28 January 2021
EMA/129214/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Thiotepa Riemser

International non-proprietary name: thiotepa

Procedure No. EMEA/H/C/005434/0000

Note

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

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List of abbreviations

ADR	Adverse drug reaction
ALL	Acute lymphoblastic leukaemia
AML	Acute myeloid leukaemia
API	Active Pharmaceutical Ingredient
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File
BP	British Pharmacopoeia
BSE/TSE	Bovine Spongiform Encephalopathy / Transmissible Spongiform Encephalopathy
CFU	Colony forming unit
CHMP	Committee for Medicinal Products for Human use
EC	European Commission
CNS	Central nervous system
EDQM	The European Directorate for the Quality of Medicines & HealthCare
EMA/EMEA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
FPM	Finished Product Manufacturer
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
HPCT	Haematopoietic progenitor cell transplantation
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Name
IPC	In-process control
IR	Infrared spectroscopy
KF	Karl Fischer titration
LOD	Loss of drying (1), Limit of Detection (2)
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIA	Manufacturing / Importer Authorisation
OOS	Out-of-Specification
NMR	Nuclear Magnetic Resonance
PBT	Persistence, bioaccumulation and toxicity
PDE	Permitted daily exposure
Ph Eur	European Pharmacopeia
PI	Product information
PIP	Paediatric Investigation Plan
PTFE	polytetrafluoro-ethylene
PVC	Polyvinyl chloride
QP	Qualified Person
QTc	Corrected QT interval
QWP	Quality Working Party
RH	Relative Humidity
SmPC	Summary of Product Characteristics
SP	United States Pharmacopoeia
TBI	Total body irradiation
TAMC	Total Aerobic Microbial Count
TYMC	Total Combined Yeasts/Moulds Count

1. Background information on the procedure

1.1. Submission of the dossier

Riemser Pharma GmbH submitted on 16 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Thiotepa Riemser, 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 25 July 2019.

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 10a of Directive 2001/83/EC.

The applicant applied for the following indication:

In combination with other chemotherapy medicinal products:

- with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;
- when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

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, complete quality data and pharmaceutical equivalence with the reference medicinal product Tepadina instead of non-clinical and clinical unless justified otherwise

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: Tepadina 15mg, 100mg Powder for concentrate for solution for infusion
- Marketing authorisation holder: ADIENNE S.r.l.S.U.
- Date of authorisation: (15-03-2010)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/10/622/001-002,

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

- Product name, strength, pharmaceutical form: Tepadina 15mg, 100mg Powder for concentrate for solution for infusion
- Marketing authorisation holder: ADIENNE S.r.l.S.U.

- Date of authorisation: (15-03-2010)
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number: EU/1/10/622/001-002,

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 from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP were:

Rapporteur: Margareta Bego

The application was received by the EMA on	16 March 2020
The procedure started on	21 May 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	10 August 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 August 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	17 September 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 October 2020

The CHMP and PRAC Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	16 November 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	10 December 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	21 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 January 2021
The outstanding issues were addressed in writing by the applicant before the CHMP during the meeting on	7 January 2021
The CHMP adopted a report on similarity with Trecondi (Appendix 1)	28 January 2021
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 Thiotepa Riemser on	28 January 2021

2. Scientific discussion

2.1. Introduction

The underlying Marketing Authorization Application for Thiotepa Riemser 15 mg and 100 mg is submitted under Article 10(1) Generic Application according to the Directive 2001/83/EC, as amended.

The proposed product is a powder for concentrate for solution for infusion.

The applicant claims essential similarity of the proposed product with the reference medicinal product, Tepadina 15 mg/ 100 mg powder for concentrate for solution for infusion. Tepadina was approved as a bibliographic application according to Article 10(a) of Directive 2001/83/EC, based on the extensively known and well established efficacy and safety profile of thiotepa.

No specific bioequivalence study has been performed and the applicant claims that no bioequivalence study is required based on the Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr **, as the product is administered as an aqueous intravenous solution and contains the same qualitative and quantitative composition in active substance as the currently approved reference medicinal product. In addition, the proposed product contains

the same excipients as the reference product and the excipients are not known to interact with the drug substance or to otherwise affect the disposition of the drug substance.

The proposed indications and posology and method of administration are identical to the reference product Tepadina. Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence. In addition, up to date published clinical data was submitted and is considered adequate discussing clinical pharmacology, efficacy and safety of thiotepa in the indications sought for adults and paediatric patients.

Thiotepa Riemser is, in combination with other chemotherapy medicinal products, indicated with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients, or when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for concentrate for solution for infusion containing 15 or 100 mg of thiotepa as active substance.

The finished product contains no additional excipients.

The product is available in type I clear glass vials fitted with bromobutyl rubber stoppers as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of thiotepa is 1,1',1"-phosphinothioylidynetrisaziridine or *tris*(1-aziridinyl)-phospine sulphide corresponding to the molecular formula $C_6H_{12}N_3PS$. It has a relative molecular mass of 189.23 g/mol and the following structure:

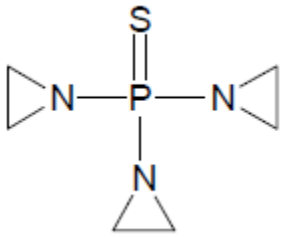

Figure 1: active substance structure

The chemical structure of thiotepa was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and IR spectroscopy. The solid-state properties of the active substance were measured by IR

spectroscopy, thermogravimetric analysis, differential scanning calorimetry, melting point range and microscopy. There is no evidence of polymorphism. The active substance is achiral.

The active substance is a white crystalline solid which is freely soluble in water in which it forms a solution of pH 6.6. It is susceptible to acid and base-mediated degradation in aqueous media.

Considering that there are monographs for thiotepa in both the British and US pharmacopoeias (BP, USP) with which the active substance complies, the above information is considered satisfactory.

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. The ASMF holder has extensive experience manufacturing thiotepa for MAHs with product on the EU market.

Thiotepa is synthesized by a single manufacturer in 2 main steps using well defined starting materials. The starting materials are considered acceptable, as are their 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. Mutagenic impurities including bromoethylamine hydrobromide and ethyleneimine are adequately purged by the process.

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. Thiotepa has a greater toxicity than its related substances. Additionally, since thiotepa is used in products intended for advanced cancer indications, it is outside the scope of a genotoxicity assessment as described in the ICH M7.
The active substance is packaged in amber type III glass containers closed with black phenolic and urea screw caps. The closure is further sealed with PVC tape. The cap liner is a laminate of polytetrafluoroethylene (PTFE) and polyethylene foam. The materials which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual control), melting point (Ph. Eur.), identity (IR, BP), water content (Ph. Eur.), assay (HPLC), related substances (HPLC), clarity of solution (Ph. Eur.), particle count (microscopy), bacterial endotoxins (Ph. Eur.), microbial limits (Ph. Eur.) and residual solvents (GC).

Limits for impurities are set according to ICH Q3A and are in line with pharmacopoeial limits for thiotepa. A significant manufacturing and degradation impurity results from polymerisation of thiotepa. This insoluble polymer is limited to very low levels by the clarity of solution and particle count tests.

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 has been presented.

Batch analysis data on three recent production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. Additional compliant batch data was provided in the ASMF.

Stability

Stability data from 21 batches of active substance from the proposed manufacturer stored in a smaller scale version of the intended commercial package for up to 36 months under long term conditions (2-8ºC) according to the ICH guidelines were provided. In addition, data from 4 of these batches stored for up to 6 months under accelerated conditions (25ºC / 60% RH) were provided. Samples were tested for description, water content, assay, related substances, clarity of solution, microbial limits and bacterial endotoxins (the latter 2 performed only at the initial test point and after 24 months' storage). There were no changes to the tested parameters which remained within specification with the exception of clarity of solution. The analytical methods used were the same as for release and are stability indicating.

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 18 months at 2-8ºC in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Thiotepa Riemser is white lyophilisate containing either 15 mg or 100 mg of the active substance. Prior to administration, the lyophilised powder is reconstituted with water for injections and diluted with 0.9% sodium chloride solution prior to infusion.

The aim of development was to produce a generic version of the reference product, Tepadina. The information provided on the development of the generic product is the same as for the reference product. The generic medicinal product has an identical qualitative and quantitative composition in the active substance and excipients as the reference product, has the same pharmaceutical form and strength as its originator and is produced by the same manufacturer using the same process which involves compounding, sterile filtration and lyophilisation. The choice of sterilisation method is justified on the basis that the lyophilizate can't be terminally sterilised.

The active substance is freely soluble in water. Since the finished product is a freeze-dried formulation and is administered as an aqueous solution, particle size and polymorphic form are not considered important properties. Stability of the thiotepa in solution is important given that is susceptible to both acid and base-mediated degradation and is also thermolabile. The stability of the active substance once in solution needs to be ensured and so storage time, temperature, sterile filtration and lyophilisation cycle are critical steps and are suitably controlled to minimise degradation.

The only excipients that are used during manufacturing process are water for injections and nitrogen gas. Water for injections is removed during lyophilisation step and nitrogen is used only during filtration and after lyophilisation. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards.

Since the product is to be administered as an aqueous intravenous solution containing the same active substance concentrations as the originator, bioequivalence studies are not needed in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98).

The powder is reconstituted before administration. The pH of the reconstituted solution is between 5.5 and 7.5, which is suitable for parenteral application and is also where the active substance is most stable. No adjustment

of the ionic strength of the reconstituted solution is necessary when it is further diluted with 0.9% sodium chloride solution in an infusion bag. The solution is in-line filtered prior to infusion.

Two compatibility studies were conducted to assess the stability of reconstituted and diluted solutions in the intended infusion equipment.

In the first study, compatibility and stability of reconstituted solution were investigated in the primary vials. Samples were analysed at regular timepoints and at the end of each study, aliquots were diluted with saline solution for further analysis, including filtration time through the intended polyethersulfone-fluid filter membrane. Suitable stability was demonstrated for 24 hours at 2-8ºC and for 12 hours at 25°C. At 25°C, a decrease in the assay was observed with OOS results after 18 hours. Compatibility with the in-line filter was demonstrated.

In the second study, compatibility of the reconstituted solution diluted with 500 ml of 0.9% sodium chloride solution for infusion in the intended PVC-free infusion bags was investigated. Therefore, the reconstituted and diluted product is considered sufficiently stable for up to 24 hours at 2-8ºC and for up to 4 hours at 25°C.

The primary packaging is either a 3 ml type I glass vial with siliconised grey bromobutyl freeze drying stopper and planar blue/silver flip-top cap (15 mg strength) or a 10 ml type I glass vial with siliconised grey bromobutyl freeze drying stopper and planar red/silver flip-top cap (100 mg strength). The materials comply 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 manufacturing process consists of five main steps: compounding, sterile filtration, lyophilisation, crimping and packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. For the 15 mg strength, validation was conducted on 3 production scale batches and repeated on a further 3 batches following equipment changes (3 batches following a change of lyophilizer, 3 more batches following change in volume of compounding vessel). For the 100 mg strength, validation was conducted on 3 pilot scale and 3 production scale batches and repeated on a further 3 batches following change in volume of compounding vessel. Extensive validation data on the sterile filtration step was also provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The time and temperature constraints employed mitigate the instability of thiotepa in solution and ensure the quality of the finished product. The IPCs 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 including appearance (visual control), identity (IR), completeness of solution (visual control), clarity of solution (Ph. Eur.), pH after reconstitution (Ph. Eur.), water content (Ph. Eur.), related compounds (BP/HPLC), insoluble substances (gravimetric), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), assay (HPLC) and uniformity of dosage units (Ph. Eur.).

The limits for impurities are considered acceptable given the long use of product from the same manufacturer in clinical practice and that the product is indicated for advanced cancer indications and is thus not in the scope of ICH M7. They are also in line with the BP monograph.

As a decomposition product of thiotepa is known to be an insoluble polymer, the content of insoluble substances is tested according to an in-house method.

The potential presence of elemental impurities in the finished product was assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities and considering the parenteral route of administration (class 1, 2A and 3 metals + Li, Sb and Cu). Analysis data on 2 batches via atomic spectroscopy was provided, demonstrating that each relevant elemental impurity was consistently well below the respective control thresholds. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed 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 no risk was identified and 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 production 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 11 production scale batches of the 15 mg strength and 3 pilot and 10 production scale batches of the 100 mg strength stored for up to 24 months under long term conditions (5±3ºC) and for up to 6 months under accelerated conditions (25ºC / 65% 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 according to the shelf-life specifications which are the same as for release with the omission of identity. For the majority of parameters, no significant changes or trends were observed. A decrease in assay was observed leading to OOS results after 24 months was explained by absorption into the stopper. Some OOS results were seen for clarity of solution under both conditions, although under long term conditions, all batches remained within specification up to 18 months. This phenomenon is explained by the known degradation pathway of thiotepa which results in insoluble polymeric material. To counteract this and as stated in the SmPC, the solution must be filtered before administration.

In addition, one batch of the 15 mg strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Thus, the finished product is not considered photosensitive but a cold chain is considered necessary during transport.

In-use stability and compatibility was already discussed in the pharmaceutical development section. The reconstituted solution is stable for up to 24 hours at 2-8ºC and for up to 12 hours at 25°C. The reconstituted

and diluted product is considered sufficiently stable for up to 24 hours at 2-8ºC and for up to 4 hours at 25°C.

Based on available stability data, the proposed shelf-life of 18 months with the following conditions as stated in the SmPC (section 6.3) is acceptable: store and transport refrigerated (2 - 8°C), do not freeze.

Adventitious agents

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

2.2.4. Discussion on chemical, and pharmaceutical aspects

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. The finished product has been demonstrated to be equivalent to the reference 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

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of thiotepa are well known. As thiotepa is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

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

2.3.2. Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment (ERA) in accordance with the Guideline on the environmental risk assessment of medicinal products for human use, EMEA/CHMP/SWP/4447/00. A risk to the environment is unlikely as the PEC action limit in phase I is not exceeded. No Phase II assessment is required. The applicant provided an experimental determination of the $\log K_{OW}$ according to OECD 123. Therefore, thiotepa is not a PBT substance as log Kow value is below 4.5.

2.3.3. Discussion on non-clinical aspects

This is a generic centralised application for a medicinal product supplied as a powder for concentrate for solution for infusion. The reference medicinal product in the EU is Tepadina 15 mg/ 100 mg powder for concentrate for solution for infusion. It was approved as a bibliographic application according to Article 10(a) of Directive 2001/83/EC, based on the extensively known and well established efficacy and safety profile of thiotepa.

A non-clinical Overview based on up to date published non-clinical data was submitted and is considered adequately discussing the pharmacodynamic, pharmacokinetic and toxicological properties of thiotepa.

The environmental risk assessment is considered complete and acceptable. The PEC surfacewater value of thiotepa is below the action limit of 0.01 µg/L and thiotepa is not a PBT substance as log Kow value is below 4.5. Considering the above data, thiotepa is not expected to pose a risk to the environment.

2.3.4. Conclusion on the non-clinical aspects

Thiotepa is not expected to pose a risk to the environment.

2.4. Clinical aspects

2.4.1. Introduction

Thiotepa Riemser contains the active substance thiotepa. Thiotepa is a cell cycle-phase independent, non-specific alkylating cytotoxic agent chemically and pharmacologically related to the nitrogen mustard. The radiomimetic action of thiotepa is believed to occur through the release of ethylenimine radicals that, similar to irradiation therapy, disrupt the bonds of DNA. One of the principal bond disruptions is initiated by alkylation of guanine at the N-7 position that severs the linkage between the purine base and the sugar and liberates alkylated guanines.

Thiotepa undergoes complex metabolism with Tepa as the major metabolite. Both thiotepa and Tepa are active structures. Tepa is assumed to interact differently with DNA, but is also thought to produce DNA lesions.

The use of thiotepa is invariably associated with haematological toxicity, while extra-haematological toxicity is absent or mild in the commonly used posologies. For this reason, thiotepa was considered an ideal drug to use at high dosage in conditioning treatments prior to haematopoietic stem cell transplantation (HSCT, also referred to as haematopoietic progenitor cell transplantation-HPCT).

The conditioning is considered the most important step in the HPCT procedure and it includes myeloablative, reduced-intensity myeloablative, and non-myeloablative regimens. Its purpose is to help eradicate the patient's disease prior to the transplant, to create marrow space for the donor cells and to suppress the host’s immune system to prevent graft rejection. This can be achieved by chemotherapy drugs and radiation because both damage cellular DNA.

Autologous or allogeneic HSCT takes advantage of the specific bone-marrow toxicity and the lack of dose limiting extra-medullary toxicity of thiotepa. The compound is frequently given in combination with cyclophosphamide and busulfan or cyclophosphamide and carboplatin, as well as in other combinations of high-dose chemotherapy regimens. In the last thirty years, HSCT has become a standard therapy in patients with advanced haematological malignancies and malignant solid tumours resistant to standard chemotherapy.

There are different conditions treated with HSCT such as lymphomas, leukaemias, CNS lymphomas, multiple myelomas, germ cell tumours or thalassaemias. In the paediatric population, sickle cell anaemia and CNS tumours are additionally treated with HSCT.

Exemption

This is a generic centralised application for a medicinal product supplied as a powder for concentrate for solution for infusion.

The applicant claims essential similarity of the proposed product with Tepadina based on the following arguments:

• The qualitative and quantitative composition of both, Thiotepa Riemser 15 mg powder for concentrate for solution for infusion and Thiotepa Riemser 100 mg powder for concentrate for solution for infusion, is identical to the reference medicinal TEPADINA 15 mg powder for concentrate for solution and TEPADINA 100 mg powder for concentrate for solution for infusion (as described in detail in module 3.2.P.1)

• They have both the same pharmaceutical form

• They are both manufactured by the same manufacturer (as described in detail in module 3.2.P.3).

No specific bioequivalence study has been performed and the applicant claims that no bioequivalence study is required justified by and based on the Guideline CPMP/EWP/QWP/1401/98 Rev. 1/Corr ** as the product is administered as an aqueous intravenous solution containing the same active substance as the currently approved reference medicinal product.

Therefore, for the current generic application the essential similarity with the reference medicinal product is only based on pharmaceutical equivalence and a biowaiver for exemption to conduct a clinical bioequivalence study has been requested.

2.4.2. Pharmacokinetics

Not applicable.

2.4.3. Pharmacodynamics

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

2.4.4. Additional data

A literature search for articles published in English language since 2010 in Pubmed for the term "thiotepa" without further restrictions resulted in 397 hits. Detailed literature searches were performed on December, 23rd 2019. 135 Publications for efficacy and safety analysis included data on autologous HPTC in adult and paediatric patients. Additionally, 3 publications provided information on specific safety aspects.

2.4.5. Post marketing experience

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

2.4.6. Discussion on clinical aspects

This is a generic centralised application for a medicinal product supplied as a powder for concentrate for solution for infusion. The reference medicinal product in the EU is Tepadina 15 mg/ 100 mg powder for concentrate for solution for infusion. It was approved as a bibliographic application according to Article 10(a) of Directive 2001/83/EC, based on the extensively known and well established efficacy and safety profile of thiotepa.

A Clinical Overview based on up to date published clinical data was submitted and is considered adequately discussing clinical pharmacology, efficacy and safety of thiotepa in the indications sought for adults and paediatric patients.

A biowaiver has been requested since the proposed generic medicinal product Thiotepa Riemser 15 mg / 100 mg powder for concentrate for solution for infusion will be administered as an aqueous intravenous solution. It has an identical qualitative and quantitative composition in active substance compared to the approved reference medicinal product, Tepadina, the same pharmaceutical form and route of administration. In addition, the proposed product contains the same excipients as the reference product and the excipients are not known to interact with the drug substance or 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.

Since this MAA concerns a re-submission of the originator product as a generic product (please refer to quality assessment), adequate justification for requesting a biowaiver has been submitted.

2.4.7. Conclusions on clinical aspects

The essential similarity with the reference medicinal product is based only on pharmaceutical equivalence. Approval is recommended from the clinical point of view.

Except for minor corrections, the product information texts are identical with the current version of the reference product Tepadina (see commented PI).

2.5. Risk management plan

Safety concerns

Table: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Myelosuppression Hypersensitivity reactions Infection Treatment related secondary malignancy Graft Versus Host Disease Mucositis Confusion, delirium, hallucination Veno-occlusive liver disease Paediatric hepatic failure Pulmonary toxicity Nervous system disorders Cardiac failure Renal failure Embolism, haemorrhage Infertility
Important potential risks	Pulmonary arterial hypertension Toxic skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis Leukoencephalopathy
Missing information	Pregnant or lactating women Elderly patients Patients with clinically significant renal disease Patients with clinically significant hepatic disease Patients with impaired cardiac function Patients with impaired pulmonary function Patients with previous brain or craniospinal irradiation Data on ethnicity/race

Pharmacovigilance plan

No additional pharmacovigilance activities.

Risk minimisation measures

Table: Summary table of risk minimisation activities by safety concern

Safety concern	risk minimisation measures
Myelosuppression	routine risk minimisation measures: - warnings in SmPC section 4.4, 4.5, recommendation in section 4.4 and information in sections 4.8 and 4.9

	- warnings and recommendation in PIL section 2 and information in section 4 - prescription status
Hypersensitivity reactions	routine risk minimisation measures: - instruction in SmPC section 4.3 to exclude patients at risk and information in section 4.8 - exclusion of patients at risk in PIL section 2 and information in section 4 - prescription status
Infection	routine risk minimisation measures: - instructions to exclude patients at risk in SmPC sections 4.3 and 4.5, recommendation in section 4.4 and information in section 4.8 - exclusion of patients of risk and warnings as well as recommendation in PIL section 2 and information in section 4 - prescription status
Treatment related secondary malignancy	routine risk minimisation measures: - warnings and information in SmPC sections 4.4 and 4.8 - warnings and information in PIL sections 2 and 4 - prescription status
Graft versus host disease	routine risk minimisation measures: - information in SmPC sections 4.8 and 5.1 - information in PIL section 4 - prescription status
Mucositis	routine risk minimisation measures: - information in SmPC section 4.8 - information in PIL section 4 - prescription status
Confusion, delirium, hallucination	routine risk minimisation measures: - information in SmPC section 4.8 - information in PIL section 4 - prescription status
Veno-occlusive liver disease	routine risk minimisation measures: - warning in SmPC section 4.4 to indicate patients at risk and information in section 4.8 - information in PIL section 4 - prescription status
Paediatric hepatic failure	routine risk minimisation measures: - information in SmPC sections 4.2, 4.4 and 4.8 - information in PIL sections 2 and 4 - prescription status
Pulmonary toxicity	routine risk minimisation measures: - warnings in SmPC section 4.4 to indicate patients at risk and information in section 4.8 - information in PIL section 4

	- prescription status
Nervous system disorders	routine risk minimisation measures: - warnings and recommendation in SmPC section 4.4 and 4.5 for patients at risk and information in section 4.8 - warnings and recommendation in PIL section 2 and information in section 4 - prescription status
Cardiac failure	routine risk minimisation measures: - warning and recommendation in SmPC section 4.4 and PIL section 2 for patients at risk and information in section 4.8 - information in PIL section 4 - prescription status
Renal failure	routine risk minimisation measures: - recommendation in SmPC section 4.4 for patients at risk and information in section 4.8 - warning in PIL section 2 and information in section 4 - prescription status
Embolism, haemorrhage	routine risk minimisation measures: - information in SmPC sections 4.5 and 4.8, recommendation for patients at risk in section 4.5 - recommendation in PIL section 2 for patients at risk and information in section 4 - prescription status
Infertility	routine risk minimisation measures: - information in SmPC sections 4.4, 4.6, 4.8 and 5.3 as well as recommendation in section 4.4 - information and recommendation in PIL sections 2 and 4 - prescription status
Pulmonary arterial hypertension	routine risk minimisation measures: - information in SmPC section 4.8 - information in PIL section 4 - prescription status
Toxic skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis	routine risk minimisation measures: - information in SmPC section 4.8 - information in PIL section 4 - prescription status
Leukoencephalopathy	routine risk minimisation measures: - information in SmPC section 4.8 - information in PIL section 4 - prescription status
Pregnant or lactating women	routine risk minimisation measures: - instructions in SmPC section 4.3 to exclude patients at risk from the therapy, recommendation and information in sections 4.6 and 5.2 - instruction in PIL section 2 to exclude patients at risk as well as recommendation in section 2

	- prescription status
Elderly patients	routine risk minimisation measures: - information and recommendation in SmPC section 4.2 - prescription status
Patients with clinically significant renal disease	routine risk minimisation measures: - information in SmPC sections 4.2, and 5.2 as well as warning in section 4.4 - warning in PIL section 2 - prescription status
Patients with clinically significant hepatic disease	routine risk minimisation measures: - information and warnings in SmPC sections 4.2, 4.4, 4.8 and 5.2 as well as recommendation in section 4.4 - warning and information in PIL sections 2 and 4 - prescription status
Patients with impaired cardiac function	routine risk minimisation measures: - warning and recommendation in SmPC section 4.4 for patients at risk - warning in PIL section 2 - prescription status
Patients with impaired pulmonary function	routine risk minimisation measures: - information in SmPC section 4.4 - prescription status
Patients with previous brain or craniospinal irradiation	routine risk minimisation measures: - warning in SmPC section 4.4 on the patients possibly at risk - prescription status
Data on ethnicity/ race	none

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 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.

2.7. Product information

2.7.1. User consultation

Conclusion from the checklist for the review of user consultation

The results of the submitted user testing report indicate that the Package Leaflet is well structured and organized and patients/users are able to act upon the information that it contains.

Bridging report for **Thiotepa Riemser 15 mg powder for concentrate for solution for infusion** includes the statement that PL for Thiotepa Riemser 100 mg (Parent PL) and Thiotepa Riemser 15 mg (Daughter PL) have identical content as well as the layout. The only difference is the strength "100 mg" and "15 mg" in the main headline and in section 6. Mock-up for Parent PL and Daughter PL are included. As Parent PL and Daughter PL are identical in terms of content and design/layout, the statement is acceptable.

The requirements of the Article 59(3) of Council Directive 2001/83/EC for Package leaflet for **Thiotepa Riemser 100 mg powder for concentrate for solution for infusion** and **Thiotepa Riemser 15 mg powder for concentrate for solution for infusion** are fulfilled.

2.7.2. Quick Response (QR) code

Not applicable

3. Benefit-risk balance

This application concerns a generic version of thiotepa powder for concentrate for solution for infusion. The reference product Tepadina is indicated, in combination with other chemotherapy medicinal products, with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients, or when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

A Clinical Overview based on up to date published clinical data was submitted and is considered adequately discussing clinical pharmacology, efficacy and safety of thiotepa in the indications sought for adults and paediatric patients.

A biowaiver has been requested since the proposed generic medicinal product Thiotepa Riemser 15 mg / 100 mg powder for concentrate for solution for infusion will be administered as an aqueous intravenous solution. It has an identical qualitative and quantitative composition in active substance compared to the approved reference medicinal product, Tepadina, the same pharmaceutical form and route of administration. In addition, the proposed product contains the same excipients as the reference product and the excipients are not known to interact with the drug substance or 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.

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. Recommendation

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

In combination with other chemotherapy medicinal products:

- with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients;
- when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.

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.

Appendix

1. CHMP AR on similarity dated 28 January 2021