יוני 2024

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,
חברת רז רוקחות מבקשת להודיעכם על עדכון העלון לרופא של התכשיר: CARMUSTINE RAZ 100 MG
מרכיב פעיל: CARMUSTINE 100 mg
צורת מינון ומתן: POWDER AND SOLVENT FOR CONCENTRATE FOR SOLUTION FOR INFUSION
התוויה מאושרת לתכשיר:
Carmustine is indicated as palliative therapy as a single agent or in established combination therapy with other
approved agents in the following:
• Brain tumors - glioblastoma, medulloblastoma, astrocytoma and metastatic brain tumors.
• Multiple myeloma - in combination with glucocorticoid such as prednisone.
• Hodgkin's disease - as secondary therapy in combination with other approved drugs in patients who relapse
while being treated with primary therapy, or who fail to respond to primary therapy.
• Non-Hodgkin's lymphomas - as secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

בהודעה זו מצוינים רק הסעיפים בהם נעשו <u>שינויים מהותיים</u> בעלון לרופא.
התוספות סומנו בצבע כחול, החמרות סומנו בצהוב, מחיקות בקו חוצה אדום.
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, גשר בעץ 31, פארק עשיות עמק חפר,ישראל.

בברכה,
יבגני קבלרצי'ק
רוקח ממונה

<u>עדכון עלון לרופא:</u>

[...]

3. PHARMACEUTICAL FORM

Powder and solvent for concentrate~~d~~ for solution for infusion.

Appearance of powder for reconstitution: Yellowish.

Appearance of solvent: Clear, colorless, mobile liquid.

Appearance of reconstituted solution: clear colorless to ~~light yellow~~ yellowish solution, essentially free from visible contamination.

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4.3. Contraindications

Carmustine Raz 100mg should not be given to individuals who:

- have demonstrated a previous hypersensitivity to the active substance (carmustine), to other nitrosoureas or to any of the excipients listed in section 6.1
- suffer from decreased circulating platelets, leucocytes or erythrocytes either from previous chemotherapy or other causes.
- **higher degree of renal impairment.**
- **Pregnancy and lactation (see section 4.6).**

4.4. Special warnings and precautions for us

Carmustine should be used only by physicians with specific experience in the field of chemotherapy.

Myelosuppression

Delayed and cumulative bone marrow depression (especially thrombocytopenia and leukopenia) that can lead to bleeding and severe infections in patients already at risk is a common and severe toxic side effect of carmustine.

Hematologic parameters (leukocytes, granulocytes, hemoglobin, platelets) should be checked prior to initiation of therapy and monitored regularly during therapy until at least 6 weeks after administration of a dose (see section 4.2). Repeated doses of ~~Carmubris~~ carmustine should not be given more frequently than every 6 weeks.

The most common and dose-limiting adverse reaction is reversible and delayed-onset myelosuppression, which usually occurs after 4 to 6 weeks and whose severity depends on the dose. The myelosuppressive effect of carmustine is cumulative.

The lowest platelet count is observed after 4 to 5 weeks, and the lowest leukocyte count is observed 5 to 6 weeks after the start of treatment. Thrombocytopenia is generally more severe than leukocytopenia, but both side effects may be dose-limiting.

Monitoring Organ Functions

In addition, hepatic, renal, and pulmonary functions should be assessed prior to treatment and monitored regularly during therapy (see Section 4.8).

Intra-arterial administration

I.a. tolerability has not been evaluated. Severe tissue damage is to be expected in case of accidental i.a. administration.

Direct application of ~~Carmubris~~ carmustine into the carotid artery should be considered experimental and has been associated with ocular toxicity.

Pulmonary Toxicity

Pulmonary toxicity has been observed in up to 30% of patients. Early-onset pulmonary toxicity (within 3 years of treatment) resulted in pulmonary infiltrates and/or pulmonary fibrosis, which in some cases was fatal. Patients ranged in age from 22 months to 72 years. Risk factors included smoking, respiratory disease, existing radiographic abnormalities, sequential or concurrent chest irradiation, and combination with other agents that may cause lung injury. The incidence of adverse reactions is likely dose-dependent. Cumulative doses of 1200-1500 mg/m^2 have been associated with an increased

likelihood of pulmonary fibrosis. Spirometry (FVC, DLCO) should be performed regularly during treatment. Patients who have a baseline spirometry value of <70% of the expected forced expiratory vital capacity (FVC) or carbon monoxide diffusing capacity (DLCO) are particularly at risk.

Cases of very late-onset pulmonary fibrosis (up to 17 years after treatment) have been observed in patients who received carmustine in childhood or adolescence.

A long-term follow-up of 17 patients who survived childhood brain tumors showed that 8 of them died of pulmonary fibrosis. Two of these 8 deaths occurred within the first 3 years of treatment and 6 within 8-13 years of treatment. The mean age (at the time of treatment) of the patients who died was 2.5 years (1-12 years) and the mean age of the long-term survivors was 10 years (5-16 years). All patients younger than 5 years at the time of treatment died of pulmonary fibrosis. Neither the carmustine dose nor additional administration of vincristine or spinal irradiation affected the fatal outcome.
Pulmonary fibrosis was found in all remaining survivors available for followup.The risk-benefit ratio of carmustine therapy must be carefully weighed because of the high risk of pulmonary toxicity.

Renal Toxicity
Renal changes with decrease in renal size, progressive azotemia, and renal failure have been observed after high-cumulative doses and after long-term treatment with carmustine and related nitrosoureas.

Liver Toxicity
Hepatic necrosis may occur after administration of doses higher than those recommended in the dosing instructions.

High-dose therapy
High-dose therapy with carmustine increases the risk and severity of infections, cardiac, hepatic, gastrointestinal, and renal toxicity, as well as nervous system disorders and electrolyte disturbances (hypokalemia, hypomagnesemia, and hypophosphatemia).

Comorbidities and poor disease status
Patients with comorbidities and poorer disease status are at higher risk for adverse events. This is especially important for elderly patients.

Local Toxicity
Reactions at the site of administration may occur during administration of ~~Carmubris~~ carmustine (see section 4.8). Considering the possibility of extravasation, close monitoring of the infusion site is recommended due to possible infiltration during administration. A specific method for managing extravasation is not currently known.
Accidental contact of the reconstituted infusion solution with the skin has resulted in burns and excessive pigmentation in the affected areas.
Local soft tissue toxicity resulting from extravasation of ~~Carmubris~~ carmustine has been reported. Infiltration of ~~Carmubris~~ carmustine may cause swelling, pain, erythema, burning, and skin necrosis.

Important information about other components:
Ethanol
This drug contains 0.57% ethanol (alcohol) by volume, or up to 7.68 g per dose. This is equivalent to 11.32 ml of beer or 4.72 ml of wine per dose. These amounts are derived from a calculated example of 320 mg carmustine (200 mg/ m^2 ~~KOF~~ BSA for 1.6 m^2) dissolved in 9.6 ml (sterile absolute ethanol) and a final infusion volume of 1696 ml (see Section 6.6). Health risk for patients suffering from alcoholism. Should be considered in pregnant or lactating women and in children and patients at increased risk due to liver disease or epilepsy. The amount of alcohol in this medicine may affect the effectiveness of other medicines. The amount of alcohol in this medicine may impair the ability to drive and operate machinery.

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4.8. Undesirable effects

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MedDRA system organ class	Frequency	Adverse effects
		Clinically important side effects are in *italics*
Infections and Infestations	Not known	Opportunistic infections (including fatal outcome)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute leukemias, bone marrow dysplasias; following long-term use.
	Not known	**Secondary malignancies**
Blood and lymphatic system disorders	Common	Anaemia.
	Very common	*Myelosuppression; onset 7-14 days, nadir 21-35 days, recovery 42-56 days; cumulative, dose related, delayed and often biphasic.*
Immune system disorders	**Not known**	**Allergic reaction**
Metabolism and nutrition disorders	**Not known**	**Electrolyte disorders (hypokalaemia, hypomagnesaemia, and hypophosphataemia)**
Nervous system disorders	Very common	Ataxia, dizziness, headache.
	Common	Encephalopathy (high-dose therapy and dose-limiting).
	Not known	Muscular pain, status epilepticus, seizure, grand mal seizure.
Eye disorders	Very common	Ocular toxicities, transient conjunctival flushing and blurred vision; retinal haemorrhages.
	Rare	**Neuroretinitis**
Cardiac disorders	Very common	Hypotension, due to alcohol content of diluent (high-dose therapy)
	Not known	Tachycardia, chest pain
Vascular disorders	Very common	Phlebitis.
	Rare	Veno-occlusive disease (high-dose therapy).

Respiratory, thoracic and mediastinal disorders	Very common	*Pulmonary toxicity[1],interstitial fibrosis (with prolonged therapy and cumulative dose > 1400 mg/m^2) Pneumonitis (for doses >450mg/m^2).*
	Rare	*Interstitial fibrosis (with lower doses).*
Gastrointestinal disorders	Very common	*emetogenic potential: >250 mg/m^2 high; ≤ 250 mg/m^2 high-moderate*
		Nausea and vomiting, severe; begins within 2- 4 h of administration and lasts for 4-6 h.
	Common	Anorexia, constipation, diarrhoea, stomatitis.
	Rare	Bleeding in the gastrointestinal tract
	Not known	Neutropenic enterocolitis
Hepatobiliary disorders	Common	Hepatotoxicity, reversible, delayed up to 60 days after administration (high-dose therapy and dose-limiting), manifested by: - bilirubin, reversible increase - alkaline phosphatase, reversible increase - SGOT, reversible increase.
Skin and subcutaneous tissue disorders	Not known	*extravasation hazard: vesicant*
	Very common	Dermatitis with topical use improves with reduced concentration of compounded product, hyperpigmentation, transient, with accidental skin contact.
	Common	Alopecia, flushing (due to alcohol content of diluent; increased with administration times <1-2 h), injection site reaction.
Renal and urinary disorders	Rare	*Renal toxicity (for cumulative doses <1,000 mg/m^2).*
Reproductive system and breast disorders	Rare	Gynecomastia.
	Not known	Infertility, teratogenesis.
General disorders and administration site conditions	Very rare	Thrombophlebitis

[1]Pulmonary toxicity is also manifested as pneumonitis and interstitial lung disease in post-marketing experience.

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6.6. Special precautions for disposal

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Reconstitution as recommended results in a clear colourless to yellowish solution which has to be further diluted to 500 ml sodium chloride for injection, or 5% glucose for injection.

The reconstituted solution must be given intravenously and should be administered by I.V. drip over one to two hour period. Injection of Carmustine over shorter periods of time may produce intense pain and burning at the site of injection.

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