Summary of Product Characteristics

1. Name of the medicinal product
TREOSULFAN RAZ 5g

2. Qualitative and quantitative composition
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 cake or 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 with malignant and non-malignant diseases, and in paediatric patients older than one month with 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 (FT_{10} regimen).

Adults with non-malignant disease
Treosulfan is given in combination with fludarabine with or without thiotepa.
The recommended dose and schedule of administration is:
• Treosulfan 14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (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 (FT_{14} 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; $FT_{10\text{-}14}TT$ regimen) or without thiotepa ($FT_{10\text{-}14}$ regimen).
The recommended dose and schedule of administration is:
• Treosulfan 10-14 g/m² body surface area (BSA) per day as a two-hour intravenous infusion, given on three consecutive days (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)**
≤ 0.5	10.0
> 0.5 – 1.0	12.0
> 1. 0	14.0

• Fludarabine 30 mg/m² BSA per day as a 0.5-hour intravenous infusion, given on five consecutive days (day -7, -6, -5, -4, -3) before stem cell infusion (day 0). The total fludarabine dose is 150 mg/m²;
• 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 after being dissolved in 100ml of water for injections.

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 (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 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” (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

(7.2%/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 (≥ 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). 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] **Not known** Septic shock[c]	**Common** Infections (bacterial, viral, fungal), sepsis[a] **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
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
Respiratory, thoracic and mediastinal disorders	**Common** Dyspnoea, epistaxis **Uncommon** Pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, oropharyngeal pain, hiccups **Not known** Laryngeal pain, cough, dysphonia	**Uncommon** Dyspnoea **Not known** Pneumonitis, pleural effusion, pharyngeal inflammation, epistaxis

Gastrointestinal disorders*	**Very common** Stomatitis/mucositis, diarrhoea, nausea, vomiting **Common** Oral pain, gastritis, dyspepsia, constipation, dysphagia, abdominal pain, oesophageal or gastrointestinal pain **Uncommon** Mouth haemorrhage, abdominal distension, dry mouth **Not known** Gastric haemorrhage, neutropenic colitis, oesophagitis, anal inflammation	**Common** Stomatitis/mucositis, diarrhoea, nausea, abdominal pain **Uncommon** Vomiting, oral pain, dysphagia, oesophageal or gastrointestinal pain **Not known** Gastric or mouth haemorrhage, neutropenic colitis
Hepatobiliary disorders*	**Uncommon** Veno-occlusive liver disease **Not known** Hepatotoxicity, hepatomegaly	**Not known** Veno-occlusive liver disease, hepatotoxicity
Skin and subcutaneous tissue disorders	**Common** Maculo-papular rash, purpura, erythema, palmar-plantar erythrodysaesthesia syndrome, pruritus, alopecia **Uncommon** Erythema multiforme, dermatitis acneiform, rash, dry skin **Not known** Skin necrosis or ulcer, dermatitis, skin hyperpigmentation[d]	**Uncommon** Maculo-papular rash **Not known** Skin necrosis, purpura, erythema
Musculoskeletal and connective tissue disorders	**Common** Pain in extremity, back pain, bone pain, arthralgia **Uncommon** Myalgia	**Not known** Pain in extremity, bone pain
Renal and urinary disorders	**Common** Acute kidney injury, haematuria **Uncommon** Urinary tract pain **Not known** Renal failure, haemorrhagic cystitis[c], dysuria	**Uncommon** Acute kidney injury **Not known** Haematuria

General disorders and administration site conditions	**Very common** Asthenic conditions (fatigue, asthenia, lethargy) **Common** Oedema, pyrexia[e], chills **Uncommon** Non-cardiac chest pain, pain	**Common** Fatigue **Not known** Non-cardiac chest pain, pyrexia[e]
Investigations	**Very common** Blood bilirubin increased **Common** Transaminases (ALT/AST) increased, γGT increased, C-reactive protein increased, weight decreased, weight increased **Uncommon** Blood alkaline phosphatase increased **Not known** Blood lactate dehydrogenase (LDH) increased	**Common** Blood bilirubin increased, transaminases (ALT/AST) increased, γGT increased **Uncommon** C-reactive protein increased **Not known** Blood alkaline phosphatase increased

* See detailed sections below.

[a] Clinically or microbiologically documented infection with grade 3 or 4 neutropenia (absolute neutrophil count [ANC] < 1.0 x 10^9/L) and sepsis.

[b] Acidosis might be a consequence of the release of methanesulfonic acid through 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 10^9/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 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). 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** Paraesthesia, seizure	**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
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 erythrodysaesthesia 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, bilirubin increased, C- reactive protein increased **Not known** γGT increased	**Common** ALT increased blood bilirubin increased **Uncommon** Transaminases (ALT/AST) increase **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 < 1.0×10^9/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 authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il.

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.

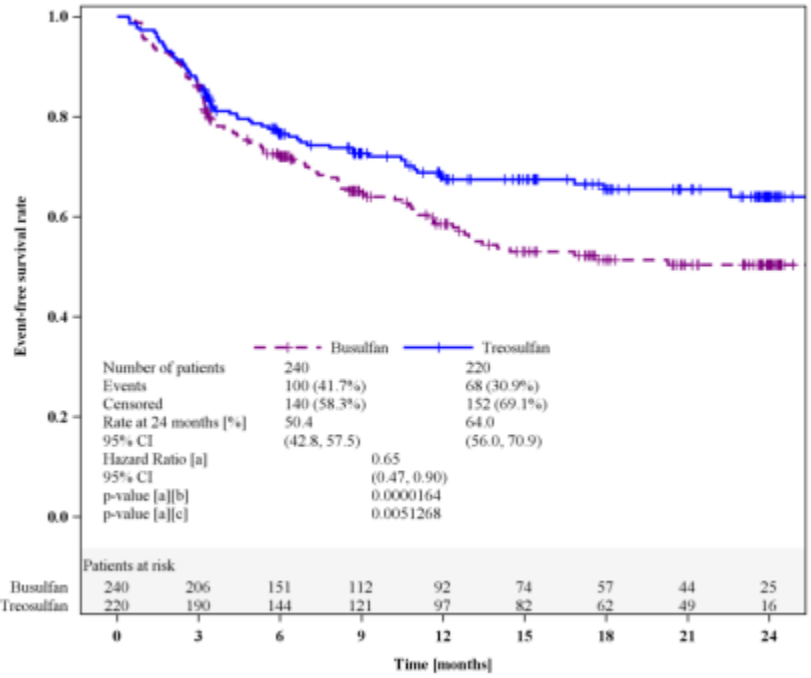
The immunosuppressive effects of treosulfan are attributed to its toxicity against primitive and committed progenitor cells, T and NK cells, reduction of cellularity of primary and secondary lymphatic organs and a preclusive effect on the 'cytokine storm' that precedes the development of Graft-versus-Host-Disease (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 (FT_{10}; 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 FT_{10} *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 FT_{10} *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 (FT_{14} 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 FT_{14} regimen plus anti-thymocyte globulin. The age of the patients ranged from 0.4 to 30.5 years, and 29% had HCT-CI scores > 2. All patients engrafted, with a median time to neutrophil engraftment of 21 (range, 12–46) days. The 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 FT_{14} plus thiotepa regimen. All patients engrafted except one, who died on day +11; the median time to neutrophil and platelet recovery was 20 days. With a median follow-up of 36 months (range, 4-73), the 5-year overall survival probability was 93% (95% CI 83-97%). No difference in terms

of outcome was observed between children and adults (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 (see section 4.2). 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. The 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 ± SD) in adult patients after a 2-hour intravenous infusion of 10, 12, or 14 g/m² treosulfan were 306 ± 94 µg/mL, 461 ± 102 µg/mL, and 494 ± 126 µg/mL, respectively.

Distribution

Treosulfan is rapidly distributed in the body; however, its penetration through the blood-brain-barrier is quite limited (see section 5.3). The volume of distribution in adult patients is about 20–30 liters. No dose accumulation with the recommended daily treatment on three consecutive days was observed. Treosulfan does not bind to plasma proteins.

Biotransformation

Under physiological conditions (pH 7.4, temperature 37 °C), the pharmacologically inactive treosulfan is converted spontaneously (non-enzymatically) into the active monoepoxide intermediate (S,S-EBDM = (2S,3S)-1,2-epoxybutane-3,4-diol-4-methanesulfonate) and finally to L-diepoxibutane (S,S-DEB = (2S,3S)-1,2:3,4-diepoxybutane).
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 ($T_{1/2ß}$) 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.

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 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.

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-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.

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
The expiry date of the product is indicated on the packaging material.
Reconstituted solutions
Chemical and physical in-use stability has been demonstrated for 12 hours at 30°C.
From a microbiological point of view, unless the method of reconstitution precludes the risk of microbiological contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage
Store below 25^0C.

Reconstituted solution:
Do not store the reconstituted product in a refrigerator (2 - 8°C) as this might cause precipitation. Solutions showing any sign of precipitation should not be used.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container
100ml Type-I clear moulded lyo glass vial with a 20 mm bromobutyl rubber stopper sealed with a 20 mm flip-off seal. Vials may or may not be sleeved with plastic shrink sleeve/bottom (puck). This plastic sleeving is not in contact with the drug product and is there to provide additional protection during transportation. This improves the safe handling of the medicinal product by both healthcare professionals and pharmaceutical personnel.

TREOSULFAN RAZ 5g 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

Treosulfan is used for intravenous infusion after being dissolved in 100 mL of water for injections.

The reconstituted solution is a clear, colourless solution.
Inspect visually prior to use. Only clear solutions without particles should be used.

Any reconstituted solution that shows evidence of precipitation should not

be used and should be destroyed with regard to legal requirements for disposal of hazardous waste (see below).
For single use only, discard any unused contents.
As with all cytotoxic substances, appropriate precautions should be taken when handling Treosulfan.
Guidelines for the safe handling of antineoplastic agents:

1. Trained personnel should reconstitute the medicinal product.
2. This should be performed in a designated area.
3. Adequate protective gloves, masks and clothing should be worn.
4. Precautions should be taken to avoid the medicinal product accidentally coming into contact with the eyes. In case the solution comes in contact with the skin or the eyes, the affected area should be washed with copious amounts of water or normal saline. A bland cream may be used to treat the transient stinging of the skin. Medical advice should be sought if the eyes are affected.
5. Cytotoxic preparations should not be handled by staff who may be pregnant.
6. Adequate care and precautions should be taken in the disposal of items (syringes, needles, etc.) used to reconstitute cytotoxic drugs.
7. The work surface should be covered with disposable plastic-backed absorbent paper.
8. 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.

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.

Instructions for reconstitution of Treosulfan
To avoid solubility problems during reconstitution the following aspects should be regarded.

1. The solvent, water for injections, is warmed to 25 - 30°C (not higher!) by using a water bath.
2. The Treosulfan is carefully removed from the inner surface of the infusion bottle by shaking.

This procedure is very important, because moistening of powder that sticks to the surface results in caking. In case caking occurs the bottle has to be shaken long and vigorously.

3. One side of the double-sided cannula is put into the rubber stopper of the water bottle. The Treosulfan bottle is then put on

the other end of the cannula with the bottom on top. The whole construction is converted and the water let run into the lower bottle while the bottle is shaken gently.

Following these instructions, the whole reconstitution procedure should take no longer than 2 minutes.

7. Marketing authorisation holder and Importer

RAZ PHARMACEUTICS LTD.,31 Gesher haetz St., Industrial Park, Emek Hefer, Israel

8. Registration number

167-98-35696-00

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