EMEA/H/C/005943/0000

Note

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

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List of abbreviations

AP	Applicant´s Part of Active Substance Master File
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASMF	Active Substance Master File = Drug Master File
BDL	Below the limit of detection
CEP	Certificate of Suitability of the Ph. Eur.
CMS	Concerned Member State
CoA	Certificate of Analysis
CQA	Critical Quality Attribute
CRS	Chemical reference substance
DL	Detection Limit
DMF	Drug Master File = Active Substance Master File, ASMF
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EP	European Pharmacopoeia
ERA	Environmental Risk Assessment
FID	Flame ionisation detection
FT-IR	Fourier transmission infra-red (spectroscopy)
HPLC	High performance liquid chromatography
IPC	In-process control test
GC	Gas chromatography
ICH	International conference on harmonisation
IR	Infra-red
KF	Karl Fisher
LDPE	Low-density polyethylene
LoA	Letter of Access
LOD	Loss on Drying
LoD	Limit of Detection

LoQ Limit of Quantitation

MAH Marketing Authorisation holder

MO Major Objection

MS Mass spectroscopy

NfG Note for guidance

NIR Near infra-red

NLT Not less than

NMR Nuclear magnetic resonance

NMT Not more than

PDA Photo diode array

PDE Permitted daily exposure

PEC Predicted Environmental Concentration

Ph. Eur. European Pharmacopoeia

PIL Patient Information Leaflet

PP Polypropylene

PVC Polyvinyl chloride

PVdC Polyvinylidene chloride

QL Quantitation limit

QOS Quality Overall Summary

(Q)SAR (Quantitative) Structure-Activity Relationship

RH Relative Humidity

RMS Reference member state

RP Restricted Part of Active Substance Master File

RSD Relative standard deviation

Rrt Relative retention time

Rt Retention time

Rt Room temperature

SD Standard deviation

SWFI Sterile water for injections

TGA Thermo-Gravimetric Analysis

TLC Thin layer chromatography

UV	Ultraviolet
XRD	X-Ray Diffraction

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare S.L.U. submitted on 11 October 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Plerixafor Accord, 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 24 June 2021.

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 on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Adult patients

Plerixafor Accord is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma or multiple myeloma whose cells mobilise poorly.

Paediatric patients (1 to less than 18 years)

Plerixafor Accord is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

1.2. Legal basis, dossier content

The legal basis for this application refers to a Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and literature references instead of non-clinical and clinical 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: Mozobil 20 mg/ml solution for injection
- Marketing authorisation holder: Genzyme Europe B.V., The Netherlands
- Date of authorisation: 31-07-2009
- Marketing authorisation granted by:
  - Union

- Union Marketing authorisation number: EU/1/09/537

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

- Product name, strength, pharmaceutical form: Mozobil 20 mg/ml solution for injection
- Marketing authorisation holder: Genzyme Europe B.V., The Netherlands
- Date of authorisation: 31-07-2009
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/09/537

1.3. Information on paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

It is considered that Plerixafor Accord is not similar to Adcetris, Gazyvaro, Kymriah, Ledaga, Minjuvi, Polivy, Poteligeo, Tecartus, Yescarta, Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro, Trecondi and Abecma within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Simona Badoi Co-Rapporteur: N/A

The Rapporteur appointed by the PRAC was:

Rapporteur: Menno van der Elst

The application was received by the EMA on	11 October 2021
The procedure started on	28 October 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 January 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 January 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 February 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 May 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	27 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	7 July 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	7 September 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	28 September 2022
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 Plerixafor Accord on	13 October 2022
The CHMP adopted a report on similarity of Plerixafor Accord with Adcetris, Gazyvaro, Kymriah, Ledaga, Minjuvi, Polivy, Poteligeo, Tecartus, Yescarta, Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro, Trecondi and Abecma on (Appendix on similarity)	13 October 2022

2. Scientific discussion

2.1. Introduction

This centralised application refers to a generic application according to Article 10(1) of Directive 2001/83/EC, as amended, for the product Plerixafor Accord 20 mg/ml solution for injection, developed by Accord S.L.U.

The reference medicinal product is Mozobil 20 mg/ml solution for injection, marked by Genzyme Europe B.V., The Netherlands, which was first approved in the Union on 31 July 2009 (Union MA No: EU/1/09/537).

The active substance of this product is plerixafor.

As both medicinal products, the reference and the generic, are aqueous solutions for injection to be administered subcutaneously and the generic contains the same active substance in the same concentration and the same excipients in identical amounts as the reference product, according to the provisions of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1) no bioequivalence studies have been submitted. Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

The reference product Mozobil is indicated for

Adult patients
Mozobil is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma or multiple myeloma whose cells mobilise poorly.

Paediatric patients (1 to less than 18 years)
Mozobil is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

The applicant has applied for all the indications of the reference product. The proposed posology and method of administration are identical to the reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as solution for injection containing 20 mg/ml of plerixafor as active substance.

Other ingredients are: sodium chloride, concentrated hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

The product is available in a 2-mL type I clear glass vial with a chlorobutyl rubber stopper and aluminium flip-off seal with polypropylene (PP) plastic blue mate top, as described in section 6.5 of the SmPC. Each vial contains 1.2 mL of solution.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of plerixafor is 1,1'-[1,4-Phenylenebis(methylene)]bis[1,4,8,11-tetraazacyclotetradecane] corresponding to the molecular formula $C_{28}H_{54}N_8$. It has a relative molecular mass of 502.78 g/mol and the following structure:

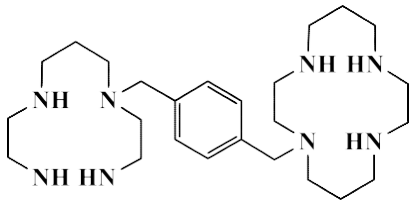

Figure 1: active substance structure

The chemical structure of plerixafor was elucidated by a combination of UV spectroscopy, elemental analysis, IR spectroscopy, mass spectroscopy, carbon nuclear magnetic resonance spectroscopy, proton nuclear magnetic resonance spectroscopy, X-ray diffraction (XRD) and differential scanning colorimetry, and relevant spectra were provided.

The active substance is a white to off-white crystalline, hygroscopic solid, soluble in dichloromethane and slightly soluble in water. Plerixafor is an achiral molecule and hence does not exhibit isomerism.

Polymorphism has not been observed for plerixafor. The solid state properties of the active substance were measured by XRD. XRD diffractograms demonstrated that the manufacturing process consistently produces the same pattern.

2.2.2.2. 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.

Plerixafor is synthesised by a single manufacturer in three main steps using commercially available well-defined starting materials with acceptable specifications.

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 is packaged with nitrogen purging in a bag, which complies with Commission Regulation (EU) No. 10/2011 as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for: appearance (visual), solubility (visual), identity (IR, HPLC), water content (KF), colour and clarity of solution (UV), residue on ignition (in-house), assay (HPLC),

related substances (HPLC), residual solvents (GC), microbial limit tests, tests for pathogens, and bacterial endotoxin test (in house).

Related substances are controlled according to ICH Q3A, and specifications were tightened during the CHMP review as requested.

Residual solvents are controlled to ICHQ3C levels, and specifications were tightened as requested by the CHMP.

The absence of benzene, elemental impurities and genotoxic impurities was demonstrated.. Based on the results, routine monitoring is not deemed necessary.

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 of commercial size batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial packaging stored under long term conditions (25ºC / 60% RH) and accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH Q1B guideline was performed. Results on stress conditions (thermal stress, humidity, UV) were also provided.

The samples were tested for all stability indicating parameters included in the specification.

The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications. No photodegradation was observed.

As per the post-approval stability commitment, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period with storage condition as proposed by the applicant.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and Pharmaceutical development

The finished product is presented as solution for injection containing 20 mg/mL of plerixafor as active substance.

The finished product was developed to be a generic equivalent to the reference medicinal product Mozobil 20 mg/mL solution for injection.

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.

A biowaiver was granted since the proposed generic medicinal product has an identical qualitative and quantitative composition compared to the approved reference medicinal product, Mozobil 20 mg/mL solution for injection, and the same pharmaceutical form and route of administration as a solution for injection for subcutaneous use. The essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

An initial risk assessment of the overall manufacturing process parameters was performed to identify the high-risk steps that may affect the CQAs of the finished product (description, pH, assay, related substances). Based on the outcome of the risk assessment development studies were performed.

Based on the results of the development studies and exhibit batch data, the risk assessment of the process parameters was updated to be low for all parameters. The process is considered well controlled, having no process parameters with high risk.

The product is sterile.

The primary packaging is a 2 mL type I clear glass vial with a chlorobutyl rubber stopper and aluminium flip-off seal with PP plastic blue mate top. The glass vials comply with Ph. Eur. type I glass. The rubber stoppers comply with Ph. Eur. monograph 3.2.9 for "rubber closures". The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated. 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 for a sterile solution in a vial.

During the procedure, one quality major objection (MO) was raised, related to inadequate GMP evidence of one of the proposed packaging sites. In response the applicant removed the concerned packaging site from the dossier.

2.2.3.3. Product specification(s)

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identity (UV, HPLC), pH, colour and clarity of solution (Ph. Eur.), bacterial endotoxins test (Ph. Eur.), extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), assay (HPLC), related substances (HPLC), sterility (Ph. Eur.), osmolality (Ph. Eur.), and Uniformity of Dosage Units (Ph. Eur.)

The potential presence of elemental impurities in the finished product has been assessed following 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. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested by CHMP) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

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.

2.2.3.4. Stability of the product

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

Samples were tested for all stability indicating parameters included in the specification/analytical procedures used are stability indicating. Under long term conditions (25ºC / 60% RH) no significant changes have been observed. Under accelerated conditions (40ºC / 75% RH) an increase in degradation products is observed but all results were within the specification limits.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Since the active substance was observed to be photostable, no photostability testing was performed on the finished product.

Based on available stability data, the proposed shelf-life of 21 months without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

2.2.3.5. Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

Plerixafor Accord has been developed as a generic of Mozobil 20 mg/mL solution for injection.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, one quality MO was raised, related to inadequate GMP evidence of one of the proposed packaging sites. In response the applicant removed the concerned packaging site from the dossier.

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.

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. Recommendation(s) 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: none.

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. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment studies (ERA) were submitted. This was justified by the applicant as the introduction of Plerixafor Accord manufactured by Accord Healthcare S.L.U. is considered unlikely to result in any significant increase in the combined sales volumes for all plerixafor containing products and the exposure of the environment to the active substance, so the ERA is expected to be similar. The applicant was asked to provide suitable information to substantiate the claim that an increase in environmental exposure of the active substance is not to be expected. In response to the request the applicant submitted a conservative calculation of the Predicted Environmental Concentration that resulted in a lower value than the action limit of 0.01 µg/l.

Calculation of the Predicted Environmental Concentration

$$PEC_{surfacewater}\ (mg/L) \qquad \frac{DOSEai\ X\ F_{pen}}{WASTEWinha\ b\ X\ DILUTION}$$

Where DOSEai = Maximum daily dose of the active ingredient consumed per inhabitant per day

= 20 mg/day

$$Fpen = \%\ of\ market\ penetration = \frac{Consumption\ (mg/yr)X100}{DDD\ (mg/day/inh)\ X\ inhabitant\ s\ X\ 365\ dy/yr} = \frac{3.62E8X100}{20mg\ X\ 496E6\ X\ 365}$$

= 0.010% = 0.0001

consumption n= maximum Orphan Drug projection for all products containing plerixafor.

DDD = Defined daily dose (DDD not defined so prescribed dose used) = 20 mg/day

Inhabitant s = number of inhabitant s in the European Union per United Nations World Population Prospects

WASTEWinha b = Amount of wastewater generated per inhibitant per day = 200 L/day

DILUTION = Dilution factor = 10

$$And\ PEC_{surfacewater}\ (mg/L) = = \frac{20\ mg/day\ X\ 0.00010}{200\ L/day\ X\ 10}$$ 0.000001 mg/mL=0.001µg/L

2.3.3. Discussion on non-clinical aspects

The applicant has not performed non-clinical studies. Non-clinical data are submitted from published literature data. This is reasonable and acceptable since plerixafor is a well-known active substance. Grounds for not providing new non-clinical data are adequately justified.

A brief discussion of the active substance and product impurities specification limits has been included in the non-clinical overview, with the conclusion that as all the impurities are within the acceptable limits, no further toxicological assessment was deemed necessary. Review of Module 3 data also shows that the limits applied to the elemental impurities, related substances and ICH classified solvents are in line with the relevant guidelines.

All excipients are compendial and there are no toxicological concerns raised with regard to the excipients.

The SmPC sections 4.6 and 5.3 are in line with those for the innovator Mozobil 20 mg/ml solution for injection, Genzyme Europe B.V., The Netherlands and are therefore acceptable.

The calculation of the PEC resulted in a lower value than the action limit of 0.01 µg/l, therefore it is agreed that a Phase II environmental fate and effect analysis is not deemed necessary. No additional environmental impact as compared to that of the originator's is anticipated related to this generic application for Plerixafor solution for injection 20 mg/mL.

2.3.4. Conclusion on the non-clinical aspects

There are no objections regarding the marketing approval of Plerixafor Accord, Solution for injection 20 mg/ml from a non-clinical point of view. The CHMP is of the opinion that the applicant has justified the absence of

non-clinical studies based on the literature review and the claim that Plerixafor Accord is a generic of the reference product Mozobil. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Plerixafor Accord in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of plerixafor based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version, is of particular relevance.

Exemption

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

According to the Appendix II of the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1): "In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required".

No bioequivalence study was conducted and none is required since the applied product is to be administered as an aqueous solution for injection for subcutaneous administration containing the same active substance in the same concentrations as the currently authorised originator product. In addition, Plerixafor Accord 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, which is accepted by the CHMP.

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

The generic medicinal product has an identical qualitative and quantitative composition in active substance and excipients compared to the approved reference medicinal product and the same pharmaceutical form and route of administration. Therefore, according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) bioequivalence studies are not required in this case.

2.4.2.2. Pharmacodynamics

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

2.4.3. Clinical efficacy

N/A

2.4.4. Clinical safety

N/A

2.4.4.1. 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

No bioequivalence study has been submitted and none are required according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 Appendix II). A biowaiver has been requested, which is acceptable from a pharmacokinetic point of view. The essential similarity with the reference medicinal product is only based on pharmaceutical equivalence.

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

A clinical overview based on published clinical data was submitted where clinical pharmacology, efficacy and safety of plerixafor were discussed. Pharmacodynamic and pharmacokinetic profiles, efficacy and safety of plerixafor are well known and adequately characterised.

According to the Directive 2001/83/EC, no further obligations are required for this generic application and Plerixafor Accord is considered essentially similar to Mozobil.

2.4.6. Conclusions on clinical aspects

There are no objections regarding the marketing approval of Plerixafor Accord, Solution for injection 20 mg/ml from a clinical point of view. A summary of the literature with regard to clinical data of Plerixafor Accord and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product Mozobil was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk Management Plan

2.5.1. Safety concerns

Summary of safety concerns	
Important identified risks	- Splenomegaly and splenic rupture
Important potential risks	- Interstitial lung disease - Myocardial infarction - Tumour cell mobilisation - Drug level NOS increased - Anxiety, hallucination (including hallucination, visual hallucination, and auditory hallucination) - Effect on embryo-foetal development (including teratogenicity and foetal growth restriction)
Missing information	- Safety profile in paediatric under 2 years of age

2.5.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.5.3. Risk minimisation measures

None.

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.6. Pharmacovigilance

2.6.1. 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.

2.6.2. 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.

2.7. Product information

2.7.1. User consultation

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 Mozobil. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of plerixafor, solution for injection. The reference product Mozobil is indicated for

Adult patients
Mozobil is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma or multiple myeloma whose cells mobilise poorly.

Paediatric patients (1 to less than 18 years)
Mozobil is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

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.

No bioequivalence studies have been submitted and none are required according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 Appendix II) since Plerixafor Accord is to be administered as an aqueous solution for injection for subcutaneous use containing the same active substance in the same concentrations as the currently authorised originator product. In addition, Plerixafor Accord 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. A biowaiver has been requested and is acceptable from a pharmacokinetic point of view.

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

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.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Plerixafor Accord is not similar to Adcetris, Gazyvaro, Kymriah, Ledaga, Minjuvi, Polivy, Poteligeo, Tecartus, Yescarta, Blenrep, Darzalex, Farydak, Imnovid, Kyprolis, Ninlaro, Trecondi and Abecma within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix.

Outcome

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

Adult patients
Plerixafor Accord is indicated in combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma or multiple myeloma whose cells mobilise poorly.

Paediatric patients (1 to less than 18 years)
Plerixafor Accord is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or
- who previously failed to collect sufficient haematopoietic stem cells.

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 marketing authorisation holder (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.