נובמבר 2024

רופא/ה נכבד/ה,

רוקח/ת נכבד/ה,

חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לרופא של התכשיר:

TREOSULFAN RAZ 5g

בהודעה זו מצוינים רק הסעיפים בהם נעשו שינויים מהותיים בעלון לרופא.

התוספות סומנו בצבע כחול, ההחמרות סומנו בצהוב והמחיקות סומנו בצבע אדום עם קו מחיקה.

העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:

www.health.gov.il וניתן לקבלו מודפס על ידי פנייה לבעל הרישום: רז רוקחות בע"מ, רחוב גשר העץ 30, פארק תעשיות עמק חפר.

בברכה,

לירון שמש

רוקחת ממונה

מרכיב פעיל וחוזק:

TREOSULFAN 5 G/VIAL

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.

להלן העדכונים המהותיים שבוצעו 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 (10.1% /11.6 %), gastrointestinal disorders (nausea [38.0%/~~30.7~~ 26.4%], stomatitis [36.4%/~~69.3~~ 66.1%], vomiting [22.5%/~~43.2~~ 42.1%], diarrhoea [14.4%/33.1%], abdominal pain [9.6%/17.4%]), fatigue (14.4%/~~2.3~~ 1.7%), hepatotoxicity (0.3%/26.4%), febrile neutropenia (10.1%/~~1.1~~ 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%/~~9.1~~ 10.7%]), aspartate transaminase (AST [4.1%/~~8.0~~ 6.6%]), and bilirubin (17.1%/~~5.7~~ 6.6%).

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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 ~~88~~ patients; median age 7 ~~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.

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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** ~~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, 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, ~~anal inflammation~~ dyspepsia, proctitis, gingival pain, ~~gastrointestinal 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, ~~hepatotoxicity~~	~~Not Known~~ ~~Veno-occlusive liver disease~~
Skin and subcutaneous tissue disorders	**Very common** Pruritus, alopecia **Common** Dermatitis exfoliative, maculo-papular rash, rash, erythema, urticaria, pain of skin, skin hyperpigmentation[b], ~~alopecia~~ **Not known** Skin ulcer, erythema multiforme, dermatitis bullous, ~~urticaria~~ dermatitis acneiform, palmar-plantar erythrodysaesthesia syndrome, dermatitis diaper[a]	**Common** Dermatitis exfoliative, maculo-papular rash ~~erythema~~ **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	**Not known** Acute kidney injury, renal failure, noninfective cystitis
General disorders and administration site conditions	**Very common** Pyrexia[c] **Common** Chills **Not known** ~~Chills~~, Face oedema, fatigue, pain	
Investigations	**Very common** ALT increased **Common** AST increased, ~~Transaminase (ALT/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 x 10^9/L.

Description of selected adverse reactions

Infections

The overall incidence of infections in ~~88~~ 121 paediatric patients was 11.46% (~~10~~14/~~88~~121) and thus comparable to that seen in adults. The frequency was higher in the paediatric age group 12–17 years (6/~~35~~39 [~~17.1~~15.4%]) compared to younger children (~~4~~7/~~53~~59 [~~7.5~~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 ~~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. 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 ~~21~~ 22 (~~16~~ 17, 26) days in paediatric patients with malignant diseases and ~~24~~ 20 (~~17~~ 15, ~~26~~ 25) days in patients with non-malignant disorders.

Nervous system disorders

Seizure in the context of an encephalitis infection was reported in one of ~~88~~ 121 paediatric patients. A report from an investigator-initiated trial performed in children with primary immunodeficiencies lists ~~four~~ five cases of seizures occurring after other treosulfan-based conditioning regimens (see section 4.4).

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5.1 Pharmacodynamic properties

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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 ~~12~~ 24 months was ~~91.4~~ 85.7% (90% CI ~~83.9~~ 77.1-~~95.5~~ 91.2%). Overall, ~~7~~ 12 of the 70 patients (~~10.0~~ 17.1%) died, ~~two~~ 8 patients because of relapse/progression, ~~three~~ and 4 patients transplant-related. The freedom from transplant-related ~~and two further patients for other reasons~~ mortality until day +100 after HSCT (primary endpoint) was 98.6% (90% CI 93.4–~~99.7~~ 99.9%). ~~because one of the 70 patients died due to transplantation/treatment-related cause until day +100 after HSCT.~~

One transplant/treatment-related death was noted until day +100 after HSCT. Transplant-related mortality at ~~12~~ 24 months was ~~2.9~~ 4.6% (90% CI ~~0.9~~ 1.8 – ~~8.9~~ 11.4%).

Sixteen ~~Eleven~~ patients suffered from relapse/progression. The cumulative incidence of relapse/progression was ~~15.7~~ 23.0% (90% CI ~~8.6~~ 14.7- ~~22.9~~ 31.3%) at month +24.

~~The European Medicines Agency has deferred the obligation to submit the results of a study with treosulfan-based conditioning in paediatric patients with non-malignant diseases (see section 4.2 for information on paediatric use).~~

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

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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).

~~Mean apparent terminal half-life of treosulfan was comparable between the different age groups and ranged between 1.3 and 1.6 hours.~~

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.