אוקטובר 2023

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הודעה על עדכון עלון לרופא תכשיר
בוסולפאן רז 6 מ"ג/מ"ל BUSULFAN RAZ 6MG/ML

חברת רז רוקחות בע"מ מבקשת להודיעכם על עדכון העלון לרופא של התכשיר בוסולפאן רז 6 מ"ג/מ"ל.

חומר פעיל: Busulfan 6 mg/ml

צורת מינון: Concentrate for Solution for Infusion

התוויה מאושרת:
BUSULFAN RAZ 6 MG/ML is indicated for use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation.

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 בכתובת
https://israeldrugs.health.gov.il/#!/medDetails/171%2090%2036140%2000

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

עלון לרופא

4.3 CONTRAINDICATIONS

BUSULFAN RAZ 6 MG/ML is contraindicated in patients with hypersensitivity to the active substance busulfan or to any of the excipients.

BUSULFAN RAZ 6 MG/ML is contraindicated in women who are pregnant and/or lactating.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Platelet and red blood cell support, as well as the use of growth factors such as G-CSF, should be employed as medically indicated.

Myelosuppression

In adults, absolute neutrophil counts <0.5 x 10^9/L at a median of 4 days post-transplant occurred in 100% of patients and recovered at median day 10 and 13 days following autologous and allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively).

In children, absolute neutrophil counts < 0.5 x 10^9/L at a median of 3 days post-transplant occurred in 100% of patients and lasted 5 and 18.5 days in autologous and allogeneic

transplant respectively. In children, thrombocytopenia (<25 x 10^9/L or requiring platelet transfusion) occurred in 100% of patients. Anaemia (haemoglobin <80 g/L) occurred in 100% of patients.

Infection

In children, infections (documented and non-documented febrile neutropenia) were experienced in 89% of patients (49/55). Mild/moderate fever was reported in 76% of patients.

Fanconi anaemia

The Fanconi anaemia cells have hypersensitivity to cross-linking agents. There is limited clinical experience of the use of busulfan as component of conditioning regimen prior to HSCT in children with Fanconi anaemia. Therefore, BUSULFAN RAZ 6 MG/ML should be used with caution in this type of patients.

Graft versus host disease

In adults, the incidence of acute graft versus host disease (a-GVHD) data was collected in OMCBUS-4 study (allogeneic) (n=61). A total of 11 patients (18%) experienced a- GVHD. The incidence of a-GVHD grades I-II was 13% (8/61), while the incidence of grade III-IV was 5% .(3/61) Acute GVHD was rated as serious in 3 patients. Chronic GVHD (c-GVHD) was reported if serious or the cause of death and was reported as the cause of death in 3 patients.

In children, the incidence of acute graft versus host disease (a-GVHD) data was collected in allogeneic patients (n=28). A total of 14 patients (50%) experienced a-GVHD. The incidence of a-GVHD grades I-II was 46.4% (13/28), while the incidence of grade III-IV was 3.6% .(1/28)Chronic GVHD was reported only if it is the cause of death: one patient died 13 months posttransplant.

Liver toxicity

In adults, 15% of serious adverse events involved liver toxicity. HVOD is a recognized potential complication of conditioning therapy post-transplant. Six of 103 patients (6%) experienced HVOD. HVOD occurred in 8.2% (5/61) allogeneic patients (fatal in 2 patients) and 2.5%(1/42) of autologous patients. Elevated bilirubin (n=3) and elevated AST (n=1) were also observed. Two of the above four patients with serious serum hepatotoxicity were among patients with diagnosed HVOD. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior stem cell transplant may be at an increased risk (see Section 4.8 ADVERSE EFFECTS).

In children grade 3 elevated transaminases were reported in 24% of patients. HVOD was reported in 15% (4/27) and 7% (2/28) of the autologous and allogenic transplant respectively. HVOD observed were neither fatal nor severe and resolved in all cases.

Repeated doses of the solvent, DMA, produced signs of liver toxicity, the first being increases in serum clinical enzymes followed by histopathological changes in the hepatocytes. Higher doses can produce hepatic necrosis and liver damage can be seen following single high exposures.

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Cardiac toxicity

Cardiac tamponade has been reported in children with thalassemia (8/400 or 2% in one series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children died and two were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. No patients treated in the BUSULFAN RAZ 6 MG/ML clinical trials experienced cardiac tamponade or other specific cardiac toxicities related to BUSULFAN RAZ 6 MG/ML. However cardiac function should be monitored regularly in patients receiving BUSULFAN RAZ 6 MG/ML (see Section 4.8 ADVERSE EFFECTS).

Pulmonary toxicity

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in Adverse Effects studies in one patient who died, although, no clear etiology was identified. In addition, busulfan might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic agents. Therefore, attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation (see Section 4.8 ADVERSE EFFECTS).

High-risk patients

HSCT is generally not recommended in high-risk patients because of poorer outcomes. High-risk patients include those of age >50 years and those with prior myeloablative transplants, organ dysfunction, poor performance status or extensive prior chemotherapy. Careful consideration of the risks and benefits of BUSULFAN RAZ 6 MG/ML is necessary in these patients. Non-myeloablative conditioning regimens, with a reduced dose or reduced duration of BUSULFAN RAZ 6 MG/ML, have demonstrated a low rate of regimen related toxicity in high-risk patients but can lead to an increase in the incidence of disease relapse (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Use in hepatic impairment

BUSULFAN RAZ 6 MG/ML as well as busulfan has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolized through the liver, caution should be observed when BUSULFAN RAZ 6 MG/ML is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. It is recommended when treating these patients that serum transaminase, alkaline phosphatase, and bilirubin should be monitored regularly 28 days following transplant for early detection of hepatotoxicity.

Use in renal impairment

Studies in renally impaired patients have not been conducted, however, as busulfan is moderately excreted in the urine, dose modification is not recommended in these patients. Caution is recommended. In a Phase I study conducted in patients with metastatic renal carcinoma, all of whom had only one functioning kidney, a conditioning regimen of once daily BUSULFAN RAZ 6 MG/ML in combination with fludarabine gave a high incidence of regimen related toxicity.

Use in the elderly

Patients older than 50 years of age have been successfully treated with BUSULFAN RAZ 6 MG/ML. Refer to Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials for information on the use of BUSULFAN RAZ 6 MG/ML in elderly patients in non-myeloablative conditioning regimens. Only limited information is available for the safe use of BUSULFAN RAZ 6 MG/ML in patients older than 60 years.

Paediatric use

Data on the use of BUSULFAN RAZ 6 MG/ML in children are limited (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials) and there have been no studies in juvenile animals. The level of DMA in BUSULFAN RAZ 6 MG/ML is higher than in other products and this may represent a particular risk to children. Pulmonary thrombosis and vasculitis were seen with DMA alone in clinical trials in adults and hepatoxicity and neurotoxic effects have been reported with DMA in the literature.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Patients should be monitored for signs of busulfan toxicity when itraconazole is used as an antifungal prophylaxis with IV busulfan.

Published studies in adults have described that ketobemidone (analgesic) might be associated with high levels of plasma busulfan; therefore, special care is recommended when combining these two drugs.

It has been reported that when using the BuCy2 regimen in adults the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the development of toxicities. A reduced incidence of Hepatic Veno-Occlusive Disease (HVOD) and other regimen related toxicity have been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24 hours.

It has also been reported that when using the BuMel regimen in paediatric patients the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

Paracetamol is described to decrease glutathione levels in blood and tissues and may therefore decrease busulfan clearance when used in combination. Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with BUSULFAN RAZ 6 MG/ML due to a possible decrease in the metabolism of busulfan.

No interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan. Periodic monitoring of renal function should be considered during therapy with BUSULFAN RAZ 6 MG/ML (see Section 4.8 ADVERSE EFFECTS).

Iron chelating agents

Decreased clearance of busulfan has been observed with deferasirox. The mechanism of this interaction is not fully elucidated. Iron chelating agents should be discontinued well in advance of administration of busulfan to avoid increased exposure to busulfan.

4.6 FERTILITY, PREGNANCY AND LACTATION

Busulfan can impair fertility. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. Therefore, men treated with BUSULFAN RAZ 6 MG/ML 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 BUSULFAN RAZ 6 MG/ML. Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in premenopausal patients. Busulfan treatment in a pre- adolescent girl prevented the onset of puberty due to ovarian failure. Busulfan may cause temporary or permanent infertility in females.

Busulfan disrupted spermatogenesis in rats, guinea-pigs, rabbits and monkeys, depleted oocytes and impaired fertility in female mice, and induced sterility in male rats and male hamsters. The solvent dimethylacetamide (DMA) was found to impair fertility in studies with male and female rodents.

Use in pregnancy – Category D

BUSULFAN RAZ 6 MG/ML is contraindicated during pregnancy. Busulfan and DMA reduced fetal weight and caused embryofetal lethality and malformations in various animal species in pre-clinical studies. For busulfan, terata were observed in the musculoskeletal system of mice, rats and rabbits, while DMA-induced malformations occurred in the heart, major vessels and oral cavity in the rat. Administration of busulfan to pregnant rats caused sterility in male and female offspring due to the destruction of germinal cells in the testes and ovaries.

There are no adequate and well-controlled studies of either busulfan or DMA in pregnant women. A few cases of congenital abnormalities have been reported with low-dose oral busulfan, not necessarily attributable to the drug, and third trimester exposure may be associated with impaired intrauterine growth.

Use in lactation

Patients who are taking BUSULFAN RAZ 6 MG/ML must be advised not to breast-feed. It is not known whether busulfan and DMA are excreted in human milk. Because of the potential for severe adverse effects, including tumourigenicity, breast-feeding should be discontinued at the start of therapy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Table 1 Adverse Reactions Reported both in Adults and Children
(Very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100))

System Organ Class	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Leukopenia Neutropenia Thrombocytopenia Anaemia Pancytopenia Febrile neutropenia		

System Organ Class	Very Common	Common	Uncommon
Nervous system disorders	Insomnia Dizziness Depression	Confusion	Delerium Nervousness Hallucination Agitation Encephalopathy Cerebral haemorrhage Seizure
Respiratory thoracic and mediastinal disorders	Dyspnoea Rhinitis Pharyngitis Cough Hiccup Epistaxis Abnormal breath sounds	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Constipation Dyspepsia Anus discomfort Abdominal pain Ascites	Oesophagitis Ileus Haematemesis	Gastrointestinal haemorrhage
Hepato-biliary disorders	Hepatomegaly Jaundice	Hepatic veno-occlusive disease	
Skin and subcutaneous tissue disorders	Rash Pruritis Alopecia	Erythema Pigmentation disorder Skin desquamation	
Investigations	Transaminases increased Bilirubin increased GGT increased Weight increased Alkaline phosphatases increased		

Note: One patient in the BUSULFAN 6 MG/ML trials experienced a fatal case of acute respiratory distress syndrome with subsequent respiratory failure associated with intestinal pulmonary fibrosis. Cardiac tamponade and alterations of cornea and lens of the eye have been reported with oral busulfan.

4.9 OVERDOSE

It must be considered that overdose of BUSULFAN RAZ 6 MG/ML will also increase exposure to DMA. In human the principal toxic effects were hepatotoxicity and central nervous system effects. CNS changes precede any of the more severe side effects. No

specific antidote for DMA overdose is known. In case of overdose, management would include general supportive care.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING OF THE PRODUCT

Any unused product or waste should be disposed of in accordance with local requirements for cytotoxic drugs.

As with other cytotoxic compounds, caution should be exercised in handling and preparing the solution of BUSULFAN RAZ 6 MG/ML:

- The use of gloves and protective clothing is recommended.
- If BUSULFAN RAZ 6 MG/ML or diluted BUSULFAN RAZ 6 MG/ML contacts the skin or mucosa, wash them thoroughly with water immediately.

Instructions for use

Do not flush residual drug in the administration tubing as rapid infusion of BUSULFAN RAZ 6 MG/ML has not been tested and is not recommended.

BUSULFAN RAZ 6 MG/ML contains no antimicrobial agent. Product is for single use in one patient only. Only a clear solution without any particles should be used. Opened vials should be used immediately to assure sterility. Discard any residue

בברכה,
רז רוקחות בע"מ