Date: 21 October 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

TRECONDI

International non-proprietary name: treosulfan
Pharmaceutical form: powder for solution for infusion
Dosage strengths: 5 g and 1 g
Route(s) of administration: intravenous use
Marketing Authorisation Holder: Opopharma Vertriebs AG
Marketing Authorisation No.: 67775
Decision and Decision date: approved on 10 August 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

AlloHSCT	Allogeneic haematopoietic stem cell transplantation
ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GC	Gas Chromatography
GLP	Good Laboratory Practice
HPLC	High Performance Liquid Chromatography
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IR	Infrared
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PE	Polyethylene
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
PVC	Polyvinyl chloride
RH	Relative Humidity
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
WFI	Water for injection

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance treosulfan of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Treosulfan in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases.

2.2.2 Approved Indication

TRECONDI in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than 1 month with malignant diseases.

2.2.3 Requested Dosage

Adults with malignant disease
Treosulfan is given in combination with fludarabine. The recommended dose and schedule of administration is:

- Treosulfan 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (days -4, -3, -2) before stem cell infusion (day 0). The total treosulfan dose is 30 g/m²;
- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (days -6, -5, -4, -3, -2) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m²;
- Treosulfan should be administered before fludarabine on days -4, -3, -2 (FT_{10} regimen).

Adults with non-malignant disease
Treosulfan is given in combination with fludarabine with or without thiotepa. The recommended dose and schedule of administration is:

- Treosulfan 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (days -6, -5, -4) before stem cell infusion (day 0). The total treosulfan dose is 42 g/m²;
- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (days -6, -5, -4, -3, -2) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m²;
- Treosulfan should be administered before fludarabine on days -6, -5, -4 (FT14 regimen).
- Thiotepa 5 mg/kg twice a day, given as two intravenous infusions over 2–4 hours on day -2 before stem cell infusion (day 0).

Paediatric population
Treosulfan is given in combination with fludarabine, with thiotepa (intensified regimen; $FT_{10\text{-}14}TT$ regimen) or without thiotepa ($FT_{10\text{-}14}$ regimen).
The recommended dose and schedule of administration is:

- Treosulfan 10-14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (days -6, -5, -4) before stem cell infusion (day 0). The total dose of treosulfan is 30-42 g/m².

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The treosulfan dose should be adapted to the patient's BSA as follows:

Body surface area (m²)	*TRECONDI dose (g/m²)*
≤ 0.5	10.0
> 0.5-1.0	12.0
> 1.0	14.0

- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (days -7, -6, -5, -4, -3) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m².
- Treosulfan should be administered before fludarabine.
- Thiotepa (intensified regimen 5 mg/kg twice a day), given as two intravenous infusions over 2–4 hours on day -2 before stem cell infusion (day 0).

The safety and efficacy of treosulfan in children less than 1 month of age has not yet been established.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	19 November 2019
Formal control completed	9 December 2019
Predecision	26 March 2020
Answers to Predecision	29 May 2020
Final Decision	10 August 2020
Decision	approval

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3 Medical Context

Allogenic stem cell transplantation (alloHSCT) is a potentially curative option for malignant diseases such as leukaemia, myelodysplastic syndromes (MDS), lymphomas and multiple myeloma (MM). It is also used in several non-malignant diseases.

AlloHSCT patients are prepared with chemotherapy alone or chemotherapy combined with radiotherapy. These conditioning regimens are:

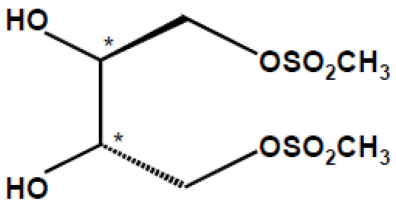
- Myeloablative radiation-containing conditioning regimens
- Myeloablative conditioning regimens without radiation
- Nonmyeloablative and reduced intensity conditioning regimens

Myeloablative conditioning is associated with a high risk of mortality and morbidity especially in the older population with co-morbidities. Therefore, conditioning regimens with lower toxicity are preferred.

4 Quality Aspects

4.1 Drug Substance

The chemical name of treosulfan is (2S,3S)-(-)-1,4-di(mesyloxy)-2,3-butanediol corresponding to the molecular formula $C_6H_{14}O_8S_2$. It has a relative molecular mass of 278.3 and the following structure:



The chemical structure of treosulfan was elucidated by a combination of elemental analysis, 1H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS) and infrared (IR) spectroscopy.
The solid state properties of the active substance were determined by differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD).
The active substance is a non-hygroscopic white crystalline powder; it is freely soluble in acetone, soluble in water, sparingly soluble in ethanol and very slightly soluble in chloroform.
Treosulfan exhibits stereoisomerism due to the presence of two chiral centres. The chiral centres have the (S)-configuration and are introduced during the synthetic process with the starting material. Enantiomeric purity is controlled routinely by specific optical rotation.
Polymorphism screening was performed and two polymorphic forms were observed. The most stable polymorphic form of treosulfan is consistently produced utilising the intended commercial manufacturing process and it was demonstrated that it does not change during storage.

Manufacture, characterisation and process controls

The active substance is obtained from a single manufacturer. It is synthesised in a convergent synthesis in 4 main steps followed by a crystallisation step from well-defined starting materials with acceptable specifications. Several synthesis intermediates are isolated.
Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable.
The characterisation of the active substance and its impurities are in accordance with the ICH guideline on chemistry of new active substances.
Treosulfan is an anti-cancer medicine indicated for the treatment of severe and life-threatening diseases. Treosulfan and its active metabolites that form in vivo (monoepoxide and diepoxide) are themselves genotoxic/cancerogenic substances. The mechanism of action is based on the conversion of treosulfan to the epoxides which alkylate DNA, resulting in the induction of DNA cross-links (as

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described in the information for healthcare professionals). The known related impurities of treosulfan are not expected to have a higher genotoxic potential than the active substance itself.
Potential and actual impurities were well discussed with regards to their origin and characterised.
The active substance is packaged in antistatic LDPE bags which comply with the EC Directive 2002/72/EC and EU Regulation 10/2011 as amended. The LDPE bags are placed into fibre drums.

Specification

The active substance specification includes tests for: description, melting point (Ph. Eur.), optical rotation (Ph. Eur.), identity (IR), assay (HPLC), clarity of the solution (Ph. Eur.), colour of the solution (Ph. Eur.), pH (Ph. Eur.), related substances (HPLC), heavy metals (Ph. Eur.), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), residual solvents (GC), and microbiology (Ph. Eur.).
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 from three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

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 (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided.
The following parameters were tested: description, melting point, assay (HPLC), clarity of the solution, colour of the solution, pH, related substances, loss on drying and microbiology. The analytical methods used were the same as for release and were stability indicating.
All tested parameters were within the specifications.
Photostability testing following the ICH guideline Q1B was performed on one batch. The results of the study show that treosulfan is not photosensitive.
Results on stress conditions: high temperature study (solid state), hydrolysis study (in buffer solution used in the analytical method, in acidic conditions, in alkaline conditions) and an oxidation study (H_2O_2) were also provided on one batch. Treosulfan showed to be unstable under acidic conditions, with approximately a third of the sample being degraded into various products. Treosulfan is hydrolysed and degraded very quickly under alkaline conditions.
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 at 25ºC / 60% RH in the proposed container.

4.2 Drug Product

Description of the product and pharmaceutical development

The finished product is presented as white crystalline powder for solution for infusion containing 1 g or 5 g of treosulfan as active substance. The product is available in a colourless type III glass vial, with rubber stopper and aluminium cap. The product is reconstituted in 0.45% sodium chloride solution. The reconstituted solution contains 50 mg treosulfan per 1 ml and appears as a clear colourless solution.
Treosulfan was developed more than two decades ago and its use is well-established (e.g. medicinal product authorised and marketed in the EU for the indication “Palliative treatment of epithelial ovarian cancer” since the 1990s). The aim of the pharmaceutical development was to develop a stable, sterile powder for solution for infusion formulation indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than one month with malignant diseases.
Due to its solubility in water, treosulfan is suitable for intravenous infusion after reconstitution. The addition of a solubilising agent is not necessary. The compound is intended to be marketed as a pure dried substance that should be dissolved in sterile reconstitution medium immediately before administration. Especially for use in the paediatric population, 0.45 % NaCl solution should be used instead of water for injection (WFI) as reconstitution medium to gain an acceptable osmolality of the

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resulting treosulfan solution. Stability over a period of 48 h at room temperature was confirmed by provided stability results.
The finished product contains no excipients; however a solvent and inert gas are used as excipients for production.
The same polymorphic form is consistently obtained by the commercial manufacturing process of the finished product by slow and controlled crystallisation. The polymorph is thermodynamically very stable. It was further demonstrated on three batches of the active substance and the finished product that the polymorphic form does not change during storage.
The compatibility of the active substance with excipients used for production is confirmed based on the finished product stability data. 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. As the excipients are not present in the finished product on administration, they are not included in the information for healthcare professionals.
The sterility of the powder is achieved by sterile filtration of the dissolved active substance and aseptic processing of the subsequent precipitation/drying and filling of the sterile powder in vials which are closed with rubber stoppers and sealed with safety caps. The active substance melts at approximately 100ºC and the re-crystallisation after cooling occurs in an uncontrolled manner. Final sterilisation could only be performed below the melting point (90-95ºC), which is not appropriate to ensure the inactivation of some microorganism and spores. Additionally, the active substance degrades when exposed to weak X-ray radiation, therefore sterilisation via gamma irradiation was also not deemed a feasible option. The choice of sterile filtration and aseptic process is considered appropriately justified, in line with CPMP/QWP/054/98 Corr “Decision trees for selection of sterilisation methods (Annex to note for guidance on development pharmaceutics)”.
The formulation and the manufacturing process used during clinical studies is the same as that intended for marketing.
An extractables study was performed and the chosen rubber material used for stoppers meets the quality requirements with regard to leachable compounds and related safety concerns. In addition, the proposed specification for the rubber stopper complies with the requirements of the Ph. Eur. monograph and biocompatibility of the rubber formulation has been demonstrated.
The absence of leachable studies using reconstituted treosulfan with 0.45% NaCl solution or WFI in the glass vials, PVC bags and PE bags was adequately justified. Representative data on the material or polymer type (e. g. glass, PE) have been generated which have proven the (physico)-chemical compatibility and form the basis for recommendations and instructions for their use. As demonstrated in the in-use study the used solvents and the used packaging materials have no apparent impact on the quality of the reconstituted solution.
The primary packaging is a type II glass vial, with rubber stopper and aluminium cap completed with plastic bottle holder. 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 manufacturing process consists of two main steps: in step 1 a sterile intermediate is produced and in step 2 the final sterile finished product is manufactured. The process is considered to be a non-standard manufacturing process.
Stability studies have been performed on the sterile intermediate finished product packed in the proposed primary container and were found satisfactory.
All manufacturing steps are well controlled by applied in-process controls which are adequate for this type of manufacturing process and pharmaceutical form.
Major steps of the manufacturing process have been validated by a number of studies on three commercial size batches of treosulfan product intermediate, which includes the preparation of the solution, sterile filtration, precipitation, drying and packing into polyethylene bags. Five different lots of the active substance were used. The sterile powder filling of treosulfan into injection vials was validated on three batches for each presentation (1000 mg and 5000 mg).
It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

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Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, uniformity of mass (Ph. Eur.), colour of solution (Ph. Eur.), clarity of solution (Ph. Eur.), particulate matter (visible) of solution (Ph. Eur.), particulate matter (sub-visible) of solution (Ph. Eur.), reconstitution time (in-house), pH (Ph. Eur.), identity (Ph. Eur.), related substances (HPLC), loss on drying (in-house), residual solvents (GC), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), assay (HPLC).

A risk assessment to evaluate the presence of elemental impurities in the finished drug product has been performed in compliance with ICH Q3D. Provided data have shown that the content of all elemental impurities remains well below the control threshold (defined as 30%) of the established permitted daily exposure (PDE).

Taking into account the provided summary of the risk assessment, additional controls for elemental impurities (i.e. in the finished product release specifications) were not required.

It was demonstrated that the wider acceptance criteria for the pH value applied to the specification for the reconstituted solution are acceptable from a safety and efficacy point of view.

A difference in the reconstitution time between the 1000 mg and 5000 mg strengths is expected and is considered acceptable. The variability of the reconstitution time is regarded as uncritical with regard to the clinical use of the product.

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 of each strength, 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 16 finished product batches (9 of 1 g strength and 7 of 5 g strength) of up to commercial scale stored for up to 72 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH), both in upright and inverted positions, 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 against tests and acceptance criteria as listed in the release specifications, with the exception of bacterial endotoxins since this parameter is not considered stability indicating. The analytical procedures used are stability indicating.

No significant changes have been observed and neither trends for increase nor for decrease of any parameter could be observed.

A finished product intermediate holding time of 12 months was supported by data.

A stability study after reconstitution of treosulfan to 50 mg/ml in 0.45% NaCl solution (compared with reconstitution in WFI) was carried out using different containers. Over a period of 48 h storage in different containers at room temperature, no trends were observed for assay and impurities or for appearance of treosulfan 50 mg/ml in 0.45 % NaCl solution. The pH-value decreases; however, all results comply with the specification criteria. Similar results were obtained after reconstitution of treosulfan to 50 mg/ml in WFI. In the context of the in-use stability studies, the assay of treosulfan did not change over the 48 hours tested, and a slight increase of an unknown impurity was observed. This impurity was then identified, showing that no new toxic impurities are formed in the reconstituted solution.

The applicant has justified properly the absence of forced degradation testing and photostability study of the finished product, arguing that since the finished product is a recrystallised and sterile-filtered active substance without any additional pharmaceutical formulation, no matrix effects caused by excipients are expected. Additionally, the physical state of active substance and finished product is comparable (i.e. same polymorphism). Therefore, it is not expected that additional factors which could significantly influence photostability exist for the finished product, and consequently the data for the active substance can be extrapolated for the finished product.

Based on the available stability data, the proposed shelf-life of 5 years at a temperature not exceeding 30°C is acceptable.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for TRECONDI, Swissmedic Preclinical Review conducted an abridged evaluation based on the EMA assessment report provided by the applicant. TRECONDI was recently (21 June 2019) approved in the EU for the same indication as applied in Switzerland. The active substance treosulfan has been approved in the EU for more than 10 years for the treatment of ovarian cancer.
The submitted nonclinical information consisted mainly of published literature and summaries of studies that had been conducted in the 1970s and 1980s (to support the marketing authorisation of treosulfan as an anti-cancer agent). In addition, the applicant also submitted new studies, e.g. studies with juvenile animals that were stated in the EU-PIP. Overall, given that the pharmaco-toxicological profile of treosulfan is well known and there is established clinical use, the nonclinical documentation provided is considered sufficient to support the approval of TRECONDI for the proposed indication.
As with other alkylating agents, the use of treosulfan is associated with a risk of secondary malignancies, adverse effects on embryo-foetal development and survival, as well as impaired fertility. This is adequately addressed in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA. The available assessment report and corresponding product information from the EMA were used as a basis for the clinical and clinical pharmacology evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see section 8.1 of this report.

6.1 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to TRECONDI was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or severe adverse reaction. See section “Undesirable effects” for how to report adverse reactions.

TRECONDI

Composition

Active substances

Treosulfan

Excipients

None

Pharmaceutical form and amount of active substance per unit

White, crystalline powder for solution for infusion.

Trecondi 1 g powder for solution for infusion
One vial contains 1 g of treosulfan.
Trecondi 5 g powder for solution for infusion
One vial contains 5 g of treosulfan.

After reconstitution, 1 mL of the solution for infusion contains 50 mg treosulfan.

Indications/possible applications

TRECONDI in combination with fludarabine is indicated as part of conditioning treatment prior to allogeneic haematopoietic stem cell transplantation (alloHSCT) in adult patients with malignant and non-malignant diseases, and in paediatric patients older than 1 month with malignant diseases.

Posology/administration

Administration of TRECONDI should be supervised by a physician experienced in conditioning treatment followed by alloHSCT.

Adults with malignant disease

TRECONDI is given in combination with fludarabine.
The recommended dose and schedule of administration is:

- TRECONDI 10 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -4, -3, -2) before stem cell infusion (day 0). The total dose of TRECONDI is 30 g/m².
- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (day -6, -5, -4, -3, -2) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m².
- TRECONDI should be administered before fludarabine on days -4, -3, -2 (FT_{10} regimen).

Adults with non-malignant disease

TRECONDI is given in combination with fludarabine with or without thiotepa.
The recommended dose and schedule of administration is:

- TRECONDI 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -6, -5, -4) before stem cell infusion (day 0). The total dose of TRECONDI is 42 g/m².
- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (day -7, -6, -5, -4, -3) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m².
- TRECONDI should be administered before fludarabine on days -6, -5, -4 (FT_{14} regimen).
- Thiotepa (intensified treatment regimen) 5 mg/kg twice a day, given as two intravenous infusions over 2–4 hours on day -2 before stem cell infusion (day 0).

Elderly patients

No patients above the age of 70 were included. No dose adjustment is necessary in any subset of the elderly population.

Renal and hepatic impairment

No dose adjustment is necessary for mild or moderate impairment, but TRECONDI is contraindicated in patients with severe impairment (see section “Contraindications”).

Paediatric population

TRECONDI is given in combination with fludarabine, with thiotepa (intensified regimen; $FT_{10\text{-}14}TT$ regimen) or without thiotepa ($FT_{10\text{-}14}$ regimen).

The recommended dose and schedule of administration is:

- TRECONDI 10-14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (day -6, -5, -4) before stem cell infusion (day 0). The total dose of TRECONDI is 30-42 g/m².
  The TRECONDI dose should be adapted to the patient's BSA as follows (see section "Pharmacokinetics"):

Body surface area (m²)	**TRECONDI dose (g/m²)**
≤ 0.5	10.0
> 0.5-1.0	12.0
> 1.0	14.0

- Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (day -7, -6, -5, -4, -3) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m².
- TRECONDI should be administered before fludarabine.
- Thiotepa (intensified regimen 5 mg/kg twice a day), given as two intravenous infusions over 2–4 hours on day -2 before stem cell infusion (day 0).

The safety and efficacy of TRECONDI in children less than 1 month of age has not yet been established.

Method of administration

TRECONDI is for intravenous use as a two-hour infusion.

Precautions to be taken before handling or administering the medicinal product

When handling TRECONDI, inhalation, skin contact or contact with mucous membranes should be avoided. Pregnant personnel should be excluded from handling cytotoxics.
Intravenous administration should be performed using a safe technique to avoid extravasation (see section "Warnings and precautions").
For instructions on reconstitution of the medicinal product before administration (see section "Other information").

Contraindications

- Hypersensitivity to the active substance
- Active non-controlled infectious disease
- Severe concomitant cardiac, lung, liver, and renal impairment
- Fanconi anaemia and other DNA breakage repair disorders
- Pregnancy and breastfeeding (see section "Pregnancy and lactation").
- Administration of live vaccine

Warnings and precautions

Myelosuppression

Profound myelosuppression with pancytopenia is the desired therapeutic effect of TRECONDI-based conditioning treatment, occurring in all patients. It is therefore recommended to monitor blood cell counts frequently until recovery of the haematopoietic system.
During phases of severe neutropenia (median duration of neutropenic period is 14-17.5 days in adults and 21-24 days in paediatric patients) the risk of infection is increased. Prophylactic or empiric anti-infective treatment (bacterial, viral, fungal) should therefore be considered. Growth factors (G-CSF, GM-CSF), platelet and/or red blood cell support should be given as indicated.

Secondary malignancies

Secondary malignancies are well-established complications in long-term survivors after alloHSCT. How much TRECONDI contributes to their occurrence is unknown. The possible risk of a second malignancy should be explained to the patient. On the basis of human data, TRECONDI has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen.

Mucositis

Oral mucositis (including high-grade severity) is a very common undesirable effect of TRECONDI-based conditioning followed by alloHSCT (see section “Undesirable effects”). Use of mucositis prophylaxis (e.g. topical antimicrobials, barrier protectants, ice and adequate oral hygiene) is recommended.

Vaccines

Concomitant use of live attenuated vaccines is not recommended.

Fertility

TRECONDI can impair fertility. Therefore, men treated with TRECONDI are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with TRECONDI. Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients (see section “Pregnancy and lactation”).

Paediatric population

Seizures

There have been isolated reports of seizures in infants (≤ 4 months of age) with primary immunodeficiencies after conditioning treatment with TRECONDI in combination with fludarabine or cyclophosphamide. Therefore, infants ≤ 4 months of age should be monitored for signs of neurological adverse reactions. Although it cannot be proven that TRECONDI was the cause, the use of appropriate prophylaxis for children younger than 1 year might be considered.

Respiratory, thoracic and mediastinal disorders

There was a significant association between age and respiratory toxicity in paediatric patients treated with TRECONDI-based conditioning.
Children younger than 1 year (mainly non-malignant diseases, especially immunodeficiencies) experienced more respiratory grade III/IV toxicity, possibly due to pulmonary infections already existing before the start of conditioning treatment.

Dermatitis diaper

Dermatitis diaper may occur in small children because of excretion of TRECONDI in the urine. Therefore, nappies should be changed frequently up to 6–8 hours after each infusion of TRECONDI.

Extravasation

TRECONDI is considered an irritant. Intravenous application should be performed using a safe technique. If extravasation is suspected, general safety measures should be implemented. No specific measure has been proven to be recommendable.

Interactions

No interaction of TRECONDI was observed in high-dose chemotherapy.
Detailed *in vitro* studies did not completely exclude potential interactions between high plasma concentrations of TRECONDI and CYP3A4, CYP2C19, or P-gp substrates. Therefore, medicinal products with a narrow therapeutic index (e.g. digoxin) that are substrates for CYP3A4, CYP2C19 or P-gp should not be given during treatment with TRECONDI.
The effect of TRECONDI on the pharmacokinetics of fludarabine is not known.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

Both sexually active men and women of childbearing potential have to use effective contraception during and up to 6 months after treatment.

PregnancyThere are no data from the use of TRECONDI in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section “Pre-clinical data”). TRECONDI is contraindicated during pregnancy (see section “Contraindications”).

Breastfeeding

It is unknown whether TRECONDI is excreted in human milk. Breastfeeding must be discontinued prior to treatment with TRECONDI.

Fertility

TRECONDI might impair fertility in men and women. Men should seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility.

As known for other alkylating conditioning agents TRECONDI can cause ovarian suppression and amenorrhoea with menopausal symptoms in pre-menopausal women.

Effects on ability to drive and use machines

TRECONDI has a moderate influence on the ability to drive and use machines. It is likely that certain adverse reactions of TRECONDI like nausea, vomiting or dizziness could affect these functions.

Undesirable effects

Summary of the safety profile

Profound myelosuppression/pancytopenia is the desired therapeutic effect of conditioning therapy and occurs in all patients.

The most commonly observed adverse reactions (adults/paediatric patients) after TRECONDI-based conditioning followed by alloHSCT include infections (13.1% /11.4%), gastrointestinal disorders (nausea [39.5%/30.7%], stomatitis [36.0%/69.3%], vomiting [22.5%/43.2%], diarrhoea [15.6%/33.0%], abdominal pain [10.4%/17%]), fatigue (15.1%/2.3%), febrile neutropenia (11.3%/1.1%), oedema (7.8%/0%), rash (7.2%/12.5%), and increases of alanine transaminase (ALT [5.1%/9.1%]), aspartate transaminase (AST [4.4%/8.0%]), gamma-glutamyl transferase (γGT [3.7%/2.3%]), and bilirubin (18.8%/5.7%).

Adults

The following of adverse reactions are derived from 5 clinical trials (including a total of 564 patients) where TRECONDI combined with fludarabine was investigated as conditioning treatment prior to alloHSCT in adult patients. TRECONDI was administered in a dose range of 10-14 g/m² BSA on 3 consecutive days.
In individual cases, adverse reactions have been added that were observed in other studies.

Adverse reactions are listed below, by system organ class and by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations*

Very common: Infections (bacterial, viral, fungal) (13.1%)
Common: Sepsis[a], C-reactive protein increased
Not known: Septic shock[c]

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)*

Not known: Treatment-related second malignancy

Blood and lymphatic system disorders*

Very common: Myelosuppression (100%), pancytopenia (100%), febrile neutropenia (11.3%)

Immune system disorders*

Common: Hypersensitivity

Metabolism and nutrition disorders

Common: Decreased appetite, weight loss, weight gain
Uncommon: Hyperglycaemia
Not known: Acidosis[b], glucose tolerance impaired, electrolyte imbalance

Psychiatric disorders

Common: Insomnia
Uncommon: Confusional state
Not known: Agitation

Nervous system disorders

Common: Headache, dizziness
Uncommon: Peripheral sensory neuropathy
Not known: Encephalopathy, intracranial haemorrhage, extrapyramidal disorder, syncope, paraesthesia

Eye disorders

Not known: Dry eye

Cardiac disorders*

Common: Cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia)
Not known: Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion

Vascular disorders
Common: Hypertension, flushing
Uncommon: Haematoma, hypotension
Not known: Embolism, haemorrhage

Respiratory, thoracic and mediastinal disorders
Common: Dyspnoea, epistaxis
Uncommon: Pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, cough, laryngeal pain, hiccups
Not known: Oropharyngeal pain, hypoxia, dysphonia

Gastrointestinal disorders*
Very common: Stomatitis/mucositis (36.0%), diarrhoea (15.6%), nausea (39.5%), vomiting (22.5%), abdominal pain (10.4%)
Common: Oral pain, gastritis, dyspepsia, constipation, dysphagia
Uncommon: Mouth haemorrhage, abdominal distension, oesophageal or gastrointestinal pain, dry mouth
Not known: Gastrointestinal haemorrhage, neutropenic colitis, oesophagitis, anal inflammation, mouth ulceration

Hepatobiliary disorders*
Very common: Bilirubin increased (18.8%)
Common: Transaminases (ALT/AST) and γGT increased, blood alkaline phosphatase increased,
Uncommon: Veno-occlusive liver disease, hepatotoxicity
Not known: Hepatic failure, hepatomegaly, hepatic pain

Skin and subcutaneous tissue disorders
Common: Maculo-papular rash, purpura, erythema, palmar-plantar erythrodysaesthesia syndrome, pruritus, alopecia
Uncommon: Erythema multiforme, dermatitis acneiform, rash, hyperhidrosis
Not known: Generalised erythema, dermatitis, skin necrosis or ulcer, skin hyperpigmentation (bronze pigmentation)[d], dry skin

Musculoskeletal and connective tissue disorders

Common: Pain in extremities, back pain, bone pain, arthralgia, myalgia

Not known: Muscular weakness

Renal and urinary disorders

Common: Acute kidney injury, haematuria

Not known: Renal failure, cystitis[c], dysuria, blood creatinine increased

General disorders and administration site conditions

Very common: Asthenic conditions (fatigue, asthenia, lethargy) (15.1%)

Common: Oedema, pyrexia[e], chills

Uncommon: Non-cardiac chest pain, pain

Not known: Injection site reaction, feeling cold, blood lactate dehydrogenase (LDH) increased

* See detailed sections below.
[a] Clinically or microbiologically documented infection with grade 3 or 4 neutropenia (absolute neutrophil count [ANC] < 1.0 x 10^9/L) and sepsis
[b] Acidosis might be a consequence of the release of methanesulfonic acid through activation/cleavage of TRECONDI in the plasma
[c] Case reports (> 2) after TRECONDI-based conditioning obtained from other sources
[d] Bronze pigmentation
[e] Fever in the absence of neutropenia where neutropenia is defined as ANC < 1.0 x 10^9/L

Description of selected adverse reactions (*):

Infections

The overall incidence of infections was 13.1% (74/564). The most frequent type was lung infection (12/74 [16.2%]). Pathogens included bacteria (e.g. *Staphylococcus*, *Enterococcus*, *Corynebacterium*), viruses (e.g. cytomegalovirus [CMV], Epstein-Barr virus [EBV], herpes) as well as fungi (e.g. candida). The infection rate was lowest in patients treated with the dose regimen of 10 g/m² of TRECONDI per day, from day -4 to -2 (7.7%).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

One of 564 adult patients (0.2%) developed a second malignancy (breast cancer). A few further cases of second malignancies after TRECONDI-based conditioning have been reported by other investigators. After long-term therapy with conventional doses of oral Treosulfan in patients with solid tumours acute myeloid leukaemia was observed in 1.4% of 553 patients.

Blood and lymphatic system disorders

Blood disorders were observed in 67 of 564 adult patients (11.9%). The most frequent adverse reaction was febrile neutropenia (11.3%). The lowest incidence was noted with the dose regimen of 10 g/m²/day, day -4 to -2 (4.1%).

The median (25%/75% percentiles) duration of neutropenia was 14 (12, 20) days with the 10 g/m² TRECONDI dose and 17.5 (14, 21) days with the 14 g/m² TRECONDI dose.

Cardiac disorders

Cardiac disorders were observed in 25 patients (4.4%). The most frequent adverse reactions were cardiac arrhythmias, e.g. atrial fibrillation (1.2%), sinus tachycardia (0.9%), supraventricular tachycardia (0.4%), and ventricular extrasystole (0.4%). Isolated cases of cardiac arrest, cardiac failure, and myocardial infarction occurred. The lowest frequency of cardiac disorders was seen with the dose regimen of 10 g/m²/day, day -4 to -2 (2.7%).

Gastrointestinal disorders

Gastrointestinal disorders were observed in 357 patients (63.3%). The most frequent adverse reactions reported were nausea (39.5%), stomatitis (36.0%), vomiting (22.5%), diarrhoea (15.6%), and abdominal pain (10.4%). The lowest frequencies of these adverse reactions were seen with the dose regimen of 10 g/m² per day, day -4 to -2 (20.4%, 30.3%, 13.1%, 5.0%, and 5.5% respectively).

Hepatobiliary disorders

The overall incidence of veno-occlusive liver disease (VOD) was 0.9% (5/564). VOD occurred only with the dose regimen of 14 g/m²/day TRECONDI. None of these cases were fatal or life-threatening.

Paediatric population

The following adverse reactions are derived from two clinical trials (including a total of 88 patients; median age 8 years [range 0–17 years]) where TRECONDI combined with fludarabine (and mostly with additional thiotepa) was administered as conditioning treatment prior to alloHSCT in paediatric patients with malignant or non-malignant diseases. TRECONDI was administered in a dose range of 10-14 g/m² BSA on three consecutive days.
Adverse reactions are listed below, by system organ class and by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Infections and infestations*

Very common: Infections (bacterial, viral, fungal) (11.4%)

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)*

Not known: Treatment-related second malignancy[a]

Blood and lymphatic system disorders*

Very common: Myelosuppression (100%), pancytopenia (100%)

Not known: Fenrile neutropenia

Metabolism and nutrition disorders

Not known: Alkalosis, electrolyte imbalance, hypomagnesaemia

Nervous system disorders*

Not known: Headache, paraesthesia, seizure

Eye disorders

Not known: Conjunctival haemorrhage, dry eye

Vascular disorders

Not known: Capillary leak syndrome, hypertension, hypotension

Respiratory, thoracic and mediastinal disorders

Common: Oropharyngeal pain, epistaxis

Not known: Hypoxia

Gastrointestinal disorders*

Very common: Stomatitis/mucositis (69.3%), diarrhoea (33.0%), nausea (30.7%), vomiting (43.2%), abdominal pain (17%)

Common: Dysphagia, oral pain

Not known: Neutropenic colitis, anal inflammation, dyspepsia, proctitis, gastrointestinal pain, constipation

Hepatobiliary disorders

Common: Transaminases (ALT/AST) increased, bilirubin increased

Not known: Veno occlusive liver disease, hepatomegaly, hepatotoxicity, γGT increased

Skin and subcutaneous tissue disorders

Very common: Pruritus (11.4 %)

Common: Dermatitis exfoliative, maculo-papular rash, rash, erythema, pain of skin, skin hyperpigmentation (bronze pigmentation)[b], alopecia

Not known: Skin ulcer, erythema multiforme, urticaria, dermatitis bullous, dermatitis acneiform, palmar plantar erythrodysaesthesia syndrome, dermatitis diaper[a]

Musculoskeletal and connective tissue disorders

Not known: Pain in extremities

Renal and urinary disorders

Not known: Acute kidney injury, renal failure, noninfective cystitis

Reproductive system and breast disorders

Not known: Scrotal erythema

General disorders and administration site conditions

Very common: Pyrexia (14.8%)[c]

Not known: Chills, fatigue, pain

* See detailed sections below.
[c] Case reports (> 1) after TRECONDI-based conditioning obtained from other sources
[b] Bronze pigmentation
[e] Fever in the absence of neutropenia where neutropenia is defined as ANC < 1.0 x 10^9/L

Description of selected adverse reactions (*)

Infections

The overall incidence of infections in 88 paediatric patients was 11.4% (10/88) and thus comparable to that seen in adults. The frequency was higher in the paediatric age group 12–17 years (6/35 [17.1%]) compared to younger children (4/53 [7.5%]).

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Five cases of a second malignancy (myelodysplastic syndrome, acute lymphoblastic leukaemia, Ewing's sarcoma) were reported by other investigators after TRECONDI-based conditioning. All five paediatric patients received alloHSCT for primary immunodeficiencies, i.e. diseases with an increased risk for neoplasias per se.

Blood and lymphatic system disorders

The median (25%/75% percentiles) duration of neutropenia was 21 (16, 26) days in paediatric patients with malignant diseases and 24 (17, 26) days in patients with non-malignant disorders.

Nervous system disorders

Seizure in the context of an encephalitis infection was reported in one of the 88 paediatric patients. A report from an investigator-initiated trial performed in children with primary immunodeficiencies lists four cases of seizures occurring after other TRECONDI-based conditioning regimens (see section "Undesirable effects")

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or severe adverse reaction via the EIViS (Electronic Vigilance System) online portal. You can find more information on this under www.swissmedic.ch.

Overdose

Signs and symptoms

The principal toxic effect of TRECONDI is profound myeloablation and pancytopenia. In addition, acidosis, skin toxicity, nausea, vomiting and gastritis may occur. In the absence of haematopoietic stem cell transplantation, the recommended dose of TRECONDI would constitute an overdose.

Treatment

No specific antidote of TRECONDI overdose is known. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

Properties/effects

ATC code

L91AB02
Pharmacotherapeutic group: Antineoplastic agents, alkylating agents

Mechanism of action/pharmacodynamics

TRECONDI is a prodrug of a bifunctional alkylating agent with cytotoxic activity to haematopoietic precursor cells. The activity of TRECONDI is due to the spontaneous conversion into a mono-epoxide intermediate and L-diepoxybutan (see section "Pharmacokinetics").
The epoxides formed alkylate nucleophilic centres of deoxyribonucleic acid (DNA) and are able to induce DNA cross-links which are considered responsible for the stem cell depleting and antineoplastic effects.

Clinical efficacy

In the pivotal phase III trial (MC-FludT.14/L Trial II), adult patients with acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) and increased risk for standard conditioning therapies because of higher age (≥ 50 years) or comorbidities (haematopoietic cell transplantation comorbidity index [HCT-CI] score > 2) were randomised to receive a conditioning regimen with 3 × 10 g/m² TRECONDI combined with fludarabine (FT_{10}; n = 220) or a regimen of intravenous busulfan (total dose 6.4 mg/kg) combined with fludarabine (FB2; n = 240), followed by alloHSCT. 64% of patients had AML and 36% MDS. The median age of patients was 60 years (range 31–70 years); 25% of patients were older than 65 years.
The primary endpoint of this study was event-free survival (EFS) after 2 years. Events were defined as relapse of disease, graft failure or death (whatever occurred first). Non-inferiority of FT_{10} versus the reference FB2 was statistically proven. After 2 years, 30.9% of patients in the treosulfan arm had an EFS event vs. 41.7% in the busulfan arm. The EFS after 2 years was 64% in the treosulfan arm vs. 50.4% in the busulfan arm, with a hazard ratio of 0.65 (CI 95% 0.47, 0.90).
After 24 months, the overall survival in the treosulfan arm was 71.3% vs. 56.4% in the busulfan arm. The cumulative incidence of acute GvHD was 52.1% (grade III-IV: 6.4%) in the treosulfan arm and 58.8% (grade III-IV: 9.6%) in the busulfan arm. Chronic GvHD (up to 2 years after the alloHSCT) was observed in 60.1% of patients in the treosulfan arm and in 60.7% in the busulfan arm.

Analyses of EFS at 2 years for various pre-defined subgroups (donor type, risk group, disease, age group, HCT-CI score, remission status at study entry, and various combinations of these parameters) were in favour of the treosulfan regimen (hazard ratio [HR] of FT_{10} *vs.* FB2 < 1), with only one exception (risk group I of MDS patients; HR 1.14 [95% CI 0.48, 2.63]).

There is limited information available on treosulfan-based conditioning (FT_{14} regimen ± thiotepa; see section “Posology and administration”) in adult patients with non-malignant disorders (NMD). The main indications for an alloHSCT with treosulfan conditioning in adult NMD patients are haemoglobinopathies (e.g. sickle cell disease, thalassaemia major [TM]), primary immune deficiency, hemophagocytic disorder, immune dysregulatory disorder and bone marrow failure).

In one study, 31 NMD patients were treated with the FT_{14} regimen plus anti-thymocyte globulin. The age of the patients ranged from 0.4 to 30.5 years, and 29% had HCT-CI scores > 2. All patients engrafted, with a median time to neutrophil engraftment of 21 (range, 12–46) days. The 2-year projected overall survival was 90%. Complete disease responses were observed in 28 patients (90%), as measured by clinical symptoms and laboratory assays.[1]

[1] Burroughs LM et al., Biology of Blood and Marrow Transplantation 2014; 20(12):1996-2003

An Italian group treated 60 TM patients (age range 1-37 years; including 12 adults) with the FT 14 plus thiotepa regimen. All patients engrafted except one, who died on day +11. The median time to neutrophil and platelet recovery was 20 days. With a median follow-up of 36 months (range, 4-73), the 5-year overall survival probability was 93% (95% CI 83-97%). No difference in terms of outcome was observed between children and adults.[2]

A retrospective comparison of treosulfan-based (n = 16) versus busulfan-based (n = 81) conditioning in adult patients revealed quite comparable survival rates (70.3 ± 15.1% vs. 69.3 ± 5.5%), while risk for acute GvHD was lower in the treosulfan group (odds ratio 0.28; 95% CI 0.12 0.67; P = 0.004).[3].

Paediatric population

The efficacy and safety of treosulfan-based conditioning was evaluated in 70 patients with acute lymphoblastic leukaemia (ALL), AML, MDS, or juvenile myelomonocytic leukaemia (JMML) who received a conditioning regimen with treosulfan and fludarabine with (n = 65) or without (n = 5) thiotepa (see section “Posology and administration”). A total of 37 patients (52.9%) were younger than 12 years.
No patient experienced a primary graft failure but one patient with ALL experienced a secondary graft failure. The incidence of complete donor-type chimerism was 94.2% (90% CI 87.2-98.0%) at day +28 visit, 91.3% (90% CI 83.6-96.1%) at day +100 visit and 91.2% (90% CI 82.4-96.5%) at month 12 visit. The overall survival at 12 months is 91.4% (90% CI 83.9-95.5%). A total of 7 of the 70 patients (10.0%) died, two patients because of relapse/progression, three patients transplant-related and two further patients for other reasons. The freedom from transplant-related mortality until day +100 after HSCT (primary endpoint) is 98.6% (90% CI 93.4–99.7%). Transplant related mortality at 12 months is 2.9% (90% CI 0.9 – 8.9%). Eleven patients had a relapse/progression. The cumulative incidence of relapse/progression is 15.7% (90% CI 8.6-22.9%) at month +12.

The European Medicines Agency has deferred the obligation to submit the results of a study with treosulfan-based conditioning in paediatric patients with non-malignant diseases (see section “Posology and administration” for information on paediatric use).

Pharmacokinetics

Treosulfan is a prodrug that is spontaneously converted under physiological conditions (pH 7.4; 37 °C) into a monoepoxide intermediate and L-diepoxybutane with a half-life of 2.2 hours.

[2] Bernardo ME et al.; Blood 2012; 120(2):473-6.

[3] Caocci G et al.; American Journal of Hematology 2017; 92(12):1303-1310

Resorption

After intravenous administration, peak plasma levels are reached at the end of the infusion time. Maximum plasma levels (mean ± SD) in adult patients after a 2-hour intravenous infusion of 10, 12, or 14 g/m² treosulfan were 306 ± 94 µg/mL, 461 ± 102 µg/mL, and 494 ± 126 µg/mL, respectively.

Distribution

Treosulfan is rapidly distributed in the body; however, its penetration through the blood-brain-barrier is quite limited (see section “Pre-clinical data”). The volume of distribution in adult patients is about 20–30 litres. No dose accumulation with the recommended daily treatment on three consecutive days was observed.
Treosulfan does not bind to plasma proteins.

Biotransformation

Under physiological conditions (pH 7.4, temperature 37 °C), the pharmacologically inactive treosulfan is converted spontaneously (non-enzymatically) into the active monoepoxide intermediate (S,S-EBDM = (2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate) and finally to L-diepoxibutane (S,S-DEB = (2S,3S)-1,2:3,4-diepoxybutane).
At concentrations up to 100 µM, treosulfan has no unequivocal effect on CYP1A2, 2C9, 2C19, 2D6, or 3A4 activities *in vitro*. Therefore, treosulfan is unlikely to participate in, or contribute to, potential CYP450-mediated interactions *in vivo*.

Elimination

Plasma concentrations of treosulfan decline exponentially and are best described by a first order elimination process.
The terminal half-life ($T_{1/2ß}$) of intravenously administered treosulfan (up to 47 g/m²) is approximately 2 hours. Approximately 25–40% of the treosulfan dose is excreted unchanged with the urine within 24 hours, nearly 90% of which within the first 6 hours after administration.

Linearity/non-linearity

Regression analysis of the area under the curve ($AUC_{0-\infty}$) versus treosulfan dose indicated a linear correlation.

Kinetics of special populations

Renal and hepatic impairment

No pharmacokinetic studies with treosulfan were done in patients with severe renal or hepatic impairment, because such patients are generally excluded from alloHSCT. About 25–40% of treosulfan is excreted in urine. An influence of renal function on renal clearance of treosulfan was not observed.

Paediatric population

Conventional dose calculation simply based on BSA results in a significantly higher exposure (AUC) of smaller children and infants with low BSA compared to adolescents or adults. Therefore, dosing of treosulfan in paediatric patients has to be adapted to the BSA (see section “Posology and administration”).
Mean apparent terminal half-life of treosulfan was comparable between the different age groups and ranged between 1.3 and 1.6 hours.

Preclinical data

Due to its alkylating mechanism of action treosulfan is characterised as a genotoxic compound with carcinogenic potential. Specific reproductive and developmental toxicity studies on treosulfan in animals were not conducted. However, during chronic toxicity tests in rats spermatogenesis and ovarian function were significantly affected. Published literature data report on gonadotoxicity of treosulfan in pre-pubertal and pubertal male and female mice.
Published data concerning treatment of mice and rats with L-diepoxibutane (the alkylating transformation product of treosulfan) revealed impairment of fertility, uterine-ovarian and sperm development.

Juvenile animal studies

In juvenile rat toxicity studies treosulfan induced slight retardation of physical development and a slightly delayed time-point of vaginal opening in females. A very low penetration of blood-brain-barrier by treosulfan was observed in rats. The treosulfan concentrations in brain tissue were 95%–98% lower than in plasma. However, an approximately 3-fold higher exposure in brain tissue of juvenile rats in comparison to young adults was found.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

This medicinal product may only be used until the date given after “EXP” on the container.

Shelf life after opening

After reconstitution with sodium chloride 4.5 mg/mL (0.45%) solution, chemical and physical stability has been demonstrated for 2 days at 25 °C.

The preparation contains no preservatives. After reconstitution with sodium chloride 4.5 mg/mL (0.45%) solution, chemical and physical in-use stability has been demonstrated for 2 days at 25 °C. From a microbiological point of view, the reconstituted product should be used immediately after opening.
If not used immediately, in-use storage times and conditions are the responsibility of the user. Do not store in a refrigerator (2 °C-8 °C) as this might cause precipitation.

Special precautions for storage

Store in the original packaging, below 30 °C. Store out of the reach of children.

Precautions for handling

As with all cytotoxic substances, appropriate precautions should be taken when handling treosulfan.

Trained personnel should reconstitute the medicinal product. When handling treosulfan, inhalation, skin contact or contact with mucous membranes should be avoided (the use of adequate protective disposable gloves, goggles, gown and mask is recommended). Contaminated body parts should be carefully rinsed with water and soap. The eyes should be rinsed with sodium chloride 9 mg/mL (0.9%) solution. If possible it is recommended to work on a special safety workbench, equipped with laminar flow, with liquid-impermeable, absorbent disposable foil. Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic medicinal products. Use Luer-lock fittings on all syringes and sets. Large bore needles are recommended to minimise pressure and the possible formation of aerosols. The latter may also be reduced by the use of a venting needle.
Pregnant personnel should be excluded from handling cytotoxics.

<u>Instructions for reconstitution of treosulfan:</u>

1. Treosulfan is reconstituted in its original glass container. Reconstituted solutions of treosulfan may be combined into a larger glass vial, PVC bag or PE bag.
2. To avoid solubility problems, warm the solvent, sodium chloride 4.5 mg/mL (0.45%) solution, to 25 °C - 30 °C (not higher), for example by using a water bath.
3. Remove the treosulfan powder carefully from the inner surface of the vial by shaking. This procedure is very important, because moistening of powder that sticks to the surface results in caking. If this happens, vigorously shake the vial to redissolve the cake.
4. Reconstitute each vial of Trecondi containing 1 g treosulfan in 20 mL of pre-warmed (maximum 30 °C) sodium chloride 4.5 mg/mL (0.45%) solution by shaking.
Reconstitute each vial of Trecondi containing 5 g treosulfan in 100 mL of pre warmed (maximum 30 °C) sodium chloride 4.5 mg/mL (0.45%) solution by shaking.

For preparation of sodium chloride 4.5 mg/mL (0.45%) solution equivalent volumes of sodium chloride 9 mg/mL (0.9%) solution and water for injections can be mixed.

The reconstituted solution contains 50 mg treosulfan per mL and appears as a clear colourless solution. Solutions showing any sign of precipitation should not be used.

Treosulfan has mutagenic and carcinogenic potential. Remnants of the medicinal product as well as all materials that have been used for reconstitution and administration must be destroyed according to standard procedures applicable to antineoplastic agents, with due regard to current laws related to the disposal of hazardous waste.

Marketing authorisation number

67775 (Swissmedic)

Pack sizes

1 g, 1 vial (A)
1 g, 5 vials (A)
5 g, 1 vial (A)
5 g, 5 vials (A)

Marketing authorisation holder

OpoPharma AG, Rümlang

Date of revision of the text

August 2020