SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM)

RIBOMUSTIN 25 mg (powder for concentrate for solution for infusion). For single use only.

RIBOMUSTIN 100 mg (powder for concentrate for solution for infusion). For single use only.

COMPOSITION

RIBOMUSTIN 25 mg: One vial contains 25 mg bendamustine hydrochloride (sterile active ingredient).

RIBOMUSTIN 100 mg: One vial contains 100 mg bendamustine hydrochloride (sterile active ingredient).

1 ml of the concentrate contains 2,5 mg bendamustine hydrochloride when reconstituted according to DOSAGE AND DIRECTIONS FOR USE - Instructions for use.

Inactive ingredients: mannitol

PHARMACOLOGICAL CLASSIFICATION

A. 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Bendamustine hydrochloride is an alkylating antitumour agent. 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 carcinoma and various leukaemias) 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).

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.

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 litre. Under steady-state conditions following i.v. bolus injection the volume of distribution was 15,8 – 20,5 ℓ.

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 dihydroxybendamustine. 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/m^2 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 to 70 % tumour infiltration of the liver and mild or moderate hepatic impairment [serum bilirubin < 34,2 µmol/ℓ (2,0 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, $t_{1/2ß}$, 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 subjects

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

INDICATIONS

- First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate.
- First-line treatment of indolent CD 20 positive non-Hodgkin’s lymphoma in combination with rituximab.

- 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 in RIBOMUSTIN
- Pregnancy and lactation (See **Pregnancy and Lactation**)
- Severe hepatic impairment [serum bilirubin > 34,2 µmol/ℓ (2,0 mg/dl)]
- Jaundice
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10^9/ℓ or < 75 x 10^9/ℓ, respectively)
- Major surgery less than 30 days before start of treatment
- Infections, especially involving leukocytopenia
- Yellow fever vaccination or any other live (attenuated) vaccination
- Congenital QT prolongation
- Concomitant medicines causing QT prolongation

WARNINGS AND SPECIAL PRECAUTIONS

Myelosuppression

Patients treated with RIBOMUSTIN experience myelosuppression. 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 x 10^9/ℓ or > 100 x 10^9/ℓ, respectively.

Infections

The CD4/CD8 ratio may be reduced. A reduction of the lymphocyte count was seen. In immunosuppressed patients, the risk of infection (e.g. with herpes zoster) may be increased. Cases of tuberculosis have been less frequently reported compared to other infections. Latent or dormant tuberculosis may become active.

Infection, including pneumonia and sepsis, has been reported. Infection has been associated with hospitalisation, septic shock and death. Patients with neutropenia and/or lymphopenia following treatment with RIBOMUSTIN are more susceptible to infections including tuberculosis. Patients with myelosuppression following RIBOMUSTIN treatment should be advised to contact a medical practitioner if they have symptoms or signs of infection, including fever or respiratory symptoms. The presence of tuberculosis should be excluded before treatment with RIBOMUSTIN is commenced.

Skin reactions

A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema. Some of these events occurred when RIBOMUSTIN was given in combination with other anticancer agents.

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 RIBOMUSTIN is suspected, treatment should be discontinued.

Patients with cardiac disorders

During treatment with RIBOMUSTIN the concentration of potassium in the blood must be closely monitored. When serum potassium levels are < 3,5 mEq/ℓ (3,5 mmol/ℓ), an ECG recording must be performed and potassium supplement must be given.

QTcf was prolonged by more than 30 msecs in 4 of 9 patients studied.

Nausea, vomiting

An antiemetic should 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 fluid volume status and 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. However, there have been cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when RIBOMUSTIN and allopurinol are administered concomitantly.

Anaphylaxis

Infusion reactions to RIBOMUSTIN have occurred commonly in clinical trials. Symptoms include fever, chills, pruritus and rash.
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.
In patients who experienced Grade 3 or worse allergic-type reactions, RIBOMUSTIN should be discontinued.

Contraception

RIBOMUSTIN 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 RIBOMUSTIN 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.

There have been 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.

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 SIDE EFFECTS). Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving and using machines.

INTERACTIONS

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

When RIBOMUSTIN is combined with myelosuppressive agents, the effect of RIBOMUSTIN and/or the co-administered 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 ciclosporin 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.

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

Incompatibilities

RIBOMUSTIN must not be mixed with other medicinal products except those mentioned in DOSAGE AND DIRECTIONS FOR USE, Instructions for use.

PREGNANCY AND LACTATION

Pregnancy

There are no adequate data from the use of RIBOMUSTIN in pregnant women.
In nonclinical studies RIBOMUSTIN was embryo-/foetolethal, teratogenic and genotoxic.
Therefore, RIBOMUSTIN is contraindicated during pregnancy (see CONTRAINDICATIONS).

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.

Breastfeeding

It is not known whether RIBOMUSTIN passes into the breast milk. Treatment with RIBOMUSTIN is therefore contraindicated during breastfeeding (see CONTRAINDICATIONS). Mothers on RIBOMUSTIN must not breastfeed their babies.

DOSAGE AND DIRECTIONS FOR USE

For intravenous infusion over 30 to 60 minutes.

Infusion must be administered under the supervision of a medical practitioner 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 x 10^9/ℓ or < 75 x 10^9/ℓ, respectively (see CONTRAINDICATIONS).

Monotherapy for chronic lymphocytic leukaemia

100 mg/m^2 body surface area RIBOMUSTIN on days 1 and 2; every 4 weeks.

Combination treatment for first-line indolent non-Hodgkin's lymphoma

90 mg/m^2 body surface area RIBOMUSTIN on days 1 and 2 in combination with 375 mg/m^2 body surface area rituximab as a slow i.v. infusion on day 1; every 4 weeks.

Monotherapy for indolent non-Hodgkin's lymphomas refractory to rituximab

120 mg/m^2 body surface area RIBOMUSTIN on days 1 and 2; every 3 weeks.

Multiple Myeloma

120-150 mg/m^2 body surface area RIBOMUSTIN on days 1 and 2, 60 mg/m^2 body surface area prednisone i.v. or orally on days 1 to 4; every 4 weeks.

Treatment should be terminated or delayed if leukocyte and/or platelet values dropped to ≤ 3 x 10^9/ℓ or ≤ 75 x 10^9/ℓ, respectively. Treatment can be continued after leukocyte values have increased to > 4 x 10^9/ℓ and platelet values to > 100 x 10^9/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 WARNINGS AND SPECIAL PRECAUTIONS).

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 **Instructions for use**.

Hepatic impairment
On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment [serum bilirubin < 34,2 µmol/ℓ (2,0 mg/dl)].

A 30 % dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin [34,2 µmol/ℓ – 51,3 µmol/ℓ (2 – 3,0 mg/dl)].

No data is available in patients with severe hepatic impairment [serum bilirubin values of > 51,3 µmol/ℓ (3,0 mg/dl)].

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 PHARMACOLOGICAL ACTION, Pharmacokinetic properties).

Instructions for use

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.

SIDE EFFECTS

The most common side effects with RIBOMUSTIN are haematological adverse reactions (leucopenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting).

The frequency of side effects is classified as very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10 000, <1/1 000) or very rare (<1/10 000).

Infections and infestations

Very common: Infection (not otherwise specified)

Rare: Septicaemia

Very rare: Primary atypical pneumonia, tuberculosis

Blood and lymphatic system disorders

Very common: Leucopenia (not otherwise specified), thrombocytopenia

Common: Haemorrhage, anaemia, neutropenia, lymphopenia

Very rare: Haemolysis

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

Cardiac disorders

Common: Cardiac dysfunction, such as tachycardia, palpitations, angina pectoris; dysrhythmia, QT prolongation

Uncommon: Pericardial effusion

Very rare: Tachycardia, myocardial infarction, cardiac failure

Vascular disorders

Common: Hypotension, hypertension

Rare: Acute circulatory failure

Very rare: Phlebitis

Respiratory, thoracic and mediastinal disorders

Common: Pulmonary dysfunction

Very rare: Pulmonary fibrosis

Gastrointestinal disorders

Very common: Nausea, vomiting

Common: Diarrhoea, constipation, stomatitis

Very rare: Haemorrhagic oesophagitis, gastrointestinal haemorrhage

Skin and subcutaneous tissue disorders

Common: Alopecia, skin disorders (not otherwise specified)

Rare: Erythema, dermatitis, pruritus, maculo-papular rash, hyperhidrosis

Reproductive system and breast disorders

Common: Amenorrhoea

Very rare: Infertility

General disorders and administration site conditions

Very common: Mucosal inflammation, fatigue, pyrexia

Common: Pain, chills, dehydration, anorexia

Very rare: Multi-organ failure

Investigations

Very common: Decreased haemoglobin, increased creatinine, increased urea

Common: Increased AST, increased ALT, increased alkaline phosphatase, increased bilirubin, hypokalaemia.

Metabolic

Common: Tumor lysis syndrome

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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/m^2. 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.
RIBOMUSTIN and its metabolites are dialysable to a small extent.

IDENTIFICATION

White, microcrystalline lyophilisate.

PRESENTATION

RIBOMUSTIN 25 mg is available in Type I brown glass vials of 26 ml with 20 mm grey bromobutyl/silicate rubber stopper and an aluminium flip-off cap with a blue polypropylene disc. 26 ml vials contain 25 mg bendamustine hydrochloride and are supplied in packs of 1, 5, 10 and 20 vials.
RIBOMUSTIN 100 mg is available in Type I brown glass vials of 60 ml with 20 mm grey bromobutyl/silicate rubber stopper and an aluminium flip-off cap with a blue polypropylene disc. 60 ml vials contain 100 mg bendamustine hydrochloride and are supplied in packs of 1 and 5 vials.

STORAGE INSTRUCTIONS

Unopened vial:

Store at or below 25 °C.

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

KEEP OUT OF REACH OF CHILDREN

Reconstituted concentrate:

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

The reconstituted concentrate should be diluted immediately with 0,9 % sodium chloride solution for injection.

Solution for infusion:

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3,5 hours at 25 ºC and 2 days at 2 ºC to 8 ºC 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.

REGISTRATION NUMBER

RIBOMUSTIN 25 mg: 45/26/1127

RIBOMUSTIN 100 mg: 45/26/1128

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Astellas Pharma (Pty) Ltd, EOH Business Park, Gillooly's View, 5 Osborne Lane, Bedfordview, 2007

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