SCHEDULING STATUS:

S4

PROPRIETARY NAME:

BUSILVEX® (Solution for injection)

COMPOSITION:

Each 10 ml vial contains 60 mg busulfan (1 ml of concentrate contains 6 mg busulfan)

After dilution: 1 ml of solution contains 0,5 mg busulfan - refer to **Dosage and directions for use.**

PHARMACOLOGICAL CLASSIFICATION:

A 26 Cytostatics

PHARMACOLOGICAL ACTION:

Busulfan is a cytotoxic agent that results in myelosuppression. Busulfan is a bifunctional alkylating agent in which two labile methanesulphonate groups are attached to opposite ends of a four carbon alkyl chain. In aqueous media, release of the methanesulphonate groups produces carbonium ions that can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect.

Pharmacokinetics:

In studies performed to assess the pharmacokinetic profile of busulfan, the main parameters obtained were: Cl tot ranged from 2,25 and 2,74 ml.min-1.kg-1, elimination t½ ranged between 2,8 and 3,9 hours; terminal volume of distribution Vz ranged between 0,62 and 0,85 l.kg-1.

The pharmacokinetics were compared in patients receiving oral (1 mg/kg) and IV (0,8 mg/kg) busulfan. Similar blood exposure was achieved while a lower inter individual variability was observed with the IV form (24 % and 14 % for oral and IV respectively)

Busulfan achieved concentrations in the cerebrospinal fluid approximately equal to those in plasma although the concentrations are probably insufficient for antineoplastic activity. Reversible binding to plasma elements was about 7 % while irreversible binding, primarily to albumin was about 32 %.

Busulfan is metabolised by conjugation with glutathione, both spontaneously and through glutathione S-transferase (GST).

Approximately 30 % of the administered dose are excreted in the urine over 48 hours, with about 1 % as the unchanged drug. Negligible amounts are recovered in faeces.

INDICATIONS:

Conditioning treatment prior to haematopoeietic progenitor cell transplantation in adults when the combination of busulfan and cyclophosphamide (Bu/Cy2) is considered the best available option.

CONTRA-INDICATIONS:

Hypersensitivity to busulfan or to any of the excipients.

Pregnancy and lactation.

The safety and efficacy in children have not been established.

Hepatic insufficiency.

WARNINGS AND SPECIAL PRECAUTIONS:

BUSILVEX® should not be given by rapid IV injection or bolus.

The consequence of treatment with **BUSILVEX®** is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anaemia, or any combination thereof may develop. Frequent complete blood counts, including differential white blood cell counts, and quantitative platelet counts should be monitored during the treatment and until recovery is achieved. Absolute neutrophil counts < 0,5 X 10^9 /l at a median of 4 days post transplant occurred in 100 % of patients and recovered at median day 10 and 13 days following autologous and allogenic transplant respectively.

Prophylactic use of anti-infective agents should be considered for the prevention and management of infections during the neutropenic period. Thrombocytopenia (< 25 000/mm3 or requiring platelet transfusion) occurred at a median of 5-6 days in 98 % of patients. Anaemia (haemoglobin < 8.0 g/dl) occurred in 69% of patients. Platelet and red blood cell support, as well as use of growth factors such as G-CSF, should be used as indicated.

BUSILVEX® has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolised in the liver, exposure to **BUSILVEX®** is expected to increase if liver function is impaired and the use of **BUSILVEX®** in hepatic impaired populations is contra-indicated.

Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease with the recommended dose and regimen.

Serum transaminase, alkaline phosphatase, and bilirubin should be monitored regularly through post transplant day +28 for detection of hepatotoxicity.

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of **BUSILVEX®** to patients with a history of seizures, head trauma, or receiving other potentially epileptogenic drugs. Dose modification is not recommended for patients with renal impairment, however, caution is advised.

INTERACTIONS:

Administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance. Patients should be monitored for signs of busulfan toxicity when itraconazole is used as an antifungal prophylaxis with busulfan.

Ketobemidone may be associated with high levels of busulfan.

Special care is recommended when combining these two agents.

For the BuCy2 regimen it has been reported that the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the development of toxicities. A reduced incidence of HVOD and other regimen-related toxicity have been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24 hours.

Paracetamol is described to decrease glutathione levels in blood and tissues and may therefore decrease busulfan clearance when used in combination.

Phenytoin was administered for seizure prophylaxis in all patients in the clinical trials conducted with IV busulfan. The concomitant systemic administration of phenytoin to patients receiving high-dose busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase. However, no evidence of this effect has been seen in the IV data. No interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan.

No interaction was observed when busulfan was combined with fluconazole or 5-HT3 antiemetics such as ondansetron or granisetron.

PREGNANCY AND LACTATION:

Pregnancy:

BUSILVEX® is contra-indicated in pregnancy. It has caused embryofoetal lethality and malformations in pre-clinical studies. Women of childbearing potential must use effective contraception during and up to 6 months after treatment.

Lactation:

It is not known whether busulfan is excreted in breast milk. Because of the potential for tumorigenicity shown for busulfan in human and animal studies, breast feeding should be discontinued at the start of therapy.

DOSAGE AND DIRECTIONS FOR USE:

BUSILVEX® should not be given by rapid IV injection or bolus.

BUSILVEX® should be administered under the supervision of a qualified physician who is experienced in conditioning treatment prior to haematopoeietic progenitor cell transplantation, in the use of cancer chemotherapeutic agents and in the management of patients with severe pancytopenia.

It is recommended to use actual body weight for dosing.

All patients should be premedicated with anticonvulsant drugs to prevent seizures reported with the use of high dose busulfan. Antiemetics should be administered prior to the first dose and continued on a fixed schedule through its administration.

The recommended dosage and regimen is 0,8 mg/kg body weight of **BUSILVEX®** as a two hour infusion every 6 hours over 4 consecutive days, for a total of 16 doses prior to haematopoietic progenitor cell transplantation.

Obese patients: For obese or severely obese patients, dosing based on adjusted ideal body weight could be considered. Ideal body weight (IBW) should be calculated as follows (height in cm and weight in kg):

IBW (kg; men) = 50 + 0,91 X (height - 152); IBW (kg; women) = 45 + 0,91 X (height-152).

Adjusted ideal body weight (AIBW) should be calculated as follows:

AIBW = IBW + 0,25 X (actual body weight - IBW)

Administration:

BUSILVEX® must be diluted before administration. A final concentration of approximately 0.5mg/ml busulfan should be achieved (see below). **BUSILVEX®** should be administered by IV infusion via central venous catheter.

Preparation of dilution:

Procedures for proper handling and disposal of anticancer drugs should be followed.

Caution should be exercised in handling and preparing the solution. The use of gloves is recommended as skin reactions may occur with accidental exposure. If this occurs, wash the skin or mucosa immediately and thoroughly with water

BUSILVEX® must be diluted with 0,9 % sodium chloride or 5 % glucose solution for injection. The quantity of the diluent must be 10 times the volume of **BUSILVEX®** to ensure the final concentration of busulfan remains at approximately 0,5 mg/ml.

For example, for a 70 kg (actual body weight) patient, the amount of drug to be administered will be calculated as follows:

(70 kg patient) X (0,8 mg/kg)/ 6 mg/ml) = 9,3 ml **BUSILVEX®** (56 mg total dose).

To prepare the final solution for infusion, add 9,3 ml of **BUSILVEX®** to 93 ml of diluent 0,.9 % sodium chloride or 5 % dextrose solution for injection) as calculated below:

(9,3 ml **BUSILVEX®**) X (10) = 93 ml of either diluent plus the 9,3 ml **BUSILVEX®** to yield a final concentration of busulfan of 0,5 mg/ml (9,3 ml X 6 mg/ml/ 102,3 ml = 0,5 mg/ml)

Diluted **BUSILVEX®** should be used within 8 hours if stored at 20 °C.

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing.

Using a syringe fitted with a needle remove the calculated volume of **BUSILVEX®** from the vial and dispense the content of the syringe into an intravenous bag (or syringe) which already contains the calculated amount of diluent, making sure that the drug flows into and through the solution. Do not put **BUSILVEX®** into an IV bag that does not contain diluent. Always add **BUSILVEX®** to the diluent, not the diluent to **BUSILVEX**®. Mix thoroughly by inverting several times.

Do not use polycarbonate syringes with **BUSILVEX**®.

The entire prescribed dose should be administered over two hours. Prior to and following each infusion, flush the catheter line with approximately 5ml of the diluent. Do not flush residual drug in the administration tubing as rapid infusion of **BUSILVEX®** is not recommended.

Do not infuse concomitantly with another IV solution.

SIDE-EFFECTS:

Potential adverse events according to MedDRA SOC system which may be associated with the use of Busilvex include but are not limited to:

Most patients were considered high-risk for transplant, having at least one of the following risk factors such as previous transplant, active disease, refractory and/or relapsed disease and co-morbid factors such as age over 45 year.

Blood and lymphatic system disorders:

The most frequent, serious, toxic effect of busulfan is myelosuppression resulting in leukopenia (96 %), thrombocytopenia (94 %) and anaemia (88 %) in all patients.

Immune system disorders:

Graft versus host disease developed in 18% of patients, severe in 5 % and mild to moderate in 13 %.

Infections and infestations:

Although 39 % of patients experienced one or more episodes of infection, 83 % were rated as mild to moderate. Pneumonia was fatal in 1% and life-threatening in 3 % of patients. Other infections were considered severe in 3 % of patients. Fever was reported in 87 % of patients; it was mild to moderate in 84% and severe in 3 %. 47 % of patients experienced chills that were mild to moderate in 46 % and severe in 1 %.

Hepato-biliary disorders:

15 % of serious adverse events involved liver toxicity. Hepatic veno-occlusive disease (HVOD) is a recognised potential complication of conditioning therapy prior to transplant. 6 % of patients experienced HVOD, it was fatal in 2 %, severe in 2 % and moderate in 2 %. Mild to moderate jaundice developed in 8 % of patients, it was associated with graft versus host disease or hepatic veno-occlusive disease in 4 %.

Severe AST elevations occurred in 2 % of patients. These were mild to moderate increases in AST in 23 % and in ALT in 10 %.

Respiratory, thoracic and mediastinal disorders:

One patient experienced a fatal case of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis.

Adverse reactions reported as more than isolated cases are listed below, by system organ class and by frequency. Frequencies are defined as: very common (> 1/10), common (> 1/100, <1/10), uncommon (> 1/1000, < 1/100), rare (>1/10 000, < 1/1000), very rare (< 1/10 000).

System organ class	Very common	Common	Uncommon
Blood and lymphatic system disorder	Neutropenia Thrombocytopenia Anaemia Pancytopenia Febrile neutropenia		
Nervous system disorder	Insomnia Anxiety Dizziness Depression	Confusion	Delirium Nervousness Hallucination Agitation Encephalopathy Cerebral haemorrhage Seizure
Metabolism and nutrition disorder	Hyperglycaemia Hypomagnesaemia Hypokalaemia Hypocalcaemia Hypophosphataemia Oedema	Hyponatraemia	
Cardiovascular disorder	Tachycardia Hypertension Hypotension Vasodilation Thrombosis	Arrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis Decreased ejection fraction	Femoral artery thrombosis Ventricular extrasystoles Bradycardia Capillary leak syndrome
Respiratory thoracic and mediastinal disorders	Dyspnoea Rhinitis Pharyngitis Cough	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma	Hypoxia

	Hiccup Epistaxis Abnormal breath sounds	Atelectasis Pleural effusion	
Gastrointestinal disorders	Nausea Stomatitis Vomiting Anorexia Diarrhoea Constipation Dyspepsia Anus discomfort	Oesophagitis Ileus Haematemesis	Gastrointestinal haemorrhage
Hepato-biliary disorders	Hyperbilirubinaemia Jaundice, increased hepatic enzymes, blood alkaline phosphatase increased	Hepatomegaly	
Skin and subcutaneous tissue disorders	Rash Pruritis Alopecia		
Musculoskeletal connective tissue and bone disorders	Back pain Myalgia Arthralgia		
Renal and urinary disorders	Creatinine elevated Dysuria Oligurea	BUN increase Haematuria Moderate renal insufficiency	
General disorders and administration site conditions	Weight increase Fever Headache		

	Abdominal pain Asthenia Chills Pain Allergic reaction Oedema general Pain or inflammation at the injection site Chest pain		

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

There is no known antidote to busulfan other than haematopoietic progenitor cell transplantation. The main toxic effect is profound myeloablation and pancytopenia but the central nervous system, liver, lungs and gastrointestinal tract may be affected.

Treatment is symptomatic and supportive.

IDENTIFICATION:

Clear colourless solution, essentially free of particulate matter

PRESENTATION:

10ml Type I flint glass trim tip gold band vials. 8 vials are packed in a cardboard carton.

STORAGE INSTRUCTIONS:

KEEP OUT OF REACH OF CHILDREN.

Store between + 2°C and +8 °C (in refrigerator) in the closed original packaging. Do not freeze

REGISTRATION NUMBER:

37/26/0668

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

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