swissmedic

Date: 17 April 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Trecondi

International non-proprietary name:	treosulfan
Pharmaceutical form:	Powder for solution for infusion
Dosage strength(s):	5 g and 1 g
Route(s) of administration:	intravenous use
Marketing authorisation holder:	IDEOGEN AG
Marketing authorisation no.:	67775
Decision and decision date:	extension of therapeutic indication approved on 17 January 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
AlloHSCT	Allogeneic haematopoietic stem cell transplantation
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event

TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

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 and in paediatric patients older than one month with malignant and non-malignant diseases.

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	22 December 2023
Formal control completed	25 January 2024
List of Questions (LoQ)	28 May 2024
Response to LoQ	19 July 2024
Preliminary decision	1 October 2024
Response to preliminary decision	22 November 2024
Final decision	17 January 2025
Decision	approval

3 Medical context

Allogeneic stem cell transplantation (alloHSCT) is a potentially curative option for malignant diseases such as leukaemia, myelodysplastic syndromes, and lymphomas, as well as several non-malignant diseases such as primary immunodeficiencies, metabolic disorders, haemoglobinopathies and bone marrow failure syndromes.

AlloHSCT patients are prepared with conditioning chemotherapy (CTX) regimens. The various regimens used in clinical practice differ in their intensity and are currently divided into 3 categories: myeloablative conditioning (MAC), reduced intensity conditioning (RIC) and non-myeloablative conditioning (NMA). MAC causes irreversible cytopenia and requires haematopoietic stem cell (HSC) support. NMA causes minimal cytopenia and can also be given without HSC support. RIC causes variable cytopenia, and HSC support is recommended, although cytopenia may not be irreversible.

In paediatric patients, selection of conditioning regimens depends on the disease (malignant or non-malignant), disease status, and local preferences. RIC is less frequently used than in adults because children typically have fewer comorbidities precluding MAC. In addition, children with non-malignant diseases like haemoglobinopathies or metabolic disorders require an intensive MAC to ensure successful engraftment.

However, transplant-related morbidity and mortality limit the use of alloHSCT for many patients. There is a high unmet medical need for new conditioning regimens that support the ultimate goal to achieve improved OS and/or quality of life. Ideally, such a regimen should have sufficient stem cell toxicity, immunosuppressive potential and – in the case of malignant disorders – high anti-tumour activity so as to reduce the risk of disease relapse. At the same time, it should have low short- and long-term treatment-related (organ) toxicity.

4 Nonclinical aspects

The available nonclinical data are sufficient to support the requested extension of the indication. From the nonclinical point of view, there are no objections to the approval of the extension of the requested indication.

5 Clinical aspects

The evaluation of the clinical (pharmacology) data of this application has been carried out in reliance on the previous regulatory decision by the EMA. The available CHMP assessment report and the EU Summary of Product Characteristics were used as a basis for the clinical (pharmacology) evaluation (see document links below).

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see the approved Information for healthcare professionals in the Appendix of this report.

Links

- CHMP assessment report, Trecondi, dated 26 January 2023 (Procedure No. EMEA/H/C/004751/II/0014): https://www.ema.europa.eu/en/documents/variation-report/trecondi-h-c-004751-ii-0014-epar-assessment-report-variation_en.pdf
- EU Summary of Product Characteristics TRECONDI: https://www.ema.europa.eu/en/documents/product-information/trecondi-epar-product-information_en.pdf

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for 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 valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

TRECONDI

Composition

Active ingredients

Treosulfan

Auxiliary materials

None

Dosage form and amount of active substance per unit

White, crystalline powder for the preparation of a solution for infusion.

TRECONDI 1 g powder for the preparation of a solution for infusion
One vial of powder contains 1 g treosulfan.
TRECONDI 5 g powder for the preparation of a solution for infusion
One vial of powder contains 5 g treosulfan.

After reconstitution, 1 ml infusion solution contains 50 mg treosulfan.

Indications/possible applications

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

Dosage/application

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

Adults with malignant diseases

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 TRECONDI dose 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 (FT10 regimen).

Adults with non-malignant diseases

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 TRECONDI dose 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 (FT14 regimen).
- 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).

Special dosing instructions

Elderly patients
No patients over 70 years of age were included. No dose adjustment is necessary in any subgroup of elderly patients.

Kidney and liver dysfunction
No dose adjustment is required for mild or moderate impairment, but TRECONDI is contraindicated in patients with severe impairment (see section "Contraindications").

Paediatric patients older than 1 month
TRECONDI is given in combination with fludarabine with thiotepa (intensified treatment regimen; FT10-14TT regimen) or without thiotepa (FT10-14 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 TRECONDI dose is 30–42 g/m²;
- The dose of TRECONDI should be adapted to the patient’s BSA as follows (see section "Pharmacokinetics"):

Body surface area (m^2)	TRECONDI dose (g/m^2)
< 0.4	10.0
≥ 0.4 to< 0.9	12.0
≥ 0.9	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).

TRECONDI is not authorized for use in children under 1 month of age.

Method of administration

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

Precautionary measures before / during handling or before / during use of the medicinal product

When handling TRECONDI, inhalation, skin contact or contact with mucous membranes should be avoided. Pregnant personnel must 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, breastfeeding")
- 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 (see "*Blood and lymphatic system disorders*" under "*Undesirable effects*"). It is therefore recommended to monitor blood cell counts commonly until recovery of the haematopoietic system.
During phases of severe neutropenia (median duration of neutropenic period is 14–17.5 days in adults and 20-22 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 allo-HSCT (see “Undesirable effects”). Use of mucositis prophylaxis (e.g. topical antimicrobials, barrier protectants, ice and adequate oral hygiene) is recommended.

Vaccinations

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, breastfeeding").

<u>Paediatric population</u>

Seizures

There have been isolated reports of seizures in infants (≤ 4 months of age) with primary immunodeficiency 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 proved that TRECONDI was the cause, the use of clonazepam 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 one year (mainly non-malignant diseases, especially immunodeficiency) 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 commonly 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 interactions with TRECONDI were observed with high-dose chemotherapy.

Detailed *in vitro* studies did not completely exclude potential interactions between high plasma concentrations of TRECONDI and CYP3A4, CYP2C19, or P-glycoprotein (P-gp) substrates.

TRECONDI does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 using testosterone as substrate. However, using midazolam as the substrate, TRECONDI was a reversible inhibitor for CYP2C19 and 3A4. TRECONDI does not inhibit substrate transport via various transport proteins with the exception of P-gp and MATE2 at very high concentrations.

Physiologically based pharmacokinetic modelling predicted a weak (AUC ratio ≥ 1.25 and < 2) to moderate (AUC ratio ≥ 2 and < 5) interaction for CYP3A4, a weak interaction for CYP2C19, and a negligible (AUC ratio < 1.25) interaction for P-gp. Therefore, medicinal products with a low therapeutic index (e.g., Tacrolimus), that are substrates for CYP3A4 or CYP2C19, should not be given during therapy with TRECONDI.

Considering overall timing of treatments and the respective pharmacokinetic properties of concomitantly used medicinal products (e.g., half-life), the interaction potential can be reduced to “no interaction” (AUC ratio < 1.25), if all concomitantly used medicinal products are dosed 2 hours before or 8 hours after the 2-hour intravenous infusion of TRECONDI.

The effect of TRECONDI on the pharmacokinetics of fludarabine is not known.

Pregnancy, breastfeeding

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.

Pregnancy

There are no data from the use of TRECONDI in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see Section “Preclinical data“). TRECONDI is contraindicated during pregnancy (see section «Contraindications»).

Breast-feeding

It is unknown whether TRECONDI is excreted in human milk. Breast-feeding should be discontinued during treatment with TRECONDI.

Fertility

TRECONDI might impair fertility in men and women (see Section “Warnings and Precautions”). 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.

Effect on the ability to drive and operate machinery

TRECONDI has moderate influence on the ability to drive and use machines. It is likely that certain adverse reactions of TREDONDI 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 allo-HSCT include gastrointestinal disorders (stomatitis [36.4%/66.1%], vomiting [22.5%/42.1%], nausea [38.0%/26.4%], diarrhoea [14.4%/33.1%], abdominal pain

[9.6%/17.4%]), hepatotoxicity (0.3%/26.4%), increase of bilirubin (17.1%/6.6%), Weakness (fatigue, asthenia, lethargy) (14.7%/1.7%), rash including maculopapular rash (5.9%/13.2%), pyrexia (4.1%/13.2%), overall infections (including sepsis) (10.1%/11.6%), increase of alanine transaminase (ALT [4.9%/10.7%]), pruritus (2.8%/10.7%), febrile neutropenia (10.1%/1.7%), alopecia (1.5%/9.9%), decreased appetite (8.0%/0.8%) and increase of aspartate transaminase (AST [4.1%/6.6%]) and oedema (6.2%/0.8%).

Adults

The following adverse reactions are derived from 5 clinical trials (including a total of 613 patients) where TRECONDI combined with fludarabine was investigated as conditioning treatment prior to allo-HSCT in adult patients. TRECONDI was administered in a dose range of 10–14 g/m² BSA on 3 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*

Common: Infections (bacterial, viral, fungal) (all grades: 8.2%, grade 3 or higher: 4.2%), Sepsis[a] (all grades: 2.0%, grade 3 or higher: 2.0%), C-reactive protein increased (all grades: 1.6%, grade 3 or higher: 0.7%)
Not known: Septic shock

Neoplasms benign, malignant and unspecified (including cysts and polyps)*

Not known: Treatment-related second malignancy

Blood and lymphatic system disorders*

Very common: myelosuppression (all grades: 100%), pancytopenia (all grades: 100%), febrile neutropenia (all grades: 10.1%, grade 3 or higher: 10.0%)

Immune system disorders

Common: hypersensitivity (all grades: 1.1%)

Metabolism and nutrition disorders

Common: decreased appetite (all grades: 8.0%, grade 3 or higher: 1.6%), weight increased (all grades: 1.8%), weight decreased (all grades: 1.1%)
Uncommon: glucose tolerance impaired including hyperglycaemia and hypoglycaemia (all grades: 0.5%, grade 3 or higher: 0.5%), acidosis[b] (all grades: 0.3%, grade 3 or higher: 0.3%)

Psychiatric disorders

Common: insomnia (all grades: 1.0%)

Uncommon: confusional state (all grades: 0.8%, grade 3 or higher: 0.2%)

Nervous system disorders

Common: headache (all grades: 4.9%, grade 3 or higher: 0.5%), dizziness (all grades: 2.9%)

Uncommon: peripheral sensory neuropathy (all grades: 0.7%, grade 3 or higher: 0.2%), intracranial haemorrhage (all grades: 0.5%, grade 3 or higher: 0.3%), encephalopathy (all grades: 0.2%, grade 3 or higher: 0.2%), extrapyramidal disorder (all grades: 0.3%), syncope (all grades: 0.3%, grade 3 or higher: 0.3%), paraesthesia (all grades: 0.3%)

Eye disorders

Not known: Dry eye

Ear and labyrinth disorders

Uncommon: Vertigo (all grades: 0.5%)

Cardiac disorders*

Common: cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia) (all grades: 3.6%, grade 3 or higher: 0.7%)

Uncommon: cardiac arrest (all grades: 0.2%, grade 3 or higher: 0.2%), cardiac failure (all grades: 0.2%), myocardial infarction (all grades: 0.2%, grade 3 or higher: 0.2%), pericardial effusion (all grades: 0.2%)

Vascular disorders

Common: hypertension (all grades: 2.8%, grade 3 or higher: 0.7%), hypotension (all grades: 1.1%), flushing (all grades: 1.0%)

Uncommon: haematoma (all grades: 0.7%), embolism (all grades: 0.2%, grade 3 or higher: 0.2%)

Respiratory, thoracic and mediastinal disorders

Common: Epistaxis (all grades: 4.2%, grade 3 or higher: 0.2%), dyspnoea (all grades: 1.5%, grade 3 or higher: 0.5%)

Uncommon: pharyngeal or laryngeal inflammation (all grades: 0.8%, grade 3 or higher: 0.3%), hiccups (all grades: 0.8%), pleural effusion (all grades: 0.7%, grade 3 or higher: 0.3%), pneumonitis (all grades: 0.5%, grade 3 or higher: 0.2%), oropharyngeal pain (all grades: 0.5%), laryngeal pain (all grades: 0.3%), cough (all grades: 0.3%), dysphonia (all grades: 0.3%)

Gastrointestinal disorders*

Very common: nausea (all grades: 38.0%, grade 3 or higher: 3.8%), stomatitis/mucositis (all grades: 36.4%, grade 3 or higher: 5.7%), vomiting (all grades: 22.5%, grade 3 or higher: 0.5%), diarrhoea (all grades: 14.4%, grade 3 or higher: 1.6%)

Common: Abdominal pain (all grades: 9.6%, grade 3 or higher: 1.5%), constipation (all grades: 2.9%), dyspepsia (all grades: 2.6%), dysphagia (all grades: 1.5%, grade 3 or higher: 0.7%), oral pain (all grades: 1.1%, grade 3 or higher: 0.5%), gastritis (all grades: 1.0%), Oesophageal or gastrointestinal pain (all grades: 1.0%, grade 3 or higher: 0.7%)

Uncommon: Abdominal distension (all grades: 0.8%), dry mouth (all grades: 0.8%), mouth haemorrhage (all grades: 0.7%, grade 3 or higher: 0.2%), gastric haemorrhage (all grades: 0.2%, grade 3 or higher: 0.2%), neutrophilic colitis (all grades: 0.2%, grade 3 or higher: 0.2%), oesophagitis (all grades: 0.3%), anal inflammation (all grades: 0.3%)

Hepatobiliary disorders*

Very common: bilirubin increased (all grades: 17.1%, grade 3 or higher: 3.9%)

Common: Transaminases (ALT/AST) (all grades: 9.0%, grade 3 or higher: 5.9%) and γGT (all grades: 2.9%, grade 3 or higher: 2.0%) increased

Uncommon: veno-occlusive liver disease (all grades: 0.8%, grade 3 or higher: 0.2%), blood alkaline phosphatase increased (all grades: 0.7%, grade 3 or higher: 0.3%), hepatotoxicity (all grades: 0.3%, grade 3 or higher: 0.2%), hepatomegaly (all grades: 0.3%)

Skin and subcutaneous tissue disorders

Common: Maculo-papular rash (all grades: 5.2%, grade 3 or higher: 0.7%), purpura (all grades: 3.4%, grade 3 or higher: 0.2%), erythema (all grades: 3.1%, grade 3 or higher: 0.2%), pruritus (all grades: 2.8%), alopecia (all grades: 1.5%), palmar-plantar erythrodysaesthesia syndrome (all grades: 1.3%)

Uncommon: erythema multiforme (all grades: 0.7%), dermatitis acneiform (all grades: 0.7%), Rash (all grades: 0.7%), dry skin (all grades: 0.5%), skin necrosis (all grades: 0.2%, grade 3 or higher: 0.2%) or skin ulcer (all grades: 0.2%), dermatitis (all grades: 0.3%, grade 3 or higher: 0.2%), skin hyperpigmentation (all grades: 0.3%)[d]

Musculoskeletal and connective tissue disorders

Common: pain in extremity (all grades: 1.3%, grade 3 or higher: 0.2%), back pain (all grades: 1.3%), bone pain (all grades: 1.3%, grade 3 or higher: 0.2%), arthralgia (all grades: 1.0%, grade 3 or higher: 0.2 %)

Uncommon: Myalgia (all grades: 0.8%)

Renal und urinary disorders

Common: haematuria (all grades: 1.5%, grade 3 or higher: 0.3%), acute kidney injury (all grades: 1.3%, grade 3 or higher: 0.7%)
Uncommon: urinary tract pain (all grades: 0.5%), renal failure (all grades: 0.2%), dysuria (all grades: 0.3%)
Not known: haemorrhagic cystitis[c]

General disorders and administration site conditions

Very common: asthenic conditions (fatigue, asthenia, lethargy) (all grades: 14.7%, grade 3 or higher: 1.1%)
Common: oedema (all grades: 6.2%), pyrexia[s] (all grades: 4.1%, grade 3 or higher: 0.2%), chills (all grades: 1.3%)
Uncommon: non-cardiac chest pain (all grades: 0.7%, grade 3 or higher: 0.2%), pain (all grades: 0.5%)

Investigations

Uncommon: blood lactate dehydrogenase (LDH) increased (all grades: 0.3%)

* See detailed sections below.
[a] Clinically or microbiologically documented infection with grade 3 or 4 neutropenia (absolute neutrophil count [ANC] < 1.0 x 109/L) and sepsis
[b] Acidosis might be a consequence of the release of methanesulfonic acid through TRECONDI activation/cleavage 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 109/L

Description of selected side effects

Overall infections

The overall incidence of infections was 10.1% (62/613). This includes the incidence for bacterial, viral and fungal infections (50/613; 8.1%) and for overall sepsis (12/613; 2%). The most common type of infection was lung infection (10/62 [16.1%]). Pathogens included bacteria (e.g. *Staphylococcus*, *Enterococcus*, *Corynebacterium*), viruses (e.g. cytomegalovirus [CMV], Epstein-Barr virus [EBV]) as well as fungi (e.g. candida). Overall sepsis includes sepsis (9/613; 1.5%), staphylococcal sepsis (2/613; 0.3%) and enterococcal sepsis (1/613; 0.2%). 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 (8.1%).

Neoplasms benign, malignant and unspecified (including cysts and polyps)

One of 613 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 TRECONDI 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 62 of 613 adult patients (10.1%). The most common adverse reaction was febrile neutropenia (10.1%). The lowest incidence was noted with the dose regimen of 10 g/m²/day, day -4 to -2 (4.4%).

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 21 patients (3.4%). The most common adverse reactions were cardiac arrhythmias, e.g. atrial fibrillation (1.0%), sinus tachycardia (0.8%), supraventricular tachycardia (0.3%), and ventricular extrasystole (0.3%). 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 (2.6%).

Gastrointestinal disorders

Gastrointestinal disorders were observed in 379 patients (61.8%). The most frequent adverse reactions reported were nausea (38.0%), stomatitis (36.4%), vomiting (22.5%), diarrhoea (14.4%), and abdominal pain (9.6%). The lowest frequencies of these adverse reactions were seen with the dose regimen of 10 g/m² per day, day -4 to -2 (21.5%, 32.2%, 14.8%, 5.9%, and 6.7% respectively).

Hepatobiliary disorders

The overall incidence of veno-occlusive liver disease (VOD) was 0.8% (5/613). 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 adverse reactions are derived from two clinical trials (including a total of 121 patients; median age 7 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. Treosulfan 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) (all grades: 11.6%, grade 3 or higher: 5.0%)

Common: C-reactive protein increased (all grades: 2.5%, grade 3 or higher: 1.7%)

Neoplasms benign, malignant and unspecified (including cysts and polyps)*

Not known (also grade 3 or higher): Treatment-related secondary malignancy[a]

Blood and lymphatic system disorders*

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

Common: febrile neutropenia (all grades: 1.7 %, grade 3 or higher: 1.7%)

Metabolism and nutrition disorders

Uncommon: alkalosis (all grades: 0.8%, grade 3 or higher: 0.8%), electrolyte imbalance (all grades: 0.8%), hypomagnesaemia (all grades: 0.8%), decreased appetite (all grades: 0.8%)

Nervous system disorders*

Common: headache (all grades: 2.5%), paraesthesia (all grades: 1.7%, grade 3 or higher: 0.8%)

Uncommon: seizure (all grades: 0.8%)

Eye disorders

Uncommon: conjunctival haemorrhage (all grades: 0.8%), dry eye (all grades: 0.8%)

Vascular disorders

Uncommon: capillary leak syndrome (all grades: 0.8%, grade 3 or higher: 0.8%), hypertension (all grades: 0.8%, grade 3 or higher: 0.8%), hypotension (all grades: 0.8%, grade 3 or higher: 0.8%)

Respiratory, thoracic and mediastinal disorders

Common: oropharyngeal pain (all grades: 4.1%), epistaxis (all grades: 4.1%)

Uncommon: hypoxia (all grades; 0.8%, grade 3 or higher: 0.8%), cough (all grades: 0.8%)

Gastrointestinal disorders*

Very common: Stomatitis/mucositis (all grades: 66.1%, grade 3 or higher: 32.2%), vomiting (all grades: 42.1%, grade 3 or higher: 4.1%), diarrhoea (all grades: 33.1%, grade 3 or higher: 7.4%), nausea (all grades: 26.4%, grade 3 or higher: 8.3%), abdominal pain (all grades: 17.4 %, grade 3 or higher: 0.8%)

Common: anal inflammation (all grades: 3.3%), dysphagia (all grades: 2.5%, grade 3 or higher: 2.5%), oral pain (all grades: 2.5%), dyspepsia (all grades: 1.7%), proctitis (all grades: 1.7%)

Uncommon: neutropenic colitis (all grades; 0.8%, grade 3 or higher: 0.8%), gingival pain (all grades: 0.8%), oesophageal pain (all grades: 0.8%, grade 3 or higher: 0.8%), constipation (all grades: 0.8%)

Hepatobiliary disorders

Very common: hepatotoxicity (all grades: 26.4%), ALT increased (all grades: 10.7%, grade 3 or higher: 3.3%)

Common: AST increased (all grades: 6.6%, grade 3 or higher: 1.7%), blood bilirubin increased (all grades: 6.6%, grade 3 or higher: 2.5%), veno-occlusive liver disease (all grades: 1.7%), hepatomegaly (all grades: 1.7%), γGT increased (all grades: 1.7%, grade 3 or higher: 0.8%)

Skin and subcutaneous tissue disorders

Very common: pruritus (all grades: 10.7 %),

Common: alopecia (all grades: 9.9%, grade 3 or higher: 2.5%), maculo-papular rash (all grades: 7.4%, grade 3 or higher: 2.5%), rash (all grades: 5.8%), erythema (all grades: 4.1%, grade 3 or higher: 0.8%), skin hyperpigmentation [(b)] (all grades: 4.1%), pain of skin (all grades: 3.3%), dermatitis exfoliative (all grades and grade 3 or higher: 2.5%), urticaria (all grades: 2.5%), skin ulcer (all grades: 1.7%)

Uncommon: erythema multiforme (all grades: 0.8%), dermatitis bullous (all grades: 0.8%), dermatitis acneiform (all grades: 0.8%), palmar-plantar erythrodysaesthesia syndrome (all grades: 0.8%)

Not known: dermatitis diaper[a]

Musculoskeletal and connective tissue disorders

Common: Pain in extremity (all grades: 1.7%)

Renal and urinary disorders

Common: acute kidney injury (all grades: 1.7%, grade 3 or higher: 1.7%)

Uncommon: renal failure (all grades: 0.8%, grade 3 or higher: 0.8%), noninfective cystitis (all grades: 0.8%, grade 3 or higher: 0.8%), haematuria (all grades: 0.8%)

Reproductive system and breast disorders

Common: Penile pain (all grades: 1.7%)

Uncommon: scrotal erythema (all grades: 0.8%)

General disorders and administration site conditions

Very common: pyrexia (all grades: 13.2%)[c]

Common: chills (all grades: 2.5%), fatigue (all grades: 1.7%)

Uncommon: face oedema (all grades 0.8%), pain (all grades: 0.8%)

* See detailed sections below.
[a] Case reports obtained from other sources (> 1) following TRECONDI-based conditioning treatment
[b] Bronze pigmentation
[c] Fever in the absence of neutropenia where absolute neutropenia is defined as ANC < 1.0 x 109/l.

Description of selected side effects

Infections

The overall incidence of infections in the 121 paediatric patients was 11.6% (14/121) and was thus comparable to that of adults. The incidence was higher in the paediatric age group 12-17 years (6/39 [15.4 %]) than in younger children (7/ 59 [11.9 %]).

Benign, malignant and non-specific neoplasms (including cysts and polyps)

A case of secondary malignancy (myelodysplastic syndrome) was reported in a child who had received TRECONDI-based conditioning treatment for sickle cell disease approximately 12 months previously.
Six cases of secondary malignancy after TRECONDI-based conditioning treatment were reported by other investigators. Five paediatric patients received allo-HSCT for primary immunodeficiency, i.e. diseases that are inherently associated with an increased risk of neoplasia. They developed myelodysplastic syndrome, acute lymphoblastic leukaemia and Ewing's sarcoma. One patient with haemophagocytic lymphohistiocytosis developed secondary juvenile chronic myeloid leukaemia.

Diseases of the blood and lymphatic system

The median (25%/75% percentiles) duration of neutropenia was 22 (17, 26) days in paediatric patients with malignant diseases and 20 (15, 25) days in patients with non-malignant disorders. In patients with non-malignant disorders was the median duration of neutropenia and leucopenia of CTCAE grade IV statistically significantly longer in the TRECONDI group than in the busulfan group (20.0 days and 19.0 days respectively compared to 14.5 days) (see "*Myelosuppression*" under "*Warnings and precautions"*).

Diseases of the nervous system

Seizure in the context of an encephalitis infection was reported in one of 121 paediatric patients. A report from an investigator-initiated trial performed in children with primary immunodeficiencies lists five cases of seizures occurring after other TRECONDI-based conditioning regimens (see "Warnings and Precautions").

The reporting of suspected adverse reactions after authorisation is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are

requested to report any suspicion of a new or serious adverse reaction via the online portal EIViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdosing

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

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

L01AB02
Pharmacotherapeutic group: Antineoplastic agents, alkylating agents

Mechanism of action / pharmacodynamics

TRECONDI is a pro-drug 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 “Pharmacokinetic”).
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

Adult patients with malignant diseases
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 (FT10; n = 268) or a regimen of intravenous busulfan (total dose 6.4 mg/kg) combined with fludarabine (FB2; n = 283), followed by alloHSCT. Sixty-four % 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 FT10 *versus* the reference FB2 was statistically proven.
After 24 months, the 36.2 % in the treosulfan arm and the 48.4% in the busulfan arm had an EFS event. The EFS after 2 years was 65.7% in the treosulfan arm and 51.2% in the busulfan arm with a hazard ratio (HR) of 0.64 (95% CI 0.49-0.84).
After 24 months, the overall survival rate in the treosulfan arm was 72.7% and in the busulfan arm 60.2%. The cumulative incidence of acute GvHD was 52.8% (grade 3-4: 6.4%) in the treosulfan arm and 57.2 % (grade 3-4: 8.1%) in the busulfan arm. Chronic GvHD (up to 2 years after allo-HSCT) was observed in 61.7% of patients in the treosulfan arm and in 60.3% 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 always in favour of the treosulfan regimen (hazard ratio of FT10 *vs*. FB2 < 1), with only one exception (risk group II of matched related donor [MRD] patients; HR 1.18 [95% CI 0.61, 2.26]).

Adult patients with non-malignant diseases
There is limited information available on treosulfan-based conditioning (FT14 regimen ± thiotepa; see section Dosage/Application) 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, haemophagocytic disorder, immune dysregulatory disorder and bone marrow failure.

In one study, 31 NMD patients were treated with the FT14 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 two-year projected overall survival was 90%. Complete disease responses were observed in 28 patients (90%), as measured by clinical symptoms and laboratory assays.

An Italian group treated 60 TM patients (age range 1-37 years; including 12 adults) with the FT14 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.

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).

Paediatric population

Paediatric patients with malignant disorders

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. Treosulfan dose was adapted to the patient's BSA and 10, 12, or 14 g/m² body surface area per day was administered as a two-hour intravenous infusion on day -6, -5, and -4 prior to stem cell infusion (day 0). 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 after 12 months was 91.4% (90% CI 83.9- 95.5%). Overall, 7 of the 70 patients (10.0%) died within this period, two patients because of relapse/progression, three patients transplant-related and two other patients for other reasons. Freedom from transplant-related mortality up to day +100 after HSCT (primary endpoint) was 98.6% (90% CI 93.4-99.7%)
Transplant-related mortality at 12 months was 2.9% (90% CI 0.9-8.9%). Eleven patients suffered from relapse/progression. The cumulative incidence of from relapse/progression was 15.7% (90% CI 8.6-22.9%) at month + 12 months.
The overall survival at 24 months was 85.7% (90% CI 77.1–91.2%). Overall, 12 of the 70 patients (17.1%) died, 8 patients because of relapse/progression and 4 patients transplant-related. Freedom from transplant-related mortality until day +100 after HSCT (primary endpoint) was 98.6% (90% CI 93.4–99.9%). One transplant-/treatment-related death was noted until day +100 after HSCT.
Transplant-related mortality at 24 months was 4.6% (90% CI 1.8–11.4%). Sixteen patients suffered from relapse/progression. The cumulative incidence of relapse/progression was 23.0% (90% CI 14.7–31.3%) at month +24.

Paediatric patients with non-malignant diseases

The efficacy and safety of treosulfan/fludarabine ± thiotepa-based conditioning was further evaluated in 51 patients with non-malignant diseases (primary immunodeficiency, haemoglobinopathy, inborn error of metabolism and bone marrow failure syndromes). Treosulfan dose was adapted to the patient's BSA and 10, 12, or 14 g/m² body surface area per day was administered as a two-hour

intravenous infusion on day -6, -5, and -4 prior to stem cell infusion (day 0). The dosing scheme was adapted during the trial in terms of the BSA categories applied for the different doses, as a consequence 2 patients received a higher dose compared to the initial dosing scheme. Fifty evaluable patients treated with the reference conditioning regimen busulfan/fludarabine ± thiotepa served as active-control group. Busulfan dose was adapted to the patient's body weight and 3.2 to 4.8 mg/kg/day were administered on days -7, -6, -5, and -4. Most trial subjects (84% in both arms) received the intensified regimen with thiotepa given in 2 single doses of 5 mg/kg/body weight on day -2. Most patients were 28 days to 11 years of age (88.2% in the treosulfan arm and 80% in the busulfan arm). Alpha was not controlled for multiple testing in this trial. The incidence of freedom from transplantation (treatment)-related mortality until day +100 (primary endpoint) was 100.0% (90% CI 94.3%–100.0%) in the treosulfan arm and 90.0% (90% CI 80.1%–96.0%) in the busulfan arm.
After 3 years, transplant-related mortality was 3.9% (90 % CI 1.2-12.0%) with treosulfan and 14.0% (90% CI 7.8-24.5%) with busulfan. Overall survival at 1 year was 96.1% (90% CI 88.0-98.8%) with treosulfan and 88.0% with busulfan (90% CI 77.9-93.7%). After 3 years, overall survival in the treosulfan arm was 94.1% (90% CI 85.4-97.7%) and in the busulfan arm 86.0% (90% CI 75.5-92.2%). In total, 2 patients (3.9%) in the treosulfan arm and 2 patients (4.0%) in the busulfan arm experienced primary graft failure, while secondary graft failures were reported for 9 patients (18.4%) receiving treosulfan-based conditioning. No case of secondary graft failure was reported for patients receiving busulfan-based conditioning. The incidence of complete donor type chimerism at day +28 was comparable between the groups. As time progressed, the incidence of complete donor chimerism decreased in both groups, with complete donor chimerism being less sustained within the treosulfan-treated patient group.

Pharmacokinetics

Treosulfan is a pro-drug 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.

Absorption

After intravenous administration, peak plasma levels are reached at the end of the infusion time. Maximum plasma levels (mean ± standard deviation) 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 Preclinical). 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.

Metabolism

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).

Elimination

Plasma concentrations of treosulfan decline exponentially and are best described by a two-compartment-model with 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 patient groups

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; however, an influence of renal function on renal clearance of treosulfan was not observed.

Paediatric patients

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 should be adapted to the BSA (see section “Dosage/application”), which results in a comparable treosulfan exposure in children of all age groups, corresponding to an exposure of a 3 x 14 g/m² dose in adults.
Mean apparent terminal half-life of treosulfan was comparable between the different age groups and ranged between 1.3 and 1.6 hours.
PK/PD evaluation did not show a significant change of time to engraftment as function of AUC.

Preclinical data

Four-week subchronic, intravenous treatment of rats resulted in haematological changes in form of decreased levels of leucocytes and neutrophilic granulocytes; decreased relative spleen and thymus weights in the context of a lymphoid atrophy, and bone marrow depression. Lymphohistiocytic

infiltration in the skeletal musculature and histopathological changes in the urinary bladder were observed. Signs of haematuria were seen preferentially in male animals.
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 notes

Incompatibilities

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

Durability

The medicinal product may only be used until the date labelled "EXP" on the container.

Shelf life after opening

The preparation contains no preservative. After reconstitution with sodium chloride 4.5 mg/ml (0.45%) solution, chemical and physical stability has been demonstrated for 3 days at 25 °C. From a microbiological point of view, the ready-to-use preparation must be used immediately after opening. If this is not possible to be 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 storage instructions

Store in the original packaging, not above 30°C. Keep out of reach of children.

Handling instructions

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.
Instructions for reconstitution of treosulfan:

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.

Authorisation number

67775 (Swissmedic)

Packs

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

Marketing authorisation holder

Ideogen AG, Freienbach

Status of the information

October 2024