הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך 01.06.2017

שם תכשיר באנגלית ומספר הרישום:

- **RIBOMUSTIN 100 MG (152 40 33966 00 + 152 40 33966 01)**
- **RIBOMUSTIN 25 MG(152 39 33961 00 + 152 39 33961 01)**

שם בעל הרישום: _ASTELLAS PHARMA INTERNATIONAL B.V.

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
4.4 Special warnings a precautions for use	Myelosuppression Patients treated with bendamustine hydrochloride may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least ly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values 00/µl or > 100,000/µl, respectively. Infections Infection, including pneumonia and sis, has been reported. In rare cases, infection has been associated with pitalization, septic shock and death. Patients with neutropenia and/or nphopenia following treatment with ndamustine hydrochloride are more	Myelosuppression Patients treated with bendamustine hydrochloride may experience myelosuppression. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least ekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4,000/µl or > 100,000/µl, respectively. Infections Serious and fatal infections have occurred with endamustine hydrochloride, including bacterial (sepsis, pneumonia) and opportunistic infections such as neumocystis jirovecii pneumonia (PJP), varicella zoster s (VZV) and cytomegalovirus (CMV). Treatment with bendamustine hydrochloride may cause prolonged mphocytopenia (< 600/µl) and low CD4-positive T-cell T-helper cell) counts (< 200/µl) for at least 7–9 months fter the completion of treatment. Lymphocytopenia and 04-positive T-cell depletion are more pronounced when

bendamustine is combined with rituximab Patients with phopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections.. Therefore, patients should be monitored for respiratory signs and ptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of ndamustine hydrochloride should be considered if there are signs of (opportunistic) infections. Hepatitis B reactivation Reactivation of hepatitis B in patients who are chronic carriers of this virus has occurred after these patients ived bendamustine hydrochloride. Some cases resulted cute hepatic failure or a fatal outcome. Patients should sted for HBV infection before initiating treatment with amustine hydrochloride. Experts in liver disease and in the treatment of hepatitis B should be consulted before eatment is initiated in patients with positive hepatitis B ts (including those with active disease) and for patients who test positive for HBV infection during treatment. riers of HBV who require treatment with bendamustine ydrochloride should be closely monitored for signs and ptoms of active HBV infection throughout therapy and r several months following termination of therapy (see section 4.8). ~~Infection, including pneumonia and sepsis, has been ported. In rare cases, infection has been associated with hospitalization, septic shock and death. Patients with utropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to infections. Patients with myelosuppression following amustine hydrochloride treatment should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms.~~ Skin reactions A number of skin reactions have been reported. These nts have included rash, toxic skin reactions and bullous xanthema. Cases of Stevens – Johnson syndrome (SJS) d Toxic Epidermal Necrolysis (TEN), some fatal, have n reported with the use of bendamustine hydrochloride. me events occurred when bendamustine hydrochloride s given in combination with other anticancer agents, so the precise relationship is uncertain. ~~Where~~ When skin eactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are	sceptible to infections. Patients with myelosuppression following ndamustine hydrochloride treatment ld be advised to contact a physician if they have symptoms or signs of ction, including fever or respiratory symptoms. Skin reactions number of skin reactions have been eported. These events have included sh, toxic skin reactions and bullous thema. Some events occurred when damustine hydrochloride was given n combination with other anticancer agents, so the precise relationship is certain. Where skin reactions occur, may be progressive and increase in verity with further treatment. If skin actions are progressive, Ribomustin ld be withheld or discontinued. For severe skin reactions where a relationship to bendamustine ydrochloride is suspected, treatment should be discontinued. Patients with cardiac disorders During treatment with bendamustine hydrochloride the concentration of assium in the blood must be closely onitored and potassium supplement be given when K^+ <3,5 mEq/l, and G measurement must be performed. Nausea, vomiting An antiemetic may be given for the mptomatic treatment of nausea and vomiting. Tumour lysis syndrome mour lysis syndrome associated with mustin treatment has been reported patients in clinical trials. The onset ds to be within 48 hours of the first dose of Ribomustin and, without ntervention, may lead to acute renal ure and death. Preventive measures clude adequate volume status, close monitoring of blood chemistry,	

progressive, Ribomustin should be withheld or discontinued. For severe skin reactions ~~where~~ with pected ~~a~~ relationship to bendamustine hydrochloride ~~is suspected~~, treatment should be discontinued.

~~Patients with c~~Cardiac disorders

During treatment with bendamustine hydrochloride the oncentration of potassium in the blood of patients with iac disorders must be closely monitored and potassium pplement must be given when K^+ <3,5 mEq/l, and ECG measurement must be performed.

Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride reatment. Patients with concurrent or history of cardiac disease should be observed closely.

Nausea, vomiting

ntiemetic may be given for the symptomatic treatment of nausea and vomiting.

Tumour lysis syndrome

nour lysis syndrome (TLS) associated with Ribomustin ment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of ibomustin and, without intervention, may lead to acute al failure and death. Preventive measures ~~include~~ such s adequate ~~volume status~~hydration, close monitoring of blood chemistry, particularly potassium and uric acid ls, and the use of hypouricemic agents (allopurinol and uricase) should be considered prior to therapy. ~~The use of allopurinol during the first one to two weeks of bomustin therapy can be considered but not necessarily standard. However, there~~ There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal olysis reported when bendamustine and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are nerally mild and include fever, chills, pruritus and rash. n rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about particularly potassium and uric acid ls. The use of allopurinol during the rst one to two weeks of Ribomustin therapy can be considered but not ssarily as standard. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to bendamustine ochloride have occurred commonly in clinical trials. Symptoms are erally mild and include fever, chills, pruritus and rash. In rare instances ere anaphylactic and anaphylactoid ctions have occurred. Patients must sked about symptoms suggestive of usion reactions after their first cycle herapy. Measures to prevent severe reactions, including antihistamines, pyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.

atients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged.

Contraception

Bendamustine hydrochloride is teratogenic and mutagenic.

Women should not become pregnant ring treatment. Male patients should not father a child during and up to 6 months after treatment. They should ek advice about sperm conservation rior to treatment with bendamustine hydrochloride because of possible irreversible infertility.

Extravasation

An extravasal injection should be ed immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue

mptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, cluding antihistamines, antipyretics and corticosteroids ıust be considered in subsequent cycles in patients who have previously experienced infusion reactions. atients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged. Contraception damustine hydrochloride is teratogenic and mutagenic. Women should not become pregnant during treatment. ale patients should not father a child during and up to 6 months after treatment. They should seek advice about erm conservation prior to treatment with bendamustine drochloride because of possible irreversible infertility. Extravasation xtravasal injection should be stopped immediately. The needle should be removed after a short aspiration. reafter the affected area of tissue should be cooled. The ı should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.	hould be cooled. The arm should be ated. Additional treatments like the se of corticosteroids are not of clear benefit.	
omustin has major influence on the ability to drive and use machines. Ataxia,~~No studies on the effects on the ability to drive and use machines have been performed. However, ataxia,~~ peripheral neuropathy and somnolence e been reported during treatment with Ribomustin (see section 4.8). Patients should be instructed that if they perience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.	La,No studies on the effects on the lity to drive and use machines have been performed. However, ataxia,- ipheral neuropathy and somnolence ıave been reported during treatment with Ribomustin (see section 4.8). ents should be instructed that if they erience these symptoms they should oid potentially hazardous tasks such as driving and using machines.	**4.7 Effects on ability t drive and use mach**
Infections and infestations: **Very common ≥1/10** Infection NOS* Including Opportunistic infection (e.g. Herpes zoster, cytomegalovirus, hepatitis B) **Uncommon ≥1/1,000 to <1/100** Pneumocystis jirovecii pneumonia **Rare ≥1/10,000 to <1/1, 000** Sepsis **Very rare <1/10, 000** Pneumonia primary atypical Neoplasma benign, malignant: **Common ≥1/100 to <1/10** Tumour lysis syndrome **Uncommon ≥1/1,000 to <1/100**	Infections and infestations: **Very common ≥1/10** Infection NOS* **Rare ≥1/10,000 to <1/1, 000** Sepsis **Very rare <1/10, 000** Pneumonia primary atypical Neoplasma benign, malignant: **Common ≥1/100 to <1/10** Tumour lysis syndrome Blood and lymphatic system disorders: **Very common ≥1/10** Leukopenia NOS*, Thrombocytopenia	**4.8 Undesirable effects**

Myelodysplastic syndrome, acute myeloid leukemia

Blood and lymphatic system disorders:
Very common ≥1/10
Leukopenia NOS*, Thrombocytopenia
Lymphopenia
Common ≥1/100 to <1/10
Haemorrhage, Anaemia, Neutropenia
Uncommon ≥1/1,000 to <1/100
Pancytopenia
Rare ≥1/10,000 to <1/1, 000
Bone marrow failure
Very rare <1/10, 000
Haemolysis

Nervous system disorders:
Very common ≥1/10
Headache
Common ≥1/100 to <1/10
Insomnia, Dizziness
Rare ≥1/10,000 to <1/1, 000
Somnolence, Aphonia
Very rare <1/10, 000
Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis

Cardiac disorders:
Common ≥1/100 to <1/10
Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia
Uncommon ≥1/1,000 to <1/100
Pericardial effusion,
Myocardial infarction, Cardiac failure
Very rare <1/10, 000
Tachycardia~~, Myocardial infarction, Cardiac failure~~
Not known (cannot be estimated from the available data)
Atrial fibrillation

Skin and subcutaneous tissue disorders:
Common ≥1/100 to <1/10
Alopecia, Skin disorders NOS*
Rare ≥1/10,000 to <1/1, 000
Erythema, Dermatitis, Pruritus, Maculopapular Rash, ~~makular-papular rash,~~ Hyperhidrosis
Not known (cannot be estimated from the available data)
Stevens – Johnson syndrome, Toxic Epidermal Necrolysis (TEN)

Renal and urinary disorders:
Not known (cannot be estimated from the available data)
Renal failure

Description of selected adverse reactions

~~A small number of cases of Stevens-Johnson Syndrom~~
~~Toxic Epidermal Necrolysis have been reported in pati~~
~~using bendamustine in combination with allopurinol or~~

Common ≥1/100 to <1/10
Haemorrhage, Anaemia, Neutropenia
Very rare <1/10, 000
Haemolysis

Nervous system disorders:
Common ≥1/100 to <1/10
Insomnia
Rare ≥1/10,000 to <1/1, 000
Somnolence, Aphonia
Very rare <1/10, 000
Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis

Cardiac disorders:
Common ≥1/100 to <1/10
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Tachycardia, Myocardial infarction, Cardiac failure

Skin and subcutaneous tissue disorders:
Common ≥1/100 to <1/10
Alopecia, Skin disorders NOS*
Rare ≥1/10,000 to <1/1, 000
Erythema, Dermatitis, Pruritus, makular-papular rash, Hyperhidrosis

~~A small number of cases of Stevens~~
~~Johnson Syndrome and Toxic~~
~~Epidermal Necrolysis have been~~
~~reported in patients using bendamus~~
~~in combination with allopurinol or i~~
~~combination with allopurinol and~~
~~rituximab.~~

~~The CD4/CD8 ratio may be reduce~~
~~reduction of the lymphocyte count v~~
~~seen. In immuno-suppressed patien~~
~~the risk of infection (e.g. with herpe~~
~~zoster) may be increased.~~

There have been isolated reports of necrosis after accidental extra-vascu administration and toxic epidermal necrosis, tumour lysis syndrome, ar anaphylaxis.

There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders,

~~combination with allopurinol and rituximab.~~ ~~The CD4/CD8 ratio may be reduced. A reduction of th lymphocyte count was seen. In immuno-suppressed patients, the risk of infection (e.g. with herpes zoster) r be increased.~~ There have been isolated reports of necrosis after accid extra-vascular administration and ~~toxic epidermal necr~~ tumour lysis syndrome, and anaphylaxis. The risk of myelodysplastic syndrome and acute myelo leukaemias is increased in patients treated with alkylati agents (including bendamustine). The secondary malignancy may develop several years after chemother has been discontinued. ~~There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. The association with Ribomustin therapy has not been determined.~~	acute myeloid leukaemia and bronchial carcinoma. The association with Ribomustin therapy has not been determined.	

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.