דצמבר 2023

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הודעה על עדכון עלון לרופא תכשיר
טראוסולפאן רז 5 גרם Treosulfan RAZ 5G

חברת רז רוקחות בע"מ מבקשת להודיעכם על עדכון העלון לרופא של התכשיר שבנדון.

חומר פעיל: Treosulfan

צורת מינון: Powder for Solution for Infusion

התוויה מאושרת:
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.

בהודעה זו מצוינים רק הסעיפים בהם נעשו עדכונים מהותיים המהווים החמרה במידע הבטיחותי.
מידע המהווה החמרה מסומן בצהוב. מחיקות מסומנות בקו חוצה.

למידע מלא יש לעיין בעלון המעודכן.
העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug .

ניתן לקבלו מודפס על ידי פנייה לבעל הרישום: רז רוקחות בע"מ, גשר בעץ 31 , פארק תעשיות עמק חפר, ישראל.

השינויים בעלון לרופא:

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 (~~13~~10.1% /11.4%), gastrointestinal disorders (nausea [~~39.5~~38.0%/30.7%], stomatitis [36.~~0~~4%/69.3%], vomiting [22.5%/43.2%], diarrhoea [~~15.6~~14.4%/33.0%], abdominal pain [~~10.4~~9.6%/17%]), fatigue (~~15.1~~14.4%/2.3%), febrile neutropenia (~~11.3~~10.1%/1.1%), ~~oedema (7.~~decreased appetite (8~~%/.~~0~~%),~~%/0.8%), maculopapular rash (~~7~~5.2%/~~12.5~~7.4%), oedema (6.2%/0%), and increases of alanine transaminase (ALT [~~5.1~~4.9%/9.1%]), aspartate transaminase (AST [4.~~4%/8.0%]), gamma-glutamyl transferase (γGT [3.7%/2.3~~1%/8.0%]), and bilirubin (~~18.8~~17.1%/5.7%).

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 ~~564~~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*	~~**Very** **common**~~ Infections (bacterial, viral, fungal~~)~~), sepsis[a] ~~**Common**~~ ~~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** ~~Hyperglycaemia~~ Glucose tolerance impaired including hyperglycaemia and hypoglycaemia **Not known** Acidosis[b]~~, glucose tolerance impaired, electrolyte imbalance~~	**Common** Decreased appetite **Uncommon** ~~Hyperglycaemia~~ Glucose tolerance impaired including hyperglycaemia and hypoglycaemia **Not known** Acidosis[b]~~, glucose tolerance impaired, electrolyte imbalance~~

Psychiatric disorders	**Common** Insomnia **Uncommon** Confusional state ~~**Not known**~~ ~~Agitation~~	**Not known** ~~**Rare**~~ Confusional state
Nervous system disorders	**Common** Headache, dizziness **Uncommon** ~~Peripheral~~Intracranial haemorrhage, peripheral sensory neuropathy **Not known** Encephalopathy, ~~intracranial haemorrhage,~~ extrapyramidal disorder, syncope, paraesthesia	~~**Rare**~~ **Uncommon** Headache~~, peripheral sensory neuropathy~~ **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~~, hypotension~~ **Not known** Embolism~~, haemorrhage~~	**Uncommon** Hypertension **Not known** Embolism~~, haemorrhage~~
Respiratory, thoracic and mediastinal disorders	**Common** Dyspnoea, epistaxis **Uncommon** Pneumonitis, pleural effusion, pharyngeal or laryngeal inflammation, ~~cough, laryngeal~~oropharyngeal pain, hiccups **Not known** ~~Oropharyngeal~~Laryngeal pain, ~~hypoxia~~cough, dysphonia	**Uncommon** ~~Dyspnoea, pleural effusion, pharyngeal or laryngeal inflammation~~ ~~**Rare**~~ ~~Epistaxis, pneumonitis~~ Dyspnoea **Not known** ~~Hypoxia~~Pneumonitis, pleural effusion, pharyngeal inflammation, epistaxis

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

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	Not known Renal failure, haemorrhagic cystitis[c], dysuria	
General disorders and administration site conditions	**Very common** Asthenic conditions (fatigue, asthenia, lethargy) **Common** Oedema, pyrexia[e], chills **Uncommon** Non-cardiac chest pain, pain ~~**Not known**~~ ~~Injection site reaction, feeling cold~~	**Common** Fatigue ~~**Rare**~~ **Not known** Non-cardiac chest pain, oedema pyrexia[e]
Investigations	**Very common** ~~Bilirubin~~Blood bilirubin increased **Common** Transaminases (ALT/AST) increased, γGT increased, ~~blood alkaline phosphatase increased~~, C-reactive protein increased, weight decreased, weight increased **Uncommon** Blood alkaline phosphatase increased **Not known** , Blood ~~creatinine increased, blood~~ lactate dehydrogenase (LDH) increased	**Common** ~~Bilirubin~~Blood bilirubin increased, transaminases (ALT/AST) increased, γGT increased **Uncommon** ~~Blood alkaline phosphatase increased~~, C-reactive protein increased **Not known** Blood ~~LDH~~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
~~*Infections*~~
Overall infections
The overall incidence of infections was ~~13~~10.1% (~~74/564).~~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 was lung infection (~~12/74~~

10/62[16.~~2~~1%]). Pathogens included bacteria (e.g. *Staphylococcus*, *Enterococcus*, *Corynebacterium*), viruses (e.g. cytomegalovirus [CMV], Epstein-Barr virus [EBV], herpes) as well as fungi (e.g. candida). 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 (~~7.7~~8.1%).

Neoplasms benign, malignant and unspecified (including cysts and polyps)
One of ~~564~~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 ~~67~~62 of ~~564~~613 adult patients (~~11.9~~10.1%). The most frequent adverse reaction was febrile neutropenia (~~11.3~~10.1%). The lowest incidence was noted with the dose regimen of 10 g/m²/day, day -4 to -2 (4.~~1~~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 ~~25~~21 patients (3.4~~.4~~%). The most frequent adverse reactions were cardiac arrhythmias, e.g. atrial fibrillation (1.~~2~~0%), sinus tachycardia (0.~~9~~8%), supraventricular tachycardia (0.~~4~~3%), and ventricular extrasystole (0.~~4~~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.~~7~~6%).

Gastrointestinal disorders
Gastrointestinal disorders were observed in ~~357~~379 patients (~~63.3~~61.8%). The most frequent adverse reactions reported were nausea (~~39.5~~38.0%), stomatitis (36.4%), vomiting (22.5%), diarrhoea (~~15.6~~14.4%), and abdominal pain (~~10.4~~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 (~~20.4%, 30.3%, 13.1%,~~ 21.5~~.0~~%, 32.2%, 14.8%, 5.9%, and ~~5.5~~6.7% respectively).

Hepatobiliary disorders
The overall incidence of veno-occlusive liver disease (VOD) was 0.~~9~~8% (5/~~564~~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 88 patients; median age 8 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	**Not known** Alkalosis
Nervous system disorders*	**Not known** Headache, 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	**Not known** Hypoxia
Gastrointestinal disorders*	**Very common** Stomatitis/mucositis, diarrhoea, nausea, vomiting, abdominal pain **Common** Dysphagia, oral pain **Not known** Neutropenic colitis, anal	**Very common** Stomatitis/mucositis, nausea **Common** Dysphagia, diarrhoea, vomiting, abdominal pain **Not known** Neutropenic colitis

	inflammation, dyspepsia, proctitis, gastrointestinal pain, constipation	
Hepatobiliary disorders	**Not known** Veno-occlusive liver disease, hepatomegaly, hepatotoxicity	**Not known** Veno-occlusive liver disease
Skin and subcutaneous tissue disorders	**Very common** Pruritus **Common** Dermatitis exfoliative, maculo-papular rash, rash, erythema, pain of skin, skin hyperpigmentation[b], alopecia **Not known** Skin ulcer, erythema multiforme, urticaria, dermatitis bullous, dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, dermatitis diaper[a]	**Common** Dermatitis exfoliative, maculo-papular rash, erythema
Musculoskeletal and connective tissue disorders	**Not known** Pain in extremities	
Renal and urinary disorders	**Not known** Acute kidney injury, renal failure, noninfective cystitis	**Not known** Acute kidney injury, renal failure
Reproductive system and breast disorders	**Not known** Scrotal erythema	
General disorders and administration site conditions	**Very common** Pyrexia[c] **Not known** Chills, fatigue, pain	
Investigations	**Common** Transaminases (ALT/AST) increased, bilirubin increased **Not known** γGT increased	**Common** Bilirubin increased **Uncommon** Transaminases (ALT/AST) increase **Not known** γGT 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 10^9/L.

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

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

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

Nervous system disorders
Seizure in the context of an encephalitis infection was reported in one of 88 paediatric patients. A report from an investigator-initiated trial performed in children with primary immunodeficiencies lists four cases of seizures occurring after other treosulfan-based conditioning regimens (see section 4.4).

בברכה,

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