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315889-4160
144046

1. NAME OF THE MEDICINAL PRODUCT

Ribomustin 25 mg.
Ribomustin 100 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 25 mg bendamustine hydrochloride.

One vial 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 full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion

White, microcrystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.

Indolent non-Hodgkin's lymphomas as monotherapy in patients, who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen.

4.2 Posology and method of administration

For intravenous infusion over 30 - 60 minutes (see section 6.6).

Infusion must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Poor bone marrow function is related to increased chemotherapy-induced haematological toxicity. Treatment should not be started if leukocyte and/or platelet values dropped to < 3,000/ μ l or < 75,000/ μ l, respectively (see section 4.3).

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

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.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to < 3,000/ μ l or < 75,000/ μ l, respectively. Treatment can be continued after leukocyte values have increased to > 4,000/ μ l and platelet values to > 100,000/ μ l.

The leukocyte and platelet Nadir is reached after 14-20 days with regeneration after 3-5 weeks. During therapy free intervals strict monitoring of the blood count is recommended (see section 4.4).

In case of non-haematological toxicity dose reductions have to be based on the worst CTC grades in the preceding cycle. A 50% dose reduction is recommended in case of CTC grade 3 toxicity. An interruption of treatment is recommended in case of CTC grade 4 toxicity.

If a patient requires a dose modification the individually calculated reduced dose must be given on day 1 and 2 of the respective treatment cycle.

For preparation and administration instructions see section 6.6.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl).

No data is available in patients with severe hepatic impairment (serum bilirubin values of > 3.0 mg/dl) (see section 4.3).

Renal impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Experience in patients with severe renal impairment is limited.

Paediatric patients

There is no experience in children and adolescents with Ribomustin.

Elderly patients

There is no evidence that dose adjustments are necessary in elderly patients (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (see section 6.1)

During breast-feeding

Severe hepatic impairment (serum bilirubin > 3.0 mg/dl)

Jaundice

Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/ μ l or < 75,000/ μ l, respectively)

Major surgery less than 30 days before start of treatment

Infections, especially involving leukocytopenia

Yellow fever vaccination

* This table relates to section 4.8 Undesirable effects.

The table below reflects the data obtained with bendamustine hydrochloride in clinical trials.

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*			Sepsis	Pneumonia primary atypical	
Neoplasma benign, malignant		Tumour lysis syndrome				
Blood and lymphatic system disorders	Leukopenia NOS*, Thrombocytopenia	Haemorrhage, Anaemia, Neutropenia			Haemolysis	
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, Anaphylactoid reaction	Anaphylactic shock	
Nervous system disorders		Insomnia		Somnolence, Aphonia	Dysgeusia, Paraesthesia, Peripheral sensory neuropathy, Anticholinergic syndrome, Neurological disorders, Ataxia, Encephalitis	
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris, Arrhythmia	Pericardial effusion		Tachycardia, Myocardial infarction, Cardiac failure	
Vascular disorders		Hypotension, hypertension		Acute circulatory failure	Phlebitis	
Respiratory, thoracic and media-stinal disorders		Pulmonary dysfunction			Pulmonary fibrosis	
Gastrointestinal disorders	Nausea, Vomiting	Diarrhoea, Constipation, Stomatitis			haemorrhagic oesophagitis, Gastrointestinal haemorrhage	
Skin and subcutaneous tissue disorders		Alopecia, Skin disorders NOS*		Erythema, Dermatitis, Pruritus, makular-papular rash, Hyperhidrosis		
Reproductive system and breast disorders		Amenorrhoea			Infertility	
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 increase, Hypokalemia				

NOS = Not otherwise specified

4.4 Special warnings and 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 weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: Leukocyte and/or platelet values > 4,000/ μ l or > 100,000/ μ l, respectively.

Infections

Infection, including pneumonia and sepsis, has been reported. In rare cases, infection has been associated with hospitalization, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to infections. Patients with myelosuppression following bendamustine 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 events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. Where 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 where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.

Patients with cardiac disorders

During treatment with bendamustine hydrochloride the concentration of potassium in the blood must be closely monitored and potassium supplement must be given when K⁺ <3.5 mEq/l, and ECG measurement must be performed.

Nausea, vomiting

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

Tumour lysis syndrome

Tumour lysis syndrome 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 include adequate volume status, close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of Ribomustin therapy can be considered but not necessarily 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 hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions.

Patients 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 during treatment. Male patients should not father a child during and up to 6 months after treatment. They should seek advice about sperm conservation prior to treatment with bendamustine hydrochloride because of possible irreversible infertility.

Extravasation

An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

4.5 Interaction with other medicinal products and other forms of interaction

No *in-vivo* interaction studies have been performed.

When Ribomustin is combined with myelosuppressive agents, the effect of Ribomustin and/or the coadministered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of Ribomustin.

Combination of Ribomustin with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.

Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection which may lead to fatal outcome. This risk is increased in subjects who are already immunosuppressed by their underlying disease.

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

4.6 Pregnancy and lactation

Pregnancy

There are insufficient data from the use of Ribomustin in pregnant women. In nonclinical studies bendamustine hydrochloride was embryo-/fetolethal, teratogenic and genotoxic (see section 5.3). During pregnancy Ribomustin should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with Ribomustin is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. The possibility of genetic counselling should be considered.

Women of childbearing potential/contraception

Women of childbearing potential must use effective methods of contraception both before and during Ribomustin therapy.

Men being treated with Ribomustin are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with Ribomustin.

Breast-feeding

It is not known whether bendamustine passes into the breast milk, therefore, Ribomustin is contraindicated during breast-feeding (see section 4.3). Breast-feeding must be discontinued during treatment with Ribomustin.

144046

Ribomustin
Infusion
Israel
LFT 328 x 530 mm
LFT_260 FD
VTB 5065
Eq. to: N/A

18.08.2014

STUDIOKEIJZER ms

Black

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, ataxia, peripheral neuropathy and somnolence have been reported during treatment with Ribomustin (see section 4.8). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

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).

*See table of adverse reaction overleaf.

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

The CD4/CD8 ratio may be reduced. A reduction of the lymphocyte count was seen. In immuno-suppressed patients, the risk of infection (e.g. with herpes zoster) may be increased.

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

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.

4.9 Overdose

After application of a 30 min infusion of Ribomustin once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m². Cardiac events of CTC grade 2 which were compatible with ischaemic ECG changes occurred which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of Ribomustin at day 1 and 2 every 3 weeks the MTD was found to be 180 mg/m². The dose limiting toxicity was grade 4 thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

Counter measures

There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be made or haematological growth factors may be given as effective countermeasures to control haematological side-effects.

Bendamustine hydrochloride and its metabolites are dialyzable to a small extent.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, ATC code:

Bendamustine hydrochloride is an alkylating antitumour agent with unique activity. The antineoplastic and cytotoxic 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, 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).

Bendamustine hydrochloride showed an activity profile in human tumour cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumour cell lines with different resistance mechanisms at least in part due to a comparatively persistent DNA interaction. Additionally, it was shown in clinical studies that there is no complete cross-resistance of bendamustine with anthracyclines, alkylating agents or rituximab. However, the number of assessed patients is small.

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 0.8mg/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 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 received a median of 3 previous chemotherapy or biologic therapy courses. The median number of previous rituximab-containing courses was 2. The patients had no response or 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 progress within 6 months or had an untoward reaction to prior rituximab treatment. Patients received a median of 3 previous chemotherapy or biological therapy courses. The median number of previous rituximab-containing courses 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).

Patients with BP treatment have a longer median progression free survival than patients with MP (15 [95%CI 12-21] versus 12 [95%CI 10-14] months) (p=0.0566). The median time to treatment failure is 14 months with BP and 9 months with MP treatment. The duration of remission is 18 months with BP and 12 months with MP treatment. The difference in overall survival is not significantly different (35 months BP versus 33 months MP). Tolerability in both treatment arms was in line with the know safety profile of the respective medicinal products with significantly more dose reductions in the BP arm.

5.2 Pharmacokinetic properties

Distribution

The elimination half-life $t_{1/2\beta}$ after 30 min i.v. infusion of 120 mg/m² 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 lL.

More than 95% of the substance is bound to plasma proteins (primarily albumin).

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 and CYP 3A4.

Elimination

The mean total clearance after 30 min i.v. infusion of 120 mg/m² body surface area to 12 subjects was 639.4 ml/minute. About 20% of the administered dose was recovered in urine within 24 hours. Amounts excreted in urine were in the order monohydroxy-bendamustine > bendamustine > dihydroxy-bendamustine > oxidised metabolite > N-desmethyl bendamustine. In the bile, primarily polar metabolites are eliminated.

Hepatic impairment

In patients with 30 - 70% tumour infestation of the liver and mild hepatic impairment (serum bilirubin < 1.2 mg/dl) the pharmacokinetic behaviour was not changed. There was no significant difference to patients with normal liver and kidney function with respect to C_{max} , t_{max} , AUC, $t_{1/2\beta}$, volume of distribution and clearance. AUC and total body clearance of bendamustine correlate inversely with serum bilirubin.

Renal impairment

In patients with creatinine clearance >10 ml/min including dialysis dependent patients, no significant difference to patients with normal liver and kidney function was observed with respect to C_{max} , t_{max} , AUC, $t_{1/2\beta}$, volume of distribution and clearance.

Elderly subjects

Subjects up to 84 years of age were included in pharmacokinetic studies. Higher age does not influence the pharmacokinetics of bendamustine.

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Histological investigations in dogs showed macroscopic visible hyperaemia of the mucosa and haemorrhagia in the gastrointestinal tract. Microscopic investigations showed extensive changes of the lymphatic tissue indicating an immunosuppression and tubular changes of kidneys and testis, as well as atrophic, necrotic changes of the prostate epithelium.

Animal studies showed that bendamustine is embryotoxic and teratogenic.

Bendamustine induces aberrations of the chromosomes and is mutagenic in-vivo as well as in-vitro. In long-term studies in female mice bendamustine is carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

The powder should be reconstituted immediately after opening of the vial.

The reconstituted concentrate should be diluted immediately with 0.9% sodium chloride solution.

Solution for infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25 °C and 2 days at 2 °C to 8 °C in polyethylene bags.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25 °C

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the reconstituted or diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I brown glass vials of 26 ml or 60 ml with rubber stopper and an aluminium flip-off cap.

26 ml-vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 5, 10 and 20 vials.

60 ml-vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 5 vials.

Not all pack sizes may be marketed.

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, absorbing disposable foil. Pregnant personnel should be excluded from handling cytostatics.

The powder for concentrate for solution for infusion has to be reconstituted with water for injection, diluted with sodium chloride 9 mg/ml (0.9%) solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

1. Reconstitution

Reconstitute each vial of Ribomustin containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking;

Reconstitute each vial of Ribomustin containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.

The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml and appears as a clear colourless solution.

2. Dilution

As soon as a clear solution is obtained (usually after 5-10 minutes) dilute the total recommended dose of Ribomustin immediately with 0.9% NaCl solution to produce a final volume of about 500 ml.

Ribomustin must be diluted with 0.9% NaCl solution and not with any other injectable solution.

3. Administration

The solution is administered by intravenous infusion over 30-60 min.

The vials are for single use only.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. NAME OF MANUFACTURER

Temmler Werke GmbH, Germany.

8. NAME OF REGISTRATION HOLDER

Astellas Pharma International B.V. Israel.