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Development, registration and standardization
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MINISTRY OF HEALTH OF THE REPUBLIC OF BELARUS

PATIENT INFORMATION LEAFLET
for the drug

Benustin
lyophilized powder for solution for infusions
25 mg, 100 mg

Trade name Benustin
International nonproprietary name Bendamustine.
Pharmaceutical form Lyophilized powder for solution for infusions.
Description White to off-white lyophilized powder.
Composition per 1 vial
Active substance
Bendamustine hydrochloride – 25 mg (as bendamustine hydrochloride monohydrate 26.14 mg) or 100 mg (as bendamustine hydrochloride monohydrate 104.57 mg).
Excipient: mannitol.
Pharmacotherapeutic group Antineoplastic agents. Alkylating agents. Nitrogen mustard analogues.
ATC code L01AA09.
Pharmacological properties
Pharmacodynamics
Bendamustine hydrochloride is an alkylating antitumour agent. Antineoplastic and cytocidal effect of bendamustine hydrochloride is based 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 tumor cell lines (breast cancer, non-small cell and small cell lung cancer, ovarian carcinoma and different leukaemias) and *in vivo* in different experimental tumor models with tumors 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 tumor cell lines different to that of other alkylating agents. The active substance revealed no or very low cross-resistance in human tumor 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.

Pharmacokinetics

Distribution

The elimination half-life $t_{1/2ß}$ after 30 min i.v. infusion of 120 mg/m2 area to 12 subjects was 28.2 minutes.

After 30 min intravenous infusion the central volume of distribution was 19.3 l. After the following intravenous bolus injection under steady-state conditions the volume of distribution was 15.8-20.5 l.

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

Metabolism

The major route of clearance of bendamustine is hydrolysis to monohydroxy- and dihydroxy-bendamustine. Formation of N-desmethyl-bendamustine and gamma-hydroxy-bendamustine by hepatic metabolism involves cytochrome P450 isoenzyme CYP1A2. 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 CYP 3A4.

Elimination

The mean total clearance after 30 min intravenous 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% tumor infestation of the liver and mild hepatic impairment (serum bilirubin < 1.2 mg/dl) 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, $t_{1/2ß}$, 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, $t_{1/2ß}$, volume of distribution and clearance.

Elderly patients

Age factor does not exert any significant impact on pharmacokinetics of bendamustine hydrochloride.

Indications for use

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.

Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib containing treatment.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- Breast-feeding;
- Severe hepatic impairment;
- Jaundice;
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3,000/µl or < 75,000/µl, respectively);
- Surgery less than 30 days before start of treatment;
- Infections, especially involving leukocytopenia;
- Yellow fever vaccination;

Precautions

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/µl or > 100,000/µl, respectively.

Infections

Patients with neutropenia and/or lymphopenia following treatment with bendamustine hydrochloride are more susceptible to infections. Patients with myelosuppression following treatment with bendamustine hydrochloride should consult with doctor if they have symptoms or signs of infection, including fever or respiratory symptoms.

Skin reactions

A number of skin reactions have been reported for bendamustine hydrochloride 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, bendamustine hydrochloride should be withheld or discontinued. For severe skin reactions where a link to bendamustine hydrochloride is suspected, treatment should be discontinued.

Patients with cardiac disorders

During treatment with bendamustine hydrochloride 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.

Tumor lysis syndrome

Tumor lysis syndrome associated with Benustin treatment has been reported in patients in clinical trials. The onset is within 48 hours of the first dose and, without intervention, may lead to acute renal failure and death. Preventive measures include accurate monitoring of volume status or adequate hydration and close monitoring of blood chemistry, particularly potassium and uric acid levels. Allopurinol therapy during first two weeks of treatment with Benustin may be considered, but it is not obligatory. However there have been a few cases of Stevens-Johnson Syndrome and toxic epidermal necrolysis reported when bendamustine and allopurinol were 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 cases 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 exerts teratogenic and mutagenic effects.

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 use of corticosteroids are not of clear benefit.

Pregnancy and Lactation

Pregnancy

There is insufficient data from use of Benustin in pregnant women. In nonclinical studies bendamustine hydrochloride showed embryo-/fetolethal, teratogenic and genotoxic properties. During pregnancy Benustin should not be used unless clearly necessary. Mother should be informed about the risk to foetus. If treatment with Benustin 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 Benustin therapy. Treated men 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 Benustin.

Breastfeeding

It is unknown whether bendamustine passes into human milk therefore Benustin is contraindicated during breastfeeding. Breastfeeding should be discontinued during treatment with Benustin.

Effects on ability to drive and use other machines

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

Posology and method of administration

Intended for intravenous infusion over 30 – 60 minutes.

Infusion must be administered under supervision of a physician qualified and experienced in 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 have dropped to < 3,000/µl or < 75,000/µl, respectively.

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 resistant to rituximab

120 mg/m² body surface area bendamustine hydrochloride on days 1 and 2; every 3 weeks.

Multiple myeloma

120 – 150 mg/m² body surface area bendamustine hydrochloride on days 1 and 2, 60 mg/m² body surface area prednisone intravenously or orally on days 1 to 4; every 4 weeks.

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

Maximum reduction of leukocyte and platelet level is reached after 14 – 20 days with complete regeneration after 3 – 5 weeks. During therapy free intervals strict monitoring of the blood count is recommended.

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.

Hepatic impairment

According to pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin < 1.2 mg/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).

Renal impairment

According to 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.

Use in pediatric population

There is no experience in children and adolescents with bendamustine hydrochloride.

Use in elderly patients

There is no evidence that dose adjustments are necessary in elderly patients.

Special precautions for use

When handling Benustin, 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, eyes should be rinsed with physiological saline solution. If possible it is recommended to work on special safety workbenches (laminar flow) with liquid-impermeable, absorbent disposable foil. Pregnant personnel should be excluded from handling cytostatics.

Powder for concentrate for solution for infusion should be reconstituted with water for injection, diluted with sodium chloride 0.9% solution for injection and then administered by intravenous infusion. Aseptic technique is to be used.

Rules of preparation and administration of the solution

1. Reconstitution

Reconstitute each vial of Benustin, containing 25 mg of bendamustine hydrochloride in 10ml water for injection by shaking.

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

The reconstituted colorless transparent concentrate contains 2.5 mg/ml of bendamustine hydrochloride.

2. Dilution

After 5-10 minutes of exposure dilute immediately the recommended dose of Benustin in 500 ml of 0.9% solution of sodium chloride. Benustin should be diluted only with 0.9% solution of sodium chloride, other injectable solutions may not be used.

3. Administration

Solution is administered by intravenous infusion over 30-60 min.

Vials are for single use only.

Any unused product or waste material should be disposed of in accordance with requirements to disposal of cytostatics.

Powder should be reconstituted immediately after opening a vial!

Reconstituted concentrate should be diluted at once with 0.9% solution of sodium chloride!

Stability of solution for infusion

After reconstitution and dilution, chemical and physical stability of the solution has been demonstrated for 3.5 hours at 25°C and 60% RH 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.

Adverse 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).

Frequency of reactions: very common - ≥1/10; common - ≥1/100 to <1/10; uncommon - ≥1/1000 to <1/100; rare - ≥1/10000 to <1/1000; very rare - <1/10000; frequency not known (frequency cannot be estimated from available data).

Infections and infestations: very common – infections not otherwise specified; rare – sepsis; very rare – primary atypical pneumonia.

Benign and malignant neoplasms: common – tumor lysis syndrome.

Blood and lymphatic system disorders: very common – leukopenia not otherwise specified; common – haemorrhage, anaemia, neutropenia; very rare – hemolysis.

Immune system disorders: common – hypersensitivity not otherwise specified; rare – anaphylactic reaction, anaphylactoid reaction; very rare – anaphylactic shock.

Nervous system disorders: common – insomnia; rare – somnolence, aphonia; very rare – dysgeusia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, neurological disorders, ataxia, encephalitis

Cardiovascular disorders: common – hypotension, hypertension, cardiac dysfunction, such as palpitations, angina pectoris, arrhythmia; uncommon - pericardial effusion; rare – acute circulatory failure; very rare – phlebitis, tachycardia, myocardial infarction, cardiac failure.

Respiratory, thoracic and mediastinal disorders: common – pulmonary dysfunction; very rare – pulmonary fibrosis.

Gastrointestinal disorders: very common – nausea and vomiting; common – diarrhea, constipation, stomatitis; very rare – haemorrhagic oesophagitis, gastrointestinal heamorrhage.

Skin and subcutaneous tissue disorders: common – alopecia, skin disorders not otherwise specified; rare – erythema, dermatitis, pruritus, macular-papular rash, hyperhidrosis.

Reproductive system and breast disorders: common – amenorrhea; very rare – infertility.

General disorders and administration site conditions: very common – mucosal inflammation, fatigue, pyrexia; common – pain, chills, dehydration, anorexia; very rare – multiorgan failure.

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Laboratory and instrumental data: very common – haemoglobin decrease, creatinine increase, urea increase; common – AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, hypokalaemia.
Frequency not known: Stevens – Johnson syndrome and toxic epidermal necrolysis in patients administering bendamistine in combination with allopurinol or in combination with allopurinol and rituximab; reduced CD4/CD8 ratio, and reduction of lymphocytes count; in immuno-suppressed patients increased the risk of infection (e.g, herpes zoster); necrosis after accidental extra-vascular administration, toxic epidermal necrolysis, tumor lysis syndrome and anaphylaxis.

Overdose

After 30 minute infusion of Benustin once every 3 weeks the maximum tolerated dose (MTD) was 280 mg/m². Cardiac events of CTC grade 2 which were compatible with ischemic ECG changes occurred which were regarded as dose limiting.
Subsequent treatment with 30 minute infusion of Benustin on day 1 and 2 every 3 weeks MTD was 180 mg/m^2. 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 dialysable to a small extent.

Interation with other drugs

No in-vivo interaction studies have been performed.
In combination of Benustin with myelosuppressive agents the effect on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase toxicity of Benustin. Combination of Benustin 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 isoenzyme CYP1A2. Therefore, a potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.

Conditions of storage and shelf-life

Keep protected from light at temperature not higher than 25°C.

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Keep out of the reach of children.
Shelf-life for 25 mg dosage – 2 years, for 100 mg dosage – 2.5 years. Do not use after expiration of the shelf-life stated on package.

Dispensing conditions

Prescription only.

Package

25 mg in a 20 ml vial.
1 or 5 vials with patient information leaflet in a carton pack.
100 mg in a 50 ml vial.
1 vial with patient information leaflet in a carton pack.

Information about manufacturer

Manufactured by: Thymoorgan Pharmazie GmbH, Germany.
Packed by: JLLC TriplePharm, 2B Minskaya str., 223141, Logoysk, Minsk region, Republic of Belarus. Tel./fax: (+375) 1774 43 181, e-mail: triplepharm@gmail.com.