רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא של

Ribomustin 25mg/100mg

חומר פעיל:

25mg /100mg Bendamustine hydrochloride

להלן עדכונים בעלון לרופא (טקסט מסומן בצהוב משמעותו החמרה, טקסט מסומן בירוק משמעותו עדכון, ~~טקסט באדום עם קו משמעותו מחיקה~~):

[...]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of Ribomustin 25 mg contains 25 mg bendamustine hydrochloride.
One vial of Ribomustin 100 mg contains 100 mg bendamustine hydrochloride.

1 ml of the concentrate contains 2.5 mg bendamustine hydrochloride when reconstituted according to section 6.6.
For ~~a~~ the full list of excipients, see section 6.1.

[...]

4.2 Posology and method of administration

Posology

Monotherapy for chronic lymphocytic leukaemia
100 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 4 weeks up to 6 times.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab
120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks for at least 6 times.

[...]

4.4 Special warnings and precautions for use

[...]

Infections

Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections~~.~~. In case of low CD4-positive T-cell counts (< 200/µl) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. All~~Therefore~~, patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.

[...]

Skin reactions
A number of skin reactions have been reported. These events have included rash, severe cutaneous ~~toxic skin~~ reactions and bullous exanthema. Cases of Stevens – Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), some fatal, have been reported with the use of bendamustine hydrochloride. Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. When skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, Ribomustin should be withheld or discontinued. For severe skin reactions with suspected relationship to bendamustine hydrochloride, treatment should be discontinued.

[...]

Tumour lysis syndrome
Tumour lysis syndrome (TLS) associated with Ribomustin treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of Ribomustin and, without intervention, may lead to acute renal failure and death. Preventive measures such as adequate hydration, close monitoring of blood chemistry, particularly potassium and uric acid levels~~,~~ and the use of hypouricemic agents (allopurinol and rasburicase) should be considered prior to therapy. There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were ~~are~~ administered concomitantly.

[...]

4.5 Interaction with other medicinal products and other forms of interaction

[...]

Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme (see section 5.2). Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir~~,~~ and cimetidine exists.

[...]

4.8 Undesirable effects

The most common adverse reactions with bendamustine hydrochloride are hematological adverse reactions (leukopenia, thrombopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

The table below reflects the data obtained with bendamustine hydrochloride.

Table 1: Adverse reactions in patients treated with bendamustine hydrochloride.

MedDRA system organ class	**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**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Infection NOS~~*~~ Including Opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B)		Pneumocystis jirovecii pneumonia	Sepsis	Pneumonia primary atypical	
Neoplasma benign, malignant and unspecified (including cyst and polyp)		Tumour lysis syndrome	Myelodysplastic syndrome, acute myeloid leukemia			
Blood and lymphatic system disorders	Leukopenia NOS~~*~~, Thrombocytopenia Lymphopenia	Haemorrhage, Anaemia, Neutropenia	Pancytopenia	Bone marrow failure	Haemolysis	
Immune system disorders		Hypersensitivity NOS~~*~~		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders	Headache	Insomnia~~,~~ Dizziness		Somnolence, Aphonia	Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders,	

MedDRA system organ class	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	Not known (cannot be estimated from the available data)
					Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	Pericardial effusion, Myocardial infarction, Cardiac failure		Tachycardia	Atrial fibrillation
Vascular disorders		Hypotension, Hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	Pneumonitis Pulmonary alveolar haemorrhage
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS* Urticaria		Erythema, Dermatitis, Pruritus, Maculopapular Rash, Hyperhidrosis		Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN) Drug reaction with eosinophilia and systemic symptoms (DRESS)*
Reproductive system and breast disorders		Amenorrhea			Infertility	
Hepatobiliary disorder						Hepatic failure
General disorders and administration site conditions	Mucosal inflammation, Fatigue, Pyrexia	Pain, Chills, Dehydration, Anorexia			Multi organ failure	
Investigations	Haemoglobin decrease, Creatinine increase, Urea increase	AST increase, ALT increase, Alkaline phosphatase increase, Bilirubin				

MedDRA system organ class	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	Not known (cannot be estimated from the available data)
		increase, Hypokalemia				
Renal and urinary disorders						Renal failure

NOS = Not otherwise specified

(*=combination therapy with rituximab)

[...]

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

[...]

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents.
ATC code: L01AA09
Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytocidal effect of bendamustine hydrochloride is based essentially on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired. The antitumour effect of bendamustine hydrochloride has been demonstrated by several *in-vitro* studies in different human tumour cell lines (breast cancer, non-small cell and small cell lung cancer, ovarian ~~ovary~~ carcinoma and different leukaemia) and *in-vivo* in different experimental tumour models with tumours of mouse, rat and human origin (melanoma, breast cancer, sarcoma, lymphoma, leukaemia and small cell lung cancer).

[...]

Chronic lymphocytic leukaemia

The indication for use in chronic lymphocytic leukaemia is supported by a single open label study comparing bendamustine with chlorambucil. In ~~a~~ the prospective, multi-centre, randomised, study, 319 previously untreated patients with chronic lymphocytic leukaemia

stage Binet B or C requiring therapy were included. The first line therapy with bendamustine hydrochloride 100 mg/m² i.v. on days 1 and 2 (BEN) was compared to treatment with chlorambucil 0.8 mg/kg days 1 and 15 (CLB) for 6 cycles in both arms. Patients received allopurinol in order to prevent tumour lysis syndrome.
Patients with BEN have a significantly longer median progression free survival than patients with CLB treatment (21.5 versus 8.3 months, $p < 0.0001$ in the latest follow-up). Overall survival was not statistically significantly different (median not reached). The median duration of remission ~~is~~ was 19 months with BEN and 6 months with CLB treatment ($p < 0.0001$). The safety evaluation in both treatment arms did not reveal any unexpected undesirable effects in nature and frequency. The dose of BEN was reduced in 34% of the patients. Treatment with BEN was discontinued in 3.9% of patients due to allergic reactions.

Indolent non-Hodgkin's lymphomas

The indication for indolent non-Hodgkin's lymphomas relied on two uncontrolled phase II trials.
In the pivotal ~~-~~prospective, multi-centre, open study 100 patients with indolent B-cell non-Hodgkin´s lymphomas refractory to rituximab mono- or combination therapy were treated with BEN single agent. Patients had received a median of 3 previous chemotherapy or biological ~~biologic~~ therapy courses. The median number of previous rituximab-containing courses was 2. The patients had had no response or there had been progression ~~progress~~ within 6 months after rituximab treatment. The dose of BEN was 120 mg/m² i.v. on days 1 and 2 planned for at least 6 cycles. Duration of treatment depended on response (6 cycles planned). The overall response rate was 75% including 17% complete (CR and CRu) and 58% partial response as assessed by independent review committee. The median duration of remission was 40 weeks. BEN was generally well tolerated when given in this dose and schedule.
The indication is further supported by another prospective, multi-centre, open study including 77 patients. The patient population was more heterogeneous including: indolent or transformed B-cell non-Hodgkin's lymphomas refractory to rituximab mono- or combination therapy. The patients had no response or there had been progression ~~progress~~ within 6 months or had had an untoward reaction to prior rituximab treatment. Patients had received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses had been ~~was~~ 2. The overall response rate was 76% with a median duration of response of 5 months (29 [95% CI 22.1, 43.1] weeks).

[...]

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2ß}$ after 30 min i.v. infusion of 120 mg/m^2 area to 12 subjects was 28.2 minutes.
Following 30 min i.v. infusion the central volume of distribution was 19.3 l. Under steady-state conditions following i.v. bolus injection the volume of distribution was 15.8-20.5 l~~L~~.
More than 95% of the substance is bound to plasma proteins (primarily albumin).

Ribomustin™
bendamustine HCL

astellas

Biotransformation ~~Metabolism~~

A major route of clearance of bendamustine is the hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Another major route of bendamustine metabolism involves conjugation with glutathione. In-vitro bendamustine does not inhibit CYP 1A4, CYP 2C9/10, CYP 2D6, CYP 2E1 or ~~and~~ CYP 3A4.

[...]

6.3 Shelf life

~~3 years.~~ The expiry date of the product is indicated on the packaging materials.

[...]

6.6 Special precautions for disposal <and other handling>

When handling Ribomustin, inhalation, skin contact or contact with mucous membranes should be avoided (wear gloves and protective clothes!). Contaminated body parts should be carefully rinsed with water and soap, the eye should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid-impermeable, absorbent ~~absorbing~~ disposable foil. Pregnant personnel should be excluded from handling cytostatics

העלון לרופא נשלח למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתו לאתר וניתן לקבלו מודפס על ידי פניה לבעל הרישום אסטלס פארמה אינטרנשונל בי.וי., ת.ד. 11458, ראש העין.

בברכה
גאי וגנר
רוקח ממונה