

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trecondi 1 g powder for solution for infusion

Trecondi 5 g powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

When reconstituted according to section 6.6, 1 mL of the solution for infusion contains 50 mg treosulfan.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

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

Posology

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 (day -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 (day -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 (FT₁₀ 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 (day -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 (day -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 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).

Elderly

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 treosulfan is contraindicated in patients with severe impairment (see section 4.3).

Paediatric population

Treosulfan is given in combination with fludarabine, with thiotepa (intensified regimen; FT₁₀₋₁₄TT regimen) or without thiotepa (FT₁₀₋₁₄ 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 (day -6, -5, -4) before stem cell infusion (day 0). The total treosulfan dose is 30-42 g/m²;

The dose of treosulfan should be adapted to the patient's BSA as follows (see section 5.2):

Body surface area (m ²)	Treosulfan 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;
- 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.

Method of administration

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

Precautions to be taken before handling or administering the medicinal product

When handling treosulfan, 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 4.4).

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 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 (see section 4.6)
- Administration of live vaccine

4.4 Special warnings and precautions for use

Myelosuppression

Profound myelosuppression with pancytopenia is the desired therapeutic effect of treosulfan-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 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 treosulfan 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, treosulfan 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 treosulfan-based conditioning followed by alloHSCT (see section 4.8). 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

Treosulfan can impair fertility. Therefore, men treated with treosulfan 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 treosulfan.

Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients (see section 4.6).

Paediatric population

Seizures

There have been isolated reports of seizures in infants (≤ 4 months of age) with primary immunodeficiencies after conditioning treatment with treosulfan 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 treosulfan 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 treosulfan-based conditioning.

Children younger than one 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 treosulfan in the urine. Therefore, nappies should be changed frequently up to 6–8 hours after each infusion of treosulfan.

Extravasation

Treosulfan 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction of treosulfan was observed in high-dose chemotherapy.

Detailed *in vitro* studies did not completely exclude potential interactions between high plasma concentrations of treosulfan and CYP3A4, CYP2C19, or P-glycoprotein (P-gp) substrates. Physiologically-based pharmacokinetic modelling predicted a weak ($\text{AUC ratio} \geq 1.25$ and < 2) to moderate ($\text{AUC ratio} \geq 2$ and < 5) interaction for CYP3A4, a weak interaction for CYP2C19, and a negligible ($\text{AUC ratio} < 1.25$) interaction for P-gp. Therefore, medicinal products with a narrow therapeutic index (e.g. digoxin) that are substrates for CYP3A4 or CYP2C19 should not be given during treatment with treosulfan.

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” ($\text{AUC ratio} < 1.25$), if all concomitantly used medicinal products are dosed 2 hours before or 8 hours after the 2-hour intravenous infusion of treosulfan.

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

4.6 Fertility, pregnancy and 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.

Pregnancy

There are no data from the use of treosulfan in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Treosulfan is contraindicated during pregnancy (see section 4.3).

Breast-feeding

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

Fertility

Treosulfan 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 treosulfan can cause ovarian suppression and amenorrhoea with menopausal symptoms in pre-menopausal women.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Profound myelosuppression/pancytopenia is the desired therapeutic effect of conditioning therapy and occurs in all patients. Blood cell counts usually recover after HSCT.

The most commonly observed adverse reactions (adults/paediatric patients) after treosulfan-based conditioning followed by alloHSCT include overall infections (10.1% /11.6%), gastrointestinal disorders (nausea [38.0%/26.4%], stomatitis [36.4%/66.1%], vomiting [22.5%/42.1%], diarrhoea [14.4%/33.1%], abdominal pain [9.6%/17.4%]), fatigue (14.4%/1.7%), hepatotoxicity (0.3%/26.4%), febrile neutropenia (10.1%/1.7%), decreased appetite (8.0%/0.8%), maculopapular rash (5.2%/7.4%), pruritus (2.8%/10.7%), alopecia (1.5%/9.9%), pyrexia (4.1%/13.2%), oedema (6.2%/0.8%), rash (0.7%/5.8%), and increases of alanine transaminase (ALT [4.9%/10.7%]), aspartate transaminase (AST [4.1%/6.6%]), and bilirubin (17.1%/6.6%).

Adults

Tabulated list of adverse reactions

The frequencies of adverse reactions reported in the table below are derived from 5 clinical trials (including a total of 613 patients) where treosulfan combined with fludarabine was investigated as conditioning treatment prior to alloHSCT in adult patients. Treosulfan 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Infections and infestations*	Common Infections (bacterial, viral, fungal), sepsis ^a	Common Infections (bacterial, viral, fungal), sepsis ^a
	Not known Septic shock ^c	Not known Septic shock ^c
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Not known Treatment-related second malignancy	Not known Treatment-related second malignancy

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Blood and lymphatic system disorders*	Very common Myelosuppression, pancytopenia, febrile neutropenia	Very common Myelosuppression, pancytopenia, febrile neutropenia
Immune system disorders*	Common Hypersensitivity	
Metabolism and nutrition disorders	Common Decreased appetite Uncommon Glucose tolerance impaired including hyperglycaemia and hypoglycaemia Not known Acidosis ^b	Common Decreased appetite Uncommon Glucose tolerance impaired, including hyperglycaemia and hypoglycaemia Not known Acidosis ^b
Psychiatric disorders	Common Insomnia Uncommon Confusional state	Not known Confusional state
Nervous system disorders	Common Headache, dizziness Uncommon Intracranial haemorrhage, peripheral sensory neuropathy Not known Encephalopathy, extrapyramidal disorder, syncope, paraesthesia	Uncommon Headache Not known Encephalopathy, intracranial haemorrhage, syncope, peripheral sensory neuropathy
Eye disorders	Not known Dry eye	
Ear and labyrinth disorders	Uncommon Vertigo	
Cardiac disorders*	Common Cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia) Not known Cardiac arrest, cardiac failure, myocardial infarction, pericardial effusion	Uncommon Cardiac arrhythmias (e.g. atrial fibrillation, sinus arrhythmia) Not known Cardiac arrest, myocardial infarction
Vascular disorders	Common Hypertension, hypotension, flushing Uncommon Haematoma Not known Embolism	Uncommon Hypertension Not known Embolism

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Respiratory, thoracic and mediastinal disorders	<p>Common Dyspnoea, epistaxis</p> <p>Uncommon Pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, oropharyngeal pain, hiccups</p> <p>Not known Laryngeal pain, cough, dysphonia</p>	<p>Uncommon Dyspnoea</p> <p>Not known Pneumonitis, pleural effusion, pharyngeal inflammation, epistaxis</p>
Gastrointestinal disorders*	<p>Very common Stomatitis/mucositis, diarrhoea, nausea, vomiting</p> <p>Common Oral pain, gastritis, dyspepsia, constipation, dysphagia, abdominal pain, oesophageal or gastrointestinal pain</p> <p>Uncommon Mouth haemorrhage, abdominal distension, dry mouth</p> <p>Not known Gastric haemorrhage, neutropenic colitis, oesophagitis, anal inflammation</p>	<p>Common Stomatitis/mucositis, diarrhoea, nausea, abdominal pain</p> <p>Uncommon Vomiting, oral pain, dysphagia, oesophageal or gastrointestinal pain</p> <p>Not known Gastric or mouth haemorrhage, neutropenic colitis</p>
Hepatobiliary disorders*	<p>Uncommon Veno-occlusive liver disease</p> <p>Not known Hepatotoxicity, hepatomegaly</p>	<p>Not known Veno-occlusive liver disease, hepatotoxicity</p>
Skin and subcutaneous tissue disorders	<p>Common Maculo-papular rash, purpura, erythema, palmar-plantar erythrodysesthesia syndrome, pruritus, alopecia</p> <p>Uncommon Erythema multiforme, dermatitis acneiform, rash, dry skin</p> <p>Not known Skin necrosis or ulcer, dermatitis, skin hyperpigmentation^d</p>	<p>Uncommon Maculo-papular rash</p> <p>Not known Skin necrosis, purpura, erythema</p>
Musculoskeletal and connective tissue disorders	<p>Common Pain in extremity, back pain, bone pain, arthralgia</p> <p>Uncommon Myalgia</p>	<p>Not known Pain in extremity, bone pain</p>

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Renal and urinary disorders	<p>Common Acute kidney injury, haematuria</p> <p>Uncommon Urinary tract pain</p> <p>Not known Renal failure, haemorrhagic cystitis^c, dysuria</p>	<p>Uncommon Acute kidney injury</p> <p>Not known Haematuria</p>
General disorders and administration site conditions	<p>Very common Asthenic conditions (fatigue, asthenia, lethargy)</p> <p>Common Oedema, pyrexia^e, chills</p> <p>Uncommon Non-cardiac chest pain, pain</p>	<p>Common Fatigue</p> <p>Not known Non-cardiac chest pain, pyrexia^e</p>
Investigations	<p>Very common Blood bilirubin increased</p> <p>Common Transaminases (ALT/AST) increased, γGT increased, C-reactive protein increased, weight decreased, weight increased</p> <p>Uncommon Blood alkaline phosphatase increased</p> <p>Not known Blood lactate dehydrogenase (LDH) increased</p>	<p>Common Blood bilirubin increased, transaminases (ALT/AST) increased, γGT increased</p> <p>Uncommon C-reactive protein increased</p> <p>Not known Blood alkaline phosphatase increased</p>

* 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 treosulfan activation/cleavage in the plasma

^c Case reports (> 2) after treosulfan-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 adverse reactions

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 frequent 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 treosulfan 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 treosulfan-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 62 of 613 adult patients (10.1%). The most frequent 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 treosulfan dose and 17.5 (14, 21) days with the 14 g/m² treosulfan dose.

Cardiac disorders

Cardiac disorders were observed in 21 patients (3.4%). The most frequent 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 treosulfan. None of these cases were fatal or life-threatening.

Paediatric population

Tabulated list of adverse reactions

The adverse reactions reported in the table below are derived from two clinical trials (including a total of 121 patients; median age 7 years [range 0–17 years]) where treosulfan combined with fludarabine (and mostly with additional thiotepea) 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency group, undesirable effects are presented in order of decreasing seriousness.

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Infections and infestations*	Very common Infections (bacterial, viral, fungal)	Common Infections (bacterial, viral, fungal)
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Not known Treatment-related second malignancy ^a	Not known Treatment-related second malignancy ^a
Blood and lymphatic system disorders*	Very common Myelosuppression, pancytopenia Not known Febrile neutropenia	Very common Myelosuppression, pancytopenia Not known Febrile neutropenia
Metabolism and nutrition disorders	Not known Alkalosis, electrolyte imbalance, hypomagnesaemia, decreased appetite	Not known Alkalosis
Nervous system disorders*	Common Headache Not known Seizure, paraesthesia	Not known Paraesthesia
Eye disorders	Not known Conjunctival haemorrhage, dry eye	
Vascular disorders	Not known Capillary leak syndrome, hypertension, hypotension	Not known Capillary leak syndrome, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Common Oropharyngeal pain, epistaxis Not known Hypoxia, cough	Not known Hypoxia
Gastrointestinal disorders*	Very common Stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain Common Dysphagia, anal inflammation, oral pain Not known Neutropenic colitis, dyspepsia, proctitis, gingival pain, oesophageal pain, constipation	Very common Stomatitis/mucositis Common Dysphagia, diarrhoea, nausea, vomiting Not known Neutropenic colitis, abdominal pain, oesophageal pain

System Organ Class (SOC)	All Adverse Reactions / Frequency	Grade 3-4 Adverse Reactions / Frequency
Hepatobiliary disorders	Very common Hepatotoxicity Not known Veno-occlusive liver disease, hepatomegaly	
Skin and subcutaneous tissue disorders	Very common Pruritus, alopecia Common Dermatitis exfoliative, maculo-papular rash, rash, erythema, urticaria, pain of skin, skin hyperpigmentation ^b Not known Skin ulcer, erythema multiforme, dermatitis bullous, dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, dermatitis diaper ^a	Common Dermatitis exfoliative, maculo-papular rash Not known Erythema
Musculoskeletal and connective tissue disorders	Not known Pain in extremity	
Renal and urinary disorders	Not known Acute kidney injury, renal failure, noninfective cystitis, haematuria	Not known Acute kidney injury, renal failure, noninfective cystitis
Reproductive system and breast disorders	Not known Scrotal erythema, penile pain	
General disorders and administration site conditions	Very common Pyrexia ^c Common Chills Not known Face oedema, fatigue, pain	
Investigations	Very common ALT increased Common AST increased, blood bilirubin increased, C-reactive protein increased Not known γGT increased	Common ALT increased, blood bilirubin increased Not known AST increased, γGT increased, C-reactive protein increased

* See detailed sections below

^a Case reports (> 1) after treosulfan-based conditioning obtained from other sources

^b Bronze pigmentation

^c Fever in the absence of neutropenia where neutropenia is defined as ANC < 1.0 x 10⁹/L

Description of selected adverse reactions

Infections

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

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

One case of a second malignancy (myelodysplastic syndrome) was reported in a child about 12 months after treosulfan-based conditioning for sickle cell disease.

Six cases of a second malignancy were reported by other investigators after treosulfan-based conditioning. Five paediatric patients received alloHSCT for primary immunodeficiencies, i.e. diseases with an increased risk for neoplasias per se. They developed myelodysplastic syndrome, acute lymphoblastic leukaemia, and Ewing's sarcoma. One patient with haemophagocytic lymphohistiocytosis developed secondary juvenile chronic myeloid leukaemia.

Blood and lymphatic system disorders

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.

Nervous system disorders

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 treosulfan-based conditioning regimens (see section 4.4).

Reporting of suspected adverse reactions

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 adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

The principal toxic effect of treosulfan 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 treosulfan would constitute an overdose. No specific antidote of treosulfan overdose is known. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, ATC code: L01AB02

Mechanism of action

Treosulfan is a prodrug of a bifunctional alkylating agent with cytotoxic activity to haematopoietic precursor cells. The activity of treosulfan is due to the spontaneous conversion into a mono-epoxide intermediate and L-diepoxybutan (see section 5.2).

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.

Pharmacodynamic effects

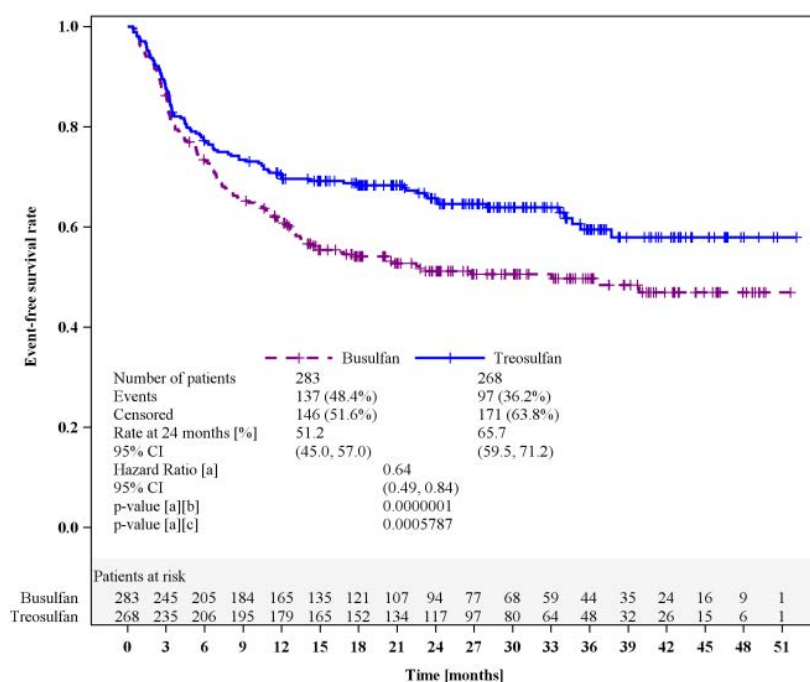
Treosulfan has a broad antineoplastic and antileukaemic activity. This was demonstrated against transplanted mouse and rat lymphomas/leukaemias, sarcomas and hepatomas, human tumour xenografts, human tumour biopsies and cell lines.

The immunosuppressive effects of treosulfan are attributed to its toxicity against primitive and committed progenitor cells, T and NK cells, reduction of cellularity of primary and secondary lymphatic organs and a preclusive effect on the 'cytokine storm' that precedes the development of Graft-versus-Host-Disease (GvHD) and is involved in the pathogenesis of veno-occlusive disease.

Clinical efficacy and safety

In the pivotal phase III trial, 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 treosulfan 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. 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 FT₁₀ *versus* the reference FB2 was statistically proven. The p-value of 0.0005787 indicates superiority of treosulfan compared to busulfan (Figure 1).

Figure 1: Kaplan-Meier estimates of event-free survival (Full Analysis Set)



^a Adjusted for donor type as factor, and risk group and centre as strata using Cox regression model.

^b For testing non-inferiority of treosulfan compared to busulfan.

^c For testing superiority of treosulfan compared to busulfan.

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 [HR] 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]). Further results are shown in Table 1.

Table 1: Treatment results at 24 months (Full analysis set)

Parameter	Treosulfan	Busulfan	Hazard ratio^b (95% CI)	P value^b
Number of patients	268	283		
Overall survival ^a ; % (95% CI)	72.7 (66.8, 77.8)	60.2 (54.0, 65.8)	0.64 (0.48, 0.87)	0.0037
Cumulative incidence of relapse/progression; % (95% CI)	22.0 (16.9, 27.1)	25.2 (20.0, 30.3)	0.82 (0.59, 1.16)	0.2631
Cumulative incidence of transplant-related mortality; % (95% CI)	12.8 (9.2, 17.7)	24.1 (19.1, 30.2)	0.52 (0.34, 0.82)	0.0043
^a Based on Kaplan-Meier estimates; ^b adjusted for donor type, risk group and centre using Cox regression model				

Results of GvHD are shown in Table 2.

Table 2: Cumulative incidence of GvHD (Full analysis set)

Parameter	Treosulfan	Busulfan	P value
Number of patients	268	283	
Acute GvHD, all Grades; % (95% CI)	52.8 (46.8, 58.8)	57.2 (51.5, 63.0)	0.2038
Acute GvHD, Grades III/IV; % (95% CI)	6.4 (3.4, 9.3)	8.1 (4.9, 11.3)	0.4267
Chronic GvHD ^a ; % (95% CI)	61.7 (55.1, 68.3)	60.3 (53.8, 66.7)	0.9964
Extensive chronic GvHD ^a ; % (95% CI)	19.8 (14.5, 25.1)	28.6 (22.5, 34.7)	0.0750
^a Up to 2 years after alloHSCT			

There is limited information available on treosulfan-based conditioning (FT₁₄ regimen ± thiotepa; see section 4.2) 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 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 (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 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 (Bernardo ME et al.; *Blood* 2012; 120(2):473-6).

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

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. 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 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.

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. 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%). 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. The incidence of complete donor type chimerism was comparable between the groups.

5.2 Pharmacokinetic properties

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.

Absorption

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

Distribution

Treosulfan is rapidly distributed in the body; however, its penetration through the blood-brain-barrier is quite limited (see section 5.3). 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-diepoxybutane (S,S-DEB = (2S,3S)-1,2:3,4-diepoxybutane).

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

Elimination

Plasma concentrations of treosulfan decline exponentially and are best described by a first order elimination process fitted by a two-compartment model.

The terminal half-life ($T_{1/2\beta}$) 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.

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 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 should be adapted to the BSA (see section 4.2), which results in a comparable treosulfan exposure in children of all age groups, corresponding to an exposure of a $3 \times 14 \text{ g/m}^2$ 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.

5.3 Preclinical safety 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-diepoxybutane (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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial

5 years

Reconstituted solution for infusion

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, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. 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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Trecondi 1 g powder for solution for infusion

Colourless type I glass vial, with rubber stopper and aluminium cap containing 1 g of treosulfan.

Trecondi 5 g powder for solution for infusion

Colourless type I glass vial, with rubber stopper and aluminium cap containing 5 g of treosulfan.

Trecondi is available in packs of 1 or 5 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other 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.

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.

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1351/001 (1 g, 1 vial)
EU/1/18/1351/002 (1 g, 5 vials)
EU/1/18/1351/003 (5 g, 1 vial)
EU/1/18/1351/004 (5 g, 5 vials)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 June 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

medac Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Trecondi 1 g powder for solution for infusion

Trecondi 5 g powder for solution for infusion

treosulfan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 g treosulfan.

Each vial contains 5 g treosulfan.

After reconstitution 1 mL of solution contains 50 mg treosulfan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.

1 g

5 g

1 vial

5 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

Guidelines for the safe disposal of antineoplastic agents must be observed.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1351/001 (1 g, 1 vial)
EU/1/18/1351/002 (1 g, 5 vials)
EU/1/18/1351/003 (5 g, 1 vial)
EU/1/18/1351/004 (5 g, 5 vials)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:

NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Vial label

1. NAME OF THE MEDICINAL PRODUCT

Trecondi 1 g powder for solution for infusion
Trecondi 5 g powder for solution for infusion
treosulfan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 g treosulfan.
Each vial contains 5 g treosulfan.

After reconstitution 1 mL of solution contains 50 mg treosulfan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.

1 g
5 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after reconstitution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

medac GmbH
Theaterstr. 6
22880 Wedel
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1351/001 (1 g, 1 vial)
EU/1/18/1351/002 (1 g, 5 vials)
EU/1/18/1351/003 (5 g, 1 vial)
EU/1/18/1351/004 (5 g, 5 vials)

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Trecondi 1 g powder for solution for infusion **Trecondi 5 g powder for solution for infusion** treosulfan

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trecondi is and what it is used for
2. What you need to know before you are given Trecondi
3. How to use Trecondi
4. Possible side effects
5. How to store Trecondi
6. Contents of the pack and other information

1. What Trecondi is and what it is used for

Trecondi contains the active substance treosulfan, which belongs to a group of medicines called alkylating agents. Treosulfan is used to prepare patients for bone marrow transplant (haematopoietic stem cell transplantation). Treosulfan destroys the bone marrow cells and enables the transplant of new bone marrow cells which leads to the production of healthy blood cells.

Trecondi is used as a **treatment before blood stem cell transplantation** in adults and in adolescents and children older than one month with cancer and non-cancerous disorders.

2. What you need to know before you are given Trecondi

Do not use Trecondi

- if you are allergic to treosulfan,
- if you suffer from an active uncontrolled infection,
- if you suffer from severe heart, lung, liver or kidney diseases,
- if you suffer from hereditary DNA repair disorder, a condition that reduces the ability to repair DNA (which carries your genetic information),
- if you are pregnant, or think you may be pregnant.

Warnings and precautions

Trecondi is a cell-killing (cytotoxic) medicine that is used to decrease the number of blood cells. At the recommended dose, this is the desired effect. You will have regular blood tests during treatment to check your blood cell counts do not fall too low.

In order to prevent and treat infections, you will be given medicines, such as antibiotics, antifungals or antivirals.

Trecondi may increase the risk of having another cancer in the future.

Since inflammation of the oral mucosa is a common side effect of this medicine, you should pay attention to adequate oral hygiene. Prophylactic use of mouthwashes (e.g. with barrier protectants, antimicrobials) or application of ice within the oral cavity (lessens blood flow to the oral mucosa and reduces the amount of treosulfan reaching the cell) is recommended.

You must not receive live vaccines during treatment with treosulfan.

Trecondi may cause symptoms of the menopause (absence of menstrual periods).

Children and adolescents

Fits (seizures) may occur very rarely in infants of less than 4 months of age. Children younger than 1 year may have more severe side effects that affect breathing than older ones. Your child will be monitored for signs of side effects affecting nerves and breathing problems.

Nappy rash with ulceration of the area around the anus (perianal) may occur in infants, toddlers and children wearing nappies because treosulfan passed out in the urine can damage the skin. Therefore, nappies should be changed frequently during 6–8 hours after each dose of this medicine.

There is not sufficient information on the use of treosulfan in children aged less than 1 month.

Other medicines and Trecondi

Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility

You must not get pregnant during treatment with this medicine and up to 6 months after treatment. Use an effective method of contraception when either you or your partner is receiving this medicine.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you receive this medicine.

You should stop breast-feeding before starting treatment with this medicine.

If you are a man treated with this medicine, you should not father a child during and up to 6 months after treatment.

This medicine may make you infertile and it may not be possible for you to get pregnant after treatment with it. If you are concerned about having children, you should discuss this with your doctor before treatment. Men should seek advice about the possibility of sperm preservation before starting therapy.

Driving and using machines

This medicine can cause nausea, vomiting and dizziness which may reduce your ability to drive or use machines. If you are affected, do not drive or use machines.

3. How to use Trecondi

Use in adults

This medicine is used in combination with fludarabine.

The recommended dose is 10–14 g/m² body surface area (calculated using your height and weight).

Use in children and adolescents

This medicine is used in combination with fludarabine and in most cases also with thiotepea. The recommended dose is 10–14 g/m² body surface area.

How Trecondi is given

This medicine will be given to you by your doctor. It is given by drip (infusion) into a vein over 2 hours for 3 days before blood stem cell infusion.

If you were given more Trecondi than you should

Because this medicine is given by a doctor, you will be given the correct dose. However, if you think you have received more of this medicine than you should, tell your doctor or nurse as soon as possible.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

The most serious side effects of treosulfan therapy or the transplant procedure include:

- decrease in blood cell counts which is the intended effect of the medicine to prepare you for your transplant infusion (all patients: very common)
- infections caused by bacteria, viruses and fungi (adults: common; children and adolescents: very common)
- blocking of a vein into the liver (adults: uncommon; children and adolescents: not known)
- inflammation of the lung (pneumonitis) (adults: uncommon)

Your doctor will monitor your blood counts and liver enzymes regularly to detect and manage these events.

Adults

A list of all other side effects is set out below according to how common they are.

Very common (may affect more than 1 in 10 people)

- decreased counts of white blood cells with fever (febrile neutropenia)
- inflammation of the lining of various parts of the body, especially in the mouth (which can cause ulcers), diarrhoea, nausea, vomiting
- tiredness
- increased blood level of bilirubin (a liver pigment, often a sign of liver problems)

Common (may affect up to 1 in 10 people)

- bloodstream infection (sepsis)
- allergic reactions
- decreased appetite
- problems sleeping (insomnia)
- headache, dizziness
- changes and abnormalities in heart rhythm (heartbeat is irregular, too fast or too slow)
- high or low blood pressure, flushing
- difficulty breathing, nosebleeds
- mouth pain, inflammation of the stomach, upset stomach, belly (abdominal) pain, constipation, difficulty in swallowing, gullet or stomach pain
- a type of rash with flat or raised red bumps on the skin (maculopapular rash), red spots on the skin (purpura), redness of skin (erythema), hand and foot syndrome (palms of the hands or soles of the feet tingle, become numb, painfully swollen, or red), itching, hair loss
- pain in arms or legs, back pain, bone pain, joint pain
- sudden decrease of kidney function, blood in the urine
- retention of fluid in the body causing swelling (oedema), fever, chills
- increased liver enzymes, increased C-reactive protein (a marker of inflammation in the body), weight gain, weight loss

Uncommon (may affect up to 1 in 100 people)

- abnormal control of blood sugar level including high or low blood sugar level
- confusion
- bleeding in the brain, problems in the nerves of the arms or legs with symptoms such as numbness, reduced or increased sensitivity, tingling, burning pain (peripheral sensory neuropathy)
- a spinning sensation (vertigo)
- bruising
- fluid around the lung (pleural effusion), inflammation of throat, inflammation of or pain in voice box, hiccups
- bleeding in the mouth, feeling bloated, dry mouth
- a type of rash with red spots and sometimes with purple or blistered areas in the centre (erythema multiforme), acne, rash, dry skin
- muscle pain
- pain of the urinary tract
- chest pain not related to heart problems, pain
- increased blood level of alkaline phosphatase (your doctor will check for this)

Not known (frequency cannot be estimated from the available data)

- life-threatening condition after bloodstream infection (septic shock)
- different cancer caused by chemotherapeutic treatment (second malignancy)
- increased acidity in the blood
- abnormal brain function (encephalopathy), restless, repetitive, or involuntary movements and rapid speech (extrapyramidal disorder), fainting, sensation of tingling, pricking or numbness (paraesthesia)
- dry eye
- heart not pumping enough blood for the body's needs (heart failure), heart attack, fluid in the sac around the heart (pericardial effusion)
- blockage of a blood vessel (embolism)
- throat pain, hoarseness, cough
- gastrointestinal bleeding, inflammation of the colon, inflammation of the gullet, inflammation of the anus
- liver injury caused by medicines, enlarged liver
- inflammation of skin (dermatitis), death of skin tissue, skin ulcer, bronze pigmentation of skin
- kidney failure, inflammation of the urinary bladder with bleeding (haemorrhagic cystitis), pain on passing urine (dysuria)
- increased blood level of lactate dehydrogenase (a substance that indicates tissue or cellular damage)

Children and adolescents

A list of all other side effects is set out below according to how common they are.

Very common (may affect more than 1 in 10 people)

- inflammation of the mucosa especially in the mouth (with ulcers), diarrhoea, nausea, vomiting, abdominal pain
- liver damage
- itching, hair loss
- fever
- increased blood level of a liver enzyme (ALT)

Common (may affect up to 1 in 10 people)

- headache

- throat pain, nosebleeds
- difficulty in swallowing, inflammation of anus, mouth pain
- reddening and flaking of most of the skin of the body (dermatitis exfoliative), a type of rash with flat or raised red bumps on the skin (maculopapular rash), rash, redness of skin (erythema), hives, skin pain, bronze pigmentation of skin
- chills
- increased blood level of a liver enzyme (AST) and of bilirubin (a liver pigment, often a sign of liver problems), increased C-reactive protein (a marker of inflammation in the body)

Not known (frequency cannot be estimated from the available data)

- different cancer caused by chemotherapeutic treatment (second malignancy)
- decreased counts of white blood cells with fever (febrile neutropenia)
- less acid than normal in the blood (alkalosis), abnormal blood level of electrolytes, decreased blood level of magnesium, decreased appetite
- seizure, sensation of tingling, pricking or numbness (paraesthesia)
- bleeding in the eye, dry eye
- leakage of fluid from the capillaries (small blood vessels), high blood pressure, low blood pressure
- decrease in the oxygen supply to parts of the body (hypoxia), cough
- inflammation of the colon, upset stomach, inflammation of the lining of the rectum, pain in the gums, pain in the gullet, constipation
- enlarged liver
- skin ulcer, a type of rash with red spots and sometimes with purple or blistered areas in the centre (erythema multiforme), skin condition with fluid-filled blisters (dermatitis bullous), acne, hand and foot syndrome (palms of the hands or soles of the feet tingle, become numb, painfully swollen, or red), nappy rash with ulceration in the area surrounding the anus
- pain in arms or legs
- decrease of kidney function, kidney failure, inflammation of the urinary bladder (cystitis), blood in the urine
- redness of scrotal skin, pain in the penis
- accumulation of fluid in the tissue that causes swelling in the face, tiredness, pain
- increased blood level of a liver enzyme (gamma-glutamyl transferase)

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Trecondi

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label and carton after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

For storage conditions after reconstitution of the medicine, see the information below for healthcare professionals.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Trecondi contains

The active substance is treosulfan. This medicine contains no other ingredients.

Trecondi 1 g powder for solution for infusion

1 vial contains 1 g of treosulfan.

Trecondi 5 g powder for solution for infusion

1 vial contains 5 g of treosulfan.

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

What Trecondi looks like and contents of the pack

White crystalline powder in a glass vial with a rubber stopper and aluminium cap.

Trecondi is available in packs containing 1 or 5 vials (type I glass).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

medac

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This leaflet was last revised in <{MM/YYYY}><{month YYYY}>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

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.

Reconstituted solution for infusion

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.

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, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Do not store the reconstituted solution in a refrigerator (2 °C - 8 °C) as this might cause precipitation.

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.