For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Busulfan Kabi Injection 6mg/ml Concentrate for Solution for Infusion

WARNING MYELOSUPPRESSION
Busulfan Injection causes severe and prolonged myelosuppression at the recommended dosage. Hematopoietic progenitor cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression.

DESCRIPTION:

Busulfan Kabi Injection 6mg/ml Concentrate for Solution for Infusion is intended for intravenous administration. It is supplied as a clear, colorless, viscous solution free from visible particles. The diluted product with the compatible diluents has the same appearance as described above upon storage up to the recommended duration.

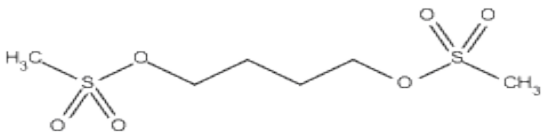
COMPOSITION:

Each ml Contains:

Busulfan USP	6 mg
N, N Dimethylacetamide Ph.Eur.	0.33ml
Polyethylene glycol USNF	0.67ml

CHEMICAL STRUCTURE:

The chemical name for Busulfan, USP is 1,4-butanediol, dimethanesulfonate. The molecular formula of Busulfan, USP is $C_6H_{14}O_6S_2$ (molecular weight- 246.30) and the structure is:



PHARMACOLOGY:

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents, alkyl sulfonates, ATC code: L01AB01.

Mechanism of action

Busulfan is a potent cytotoxic agent and a bifunctional alkylating agent. In aqueous media, release of the methanesulphonate groups produces carbonium ions which can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect.

Clinical efficacy and safety

Busulfan in combination with cyclophosphamide

In adults

Documentation on the safety and efficacy of busulfan in combination with cyclophosphamide in the BuCy2 regimen prior to conventional allogeneic and/or autologous HPCT derives from two clinical trials (OMC-BUS-4 and OMC-BUS-3).

Two prospective, single arm, open-label, uncontrolled phase II studies were conducted in

patients with haematological disease, the majority of whom had advanced disease.

Diseases included were acute leukaemia past first remission, in first or subsequent relapse, in first remission (high risk), or induction failures; chronic melogenous leukaemia in chronic or advanced phase; primary refractory or resistant relapsed Hodgkin's disease or non-Hodgkin's lymphoma, and myelodysplastic syndrome.

Patients received doses of 0.8 mg/kg busulfan every 6 hours infusion for a total 16 doses followed by cyclophosphamide at 60 mg/kg once per day for two days (BuCy2 regimen).
The primary efficacy parameters in these studies were myeloablation, engraftment, relapse, and survival.
In both studies, all patients received a 16/16 dose regimen of busulfan. No patients were discontinued from treatment due to adverse reactions related to busulfan.

All patients experienced a profound myelosuppression. The time to Absolute Neutrophil Count (ANC) greater than $0.5x10^9$ /l was 13 days (range 9-29 days) in allogenic patients (OMC-BUS 4), and 10 days (range 8-19 days) in autologous patients (OMC-BUS 3). All evaluable patients engrafted. There is no primary nor secondary graft rejection. Overall mortality and non-relapse mortality at more than 100 days post-transplant was (8/61) 13% and (6/61) 10% in allotransplanted patients, respectively. During the same period there was no death in autologous recipients.

Paediatric population
Documentation of the safety and efficacy of busulfan in combination with cyclophosphamide in the BuCy4 or with melphalan in the BuMel regimen prior to conventional allogeneic and/or autologous HPCT derives from clinical trial F60002 IN 101 G0.
The patients received the dosing mentioned in section 4.2.
All patients experienced a profound myelosuppression. The time to Absolute Neutrophil Count (ANC) greater than $0.5x10^9$/l was 21 days (range 12-47 days) in allogenic patients, and 11 days (range 10-15 days) in autologous patients. All children engrafted. There is no primary or secondary graft rejection. 93% of allogeneic patients showed complete chimerism. There was no regimen-related death through the first 100-day post-transplant and up to one year post-transplant.

Busulfan in combination with fludarabine (FB)
In adults
Documentation on the safety and efficacy of busulfan in combination with fludarabine (FB) prior to allogeneic HPCT derives from the literature review of 7 published studies involving 731 patients with myeloid and lymphoid malignancies reporting the use of intravenous busulfan infused once daily instead of four doses per day.

Patients received a conditioning regimen based on the administration of fludarabine immediately followed by single daily dose of 3.2 mg/kg busulfan over 2 or 3 consecutive days. Total dose of busulfan per patient was between 6.4 mg/kg and 9.6 mg/kg.
The FB combination allowed sufficient myeloablation modulated by the intensity of conditioning regimen through the variation of number of days of busulfan infusion. Fast and complete engraftment rates in 80-100% of patients were reported in the majority of studies. A majority of publications reported a complete donor chimerism at day+30 for 90-100% of patients. The long-term outcomes confirmed that the efficacy was maintained without unexpected effects.

Data from a recently completed prospective multicentre phase 2 study including 80 patients, aged 18 to 65 years old, diagnosed with different hematologic malignancies who underwent allo-HCT with an FB (3 days of busulfan) reduced intensity conditioning regimen became available. In this

study, all, but one, patients engrafted, at a median of 15 (range, 10-23) days after allo-HCT. The cumulative incidence of neutrophil recovery at day 28 was 98.8% (95%CI, 85.7-99.9%). Platelet engraftment occurred at a median of 9 (range, 1-16) days after allo-HCT.
The 2-year OS rate was 61.9% (95%CI, 51.1-72.7%)]. At 2 years, the cumulative incidence of NRM was 11.3% (95%CI, 5.5-19.3%), and that of relapse or progression from allo-HCT was 43.8% (95CI, 31.1-55.7%). The Kaplan-Meier estimate of DFS at 2 years was 49.9% (95%CI, 32.6-72.7).

Pharmacokinetics:

Pharmacokinetics in adults

Absorption
The pharmacokinetics of intravenous Busulfan was studied in 124 evaluable patients following a 2-hour intravenous infusion for a total of 16 doses over four days. Immediate and complete availability of the dose is obtained after intravenous infusion of Busulfan. Similar blood exposure was observed when comparing plasma concentrations in adult patients receiving oraland intravenous Busulfan at 1 mg/kg and 0.8 mg/kg respectively. Low inter (CV=21%) and intra (CV=12%) patient variability on Busulfan exposure was demonstrated through a population pharmacokinetic analysis, performed on 102 patients.

Distribution
Terminal volume of distribution Vz ranged between 0.62 and 0.85 l/kg.
Busulfan concentrations in the cerebrospinal fluid are comparable to those in plasma although these concentrations are probably insufficient for anti-neoplastic activity.
Reversible binding to plasma proteins was around 7% while irreversible binding, primarily to albumin, was about 32%.

Biotransformation
Busulfan is metabolised mainly through conjugation with glutathione (spontaneous and glutathione-S-transferase mediated). The glutathione conjugate is then further metabolised in the liver by oxidation. None of the metabolites is thought to contribute significantly to either efficacy or toxicity.

Elimination
Total clearance in plasma ranged 2.25 - 2.74 ml/minute/kg. The terminal half-life ranged from 2.8 to 3.9 hours.
Approximately 30% of the administered dose is excreted into the urine over 48 hours with 1% as unchanged Busulfan. Elimination in faeces is negligible. Irreversible protein binding may explain the incomplete recovery. Contribution of long-lasting metabolites is not excluded.

Special populations

Hepatic or renal impairment

The effects of renal dysfunction on intravenous Busulfan disposition have not been assessed.

The effects of hepatic dysfunction on intravenous Busulfan disposition have not been assessed. Nevertheless the risk of liver toxicity may be increased in this population.

No age effect on Busulfan clearance was evidenced from available intravenous Busulfan data in patients over 60 years.

Paediatric population

A continuous variation of clearance ranging from 2.52 to 3.97 ml/minute/kg has been established in children from < 6 months up to 17 years old. The terminal half life ranged from 2.24 to 2.5 h.

Inter and intra patient variabilities in plasma exposure were lower than 20% and 10%, respectively.

A population pharmacokinetic analysis has been performed in a cohort of 205 children adequately distributed with respect to bodyweight (3.5 to 62.5 kg), biological and diseases (malignant and non-malignant) characteristics, thus representative of the high heterogeneity of children undergoing HPCT. This study demonstrated that bodyweight was the predominant covariate to explain the busulfan pharmacokinetic variability in children over body surface area or age.

The recommended posology for children as detailed in section 4.2 enabled over 70% up to 90% of children ≥ 9kg in achieving the therapeutic window (900 - 1500 µmol/L.minute). However a higher variability was observed in children < 9 kg leading to 60% of children achieving the therapeutic window (900 - 1500 µmol/L.minute). For the 40% of children < 9 kg outside the target, the AUC was evenly distributed either below or above the targeted limits*; i.e.* 20% each < 900 and > 1500 µmol/L.min following 1 mg/kg. In this regard, for children < 9 kg, a monitoring of the plasma concentrations of busulfan (therapeutic drug monitoring) for dose-adjustment may improve the busulfan targeting performance, especially in extremely young children and neonates.

Pharmacokinetic/pharmacodynamic relationships:

The successful engraftment achieved in all patients during phase II trials suggests the appropriateness of the targeted AUCs. Occurrence of VOD was not related to overexposure. PK/PD relationship was observed between stomatitis and AUCs in autologous patients and between bilirubin increase and AUCs in a combined autologous and allogeneic patient analysis.

INDICATIONS:

Busulfan Injection is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

CONTRAINDICATIONS:

-Hypersensitivity to the active substance or to any of the excipients listed.

-Pregnancy.

ADVERSE EFFECTS:

Tabulated summaries of adverse reactions

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100) or not known (cannot be estimated from the available data). Undesirable effects coming from post-marketing survey have been implemented in the tables with the incidence “not known”.

Busulfan in combination with cyclophosphamide or melphalan

Adverse reactions reported both in adults and paediatric patients as more than an isolated case are listed below, by system organ class and by frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Infections and infestations	Rhinitis Pharyngitis			
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia			
Immune system disorders	Allergic reaction			
Endocrine disorders				Hypogonadism**
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypocalcaemia Hypokalaemia Hypomagnesaemia Hypophosphatemia	Hyponatraemia		
Psychiatric disorders	Anxiety Depression Insomnia	Confusion	Delirium Nervousness Hallucination Agitation	
Nervous system disorders	Headache Dizziness		Seizure Encephalopathy Cerebral haemorrhage	
Eye disorders				Cataract Corneal thinning Lens disorders***
Cardiac-disorders	Tachycardia	Arrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis	Ventricular Extrasystoles Bradycardia	
Vascular disorders	Hypertension Hypotension Thrombosis Vasodilatation		Femoral artery thrombosis Capillary leak syndrome	

System organ class	Very common	Common	Uncommon	Not known
Respiratory thoracic and mediastinal disorders	Dyspnoea Epistaxis Cough Hiccup	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia	Interstitial lung disease** Pulmonary Hypertension
Gastrointestinal disorders	Stomatitis Diarrhoea Abdominal pain Nausea Vomiting Dyspepsia Ascites Constipation Anus discomfort	Haematemesis Ileus Oesophagitis	Gastrointestinal haemorrhage	Tooth hypoplasia**
Hepato-biliary disorders	Hepatomegaly Jaundice	Veno occlusive liver disease *		
Skin and subcutaneous tissue disorders Musculoskeletal and connective tissue disorders	Rash Pruritis Alopecia Myalgia Back pain Arthralgia	Skin desquamation Erythema Pigmentation disorder		
Renal and urinary disorders	Dysuria Oligurea	Haematuria Moderate renal insufficiency		
Reproductive system and breast disorders				Premature menopause Ovarian failure**
General disorders and administration site conditions	Asthenia Chills Fever Chest pain Oedema Oedema general Pain Pain or inflammation at injection site Mucositis			

System organ class	Very common	Common	Uncommon	Not known
Investigations	Transaminases increased Bilirubin increased GGT increased Alkaline phosphatases increased Weight increased Abnormal breath sounds Creatinine elevated	Bun increase Decrease ejection fraction		

*veno occlusive liver disease is more frequent in paediatric population.

** reported in post marketing with IV Busulfan

*** reported in post marketing with oral Busulfan

Busulfan in combination with fludarabine (FB)

The incidence of each adverse reactions presented in the following table has been defined according to the highest incidence observed in published clinical trials in RIC regimen for which the population treated with FB was clearly identified, whatever the schedules of Busulfan administrations and endpoints. Adverse reactions reported as more than an isolated case are listed below, by system organ class and by frequency.

System organ class	Very common	Common	Not known*
Infections and infestations	Viral infection CMV reactivation EBV reactivation Bacterial infection	Invasive fungal infection Pulmonary infection	Brain abscess Cellulitis Sepsis
Blood and lymphatic system disorders			Febrile neutropenia
Metabolism and nutrition disorders	Hypoalbuminaemia Electrolyte disturbance Hyperglycaemia		Anorexia
Psychiatric disorders			Agitation Confusional state Hallucination
Nervous system disorders		Headache Nervous system disorders [Not Elsewhere Classified]	Cerebral haemorrhage Encephalopathy
Cardiac disorders			Atrial fibrillation
Vascular disorders		Hypertension	
Respiratory thoracic and mediastinal disorders		Pulmonary haemorrhage	Respiratory failure
Gastro-intestinal disorders	Nausea Vomiting Diarrhoea Stomatitis		Gastro-intestinal haemorrhage Tooth hypoplasia*
Hepato-biliary disorders	Veno occlusive liver disease		Jaundice Liver disorders

Skin and subcutaneous tissue disorders		Rash	
Renal and urinary disorders	Haemorrhagic cystitis**	Renal disorder	Oliguria
General disorders and administration site conditions	Mucositis		Asthenia Oedema Pain
Investigations	Transaminases increased Bilirubine increased Alkaline phosphatases increased	Creatinine elevated	Blood lactate dehydrogenase increased Blood uric acid increased Blood urea increased GGT increased Weight increased

* reported in post marketing experience
** include haemorrhagic cystitis induced by viral infection

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via national procedures.

DRUG INTERACTIONS:

No specific clinical trial was carried out to assess drug-drug interaction between intravenous busulfan and itraconazole or metronidazole. From published studies in adults, administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance. Also, there are published case reports of increased plasma levels of busulfan after administration of metronidazole. Patients who are concurrently treated with busulfan and itraconazole or metronidazole should be closely monitored for signs of busulfan toxicity.
No interaction was observed when busulfan was combined with fluconazole (antifungal agent).

Published studies in adults described that ketobemidone (analgesic) might be associated with high levels of plasma busulfan. Therefore special care is recommended when combining these two compounds.

In adults, 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 Hepatic Veno Occlusive Disease (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.

There is no common metabolism pathway between busulfan and fludarabine.
In adults, for the FB regimen, published studies did not report any mutual drug-drug interaction between intravenous busulfan and fludarabine.

In paediatric population, for the BuMel regimen it has been reported that the administration of melphalan less than 24 hours after the last oral busulfan administration may influence the development of toxicities.

Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox. The mechanism behind the interaction is not fully elucidated. It is recommended to

regularly monitor busulfan plasma concentrations and, if necessary, adjust the busulfan dose in patients who are or have recently been treated with deferasirox.

Paracetamol is described to decrease glutathione levels in blood and tissues, and may therefore decrease busulfan clearance when used in combination (see section 4.4).

Either phenytoin or benzodiazepines were administered for seizure prophylaxis in patients participating to the clinical trials conducted with intravenous busulfan (see section 4.2 and 4.4).
The concomitant systemic administration of phenytoin to patients receiving high-dose of oral busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase whereas no interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan.
No evidence of an induction effect of phenytoin has been seen on busulfan data.
A phase II clinical trial was performed to evaluate the influence of seizure prophylaxis treatment on intravenous busulfan pharmacokinetics. In this study, 24 adult patients received clonazepam (0.025-0.03 mg/kg/day as IV continuous infusions) as anticonvulsant therapy and the PK data of these patients were compared to historical data collected in patients treated with phenytoin. The analysis of data through a population pharmacokinetic method indicated no difference on intravenous busulfan clearance between phenytoin and clonazepam based therapy and therefore similar busulfan plasma exposures were achieved whatever the type of seizure prophylaxis.
No interaction was observed when busulfan was combined with $5\ HT_3$ antiemetics such as ondansetron or granisetron.

PRECAUTIONS AND WARNINGS:

The consequence of treatment with Busulfan at the recommended dose and schedule 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 platelet counts should be monitored during the treatment and until recovery is achieved.

Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period. Platelet and red

blood cell support, as well as the use of growth factors such as granulocyte colony stimulating agent (G-CSF), should be employed as medically indicated.

Hepatic impairment

Busulfan has not been studied in patients with hepatic impairment. Since Busulfan is mainly metabolized through the liver, caution should be observed when Busulfan is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment.

It is recommended when treating these patients that serum transaminase, alkaline phosphatase, and bilirubin should be monitored regularly 28 days following transplant for early detection of hepatotoxicity.

Hepatic veno-occlusive disease is a major complication that can occur during treatment with Busulfan. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior progenitor cell transplant may be at an increased risk.

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with Busulfan due to a possible decrease in the metabolism of Busulfan.

As documented in clinical studies, no treated patients experienced cardiac tamponade or other specific cardiac toxicities related to Busulfan. However cardiac function should be monitored regularly in patients receiving Busulfan.

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in Busulfan studies in one patient who died, although, no clear aetiology was identified. In addition, Busulfan might induce pulmonary toxicity that may be additive to the effects produced by other cytotoxic agents. Therefore, attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation.

Periodic monitoring of renal function should be considered during therapy with Busulfan.

Seizures have been reported with high dose Busulfan treatment. Special caution should be exercised when administering the recommended dose of Busulfan to patients with a history of seizures. Patients should receive adequate anticonvulsant prophylaxis.

The increased risk of a second malignancy should be explained to the patient. On the basis of human data, Busulfan has been classified by the International Agency for Research on Cancer (IARC) as a human carcinogen. The World Health Organisation has concluded that there is a causal relationship between Busulfan exposure and cancer. Leukaemia patients treated with Busulfan developed many different cytological abnormalities, and some developed carcinomas. Busulfan is thought to be leukemogenic.

Fertility

Busulfan can impair fertility. Therefore, men treated with busulfan are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with busulfan.

Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. Busulfan treatment in a pre-adolescent girl prevented the onset of puberty due to ovarian failure. Impotence, sterility, azoospermia, and testicular atrophy have

been reported in male patients. The solvent dimethylacetamide (DMA) may also impair fertility. DMA decreases fertility in male and female rodents (see sections 4.6 and 5.3).

Cases of thrombotic microangiopathy after hematopoietic cell transplantation (HCT), including fatal cases, have been reported in high-dose conditioning regimens in which busulfan was administered in combination with another conditioning treatment.

FERTILITY, PREGNANCY AND LACTATION:

Women of childbearing potential

Women of childbearing potential have to use effective contraception during and up to 6 months after treatment.

Pregnancy

HPCT is contraindicated in pregnant women; therefore, busulfan is contraindicated during pregnancy. Studies in animals have shown reproductive toxicity (embryo-foetal lethality and malformations)

There are no or limited amount of data from the use of busulfan or DMA in pregnant women. A few cases of congenital abnormalities have been reported with low-dose oral busulfan, not necessarily attributable to the active substance, and third trimester exposure may be associated with impaired intrauterine growth.

Breast-feeding

It is unknown whether busulfan and DMA are excreted in human milk. Because of the potential for tumorigenicity shown for busulfan in human and animal studies, breast-feeding should be discontinued during treatment with busulfan.

Fertility

Busulfan and DMA can impair fertility in man or woman. Therefore it is advised not to father child during the treatment and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Busulfan has no influence on the ability to drive and use machines.

DOSAGE AND ADMINISTRATION:

Administer Busulfan in combination with cyclophosphamide as a conditioning regimen prior to bone marrow or peripheral blood progenitor cell replacement. For adult patients, the recommended doses (BuCY2 regimen) are:

-Busulfan 0.8 mg/kg (ideal body weight or actual body weight, whichever is lower) intravenously via a central venous catheter as a two-hour infusion every six hours for four consecutive days for a total of 16 doses (Days -7, - 6, -5 and -4).

-Cyclophosphamide 60 mg/kg intravenously as a one-hour infusion on each of two days beginning no sooner than six hours following the 16^{th} dose of Busulfan (Days -3 and -2).

-Administer hematopoietic progenitor cells on Day 0.

- Premedicate patients with anticonvulsants (e.g., benzodiazepines, phenytoin, valproic acid or levetiracetam) to prevent seizures reported with the use of high dose Busulfan. Administer

anticonvulsants 12 hours prior to Busulfan to 24 hours after the last dose of Busulfan.

- Administer antiemetics prior to the first dose of Busulfan and continue on a fixed schedule through Busulfan administration.

- Busulfan clearance is best predicted when the Busulfan dose is administered based on adjusted ideal body weight. Dosing Busulfan based on actual body weight, ideal body weight or other factors can produce significant differences in Busulfan clearance among lean, normal and obese patients.

-Calculate ideal body weight (IBW) as follows (height in cm, and weight in kg):
Men:IBW (kg) = 50 + 0.91 x (height in cm -152)
Women:IBW (kg) = 45 + 0.91 x (height in cm -152)
-For obese or severely obese patients, base Busulfan dosing on adjusted ideal body weight (AIBW):
AIBW = IBW + 0.25 x (actual weight -IBW).Pediatrics: The effectiveness of Busulfan in the treatment of CML has not been specifically studied in paediatrics patients.

Method of administration
Precautions to be taken before handling or administering the medicinal product
This medicinal product must be diluted prior to administration. A final concentration of approximately 0.5 mg/ml Busulfan should be achieved. Busulfan should be administered by intravenous infusion via central venous catheter.

Busulfan should not be given by rapid intravenous, *bolus* or peripheral injection.

All patients should be pre-medicated with anticonvulsant medicinal products to prevent seizures reported with the use of high dose Busulfan.

It is recommended to administer anticonvulsants 12 h prior to Busulfan to 24 h after the last dose of Busulfan.

Antiemetics should be administered prior to the first dose of Busulfan and continued on a fixed schedule according to local practice through its administration.

Preparation and Administration Precautions

Preparation of Busulfan
Procedures for proper handling and disposal of anticancer medicinal products should be considered.

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood.

As with other cytotoxic compounds, caution should be exercised in handling and preparing the Busulfan solution:
- The use of gloves and protective clothing is recommended.
- If the concentrate or diluted Busulfan solution contacts the skin or mucosa, wash them thoroughly with water immediately.

Calculation of the quantity of Busulfan to be diluted and of the diluent

Busulfan must be diluted prior to use with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%.

The quantity of the diluent must be 10 times the volume of the Busulfan ensuring the final concentration of Busulfan remains at approximately 0.5 mg/ml. By example:

The amount of Busulfan and diluent to be administered would be calculated as follows:
for a patient with a Y kg body weight:

- Quantity of Busulfan:

$$\frac{Y\ (kg) \times D\ (mg/kg)}{6\ (mg/ml)} = A \text{ ml of Busulfan to be diluted}$$

Y: body weight of the patient in kg D: dose of Busulfan

- Quantity of diluent:

(A ml Busulfan) x (10) = B ml of diluent

To prepare the final solution for infusion, add (A) ml of Busulfan to (B) ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%)

Preparation of the solution for infusion

- Busulfan must be prepared by healthcare professional using sterile transfer techniques. Using a non polycarbonate syringe fitted with a needle:

  - The calculated volume of Busulfan must be removed from the vial.
  - The contents of the syringe must be dispensed into an intravenous bag (or syringe) which already contains the calculated amount of the selected diluent. Busulfan must always be added to the diluent, not the diluent to the Busulfan. Busulfan must not be put into an intravenous bag that does not contain sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%.
- The diluted solution must be mixed thoroughly by inverting several times.

After dilution, 1 ml of solution for infusion contains 0.5 mg of Busulfan.

Diluted Busulfan is a clear colourless solution.

Instructions for use
Prior to and following each infusion, flush the indwelling catheter line with approximately 5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

The residual medicinal product must not be flushed in the administration tubing as rapid infusion of Busulfan has not been tested and is not recommended.

The entire prescribed Busulfan dose should be delivered over two hours.

Small volumes may be administered over 2 hours using electric syringes. In this case infusion sets with minimal priming space should be used (i.e 0.3-0.6 ml), primed with medicinal product solution prior to beginning the actual Busulfan infusion and then flushed with sodium chloride

9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

Busulfan must not be infused concomitantly with another intravenous solution.

Polycarbonate syringes must not be used with Busulfan.

For single use only. Only a clear solution without any particles should be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic medicinal products.OVERDOSE:

The principal toxic effect is profound myeloablation and pancytopenia but the central nervous system, liver, lungs, and gastrointestinal tract may also be affected.

There is no known antidote to Busulfan other than haematopoietic progenitor cell transplantation. In the absence of haematopoietic progenitor cell transplantation, the recommended dose of Busulfan would constitute an overdose of Busulfan. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.

There have been two reports that Busulfan is dialyzable, thus dialysis should be considered in the case of an overdose. Since, Busulfan is metabolized through conjugation with glutathione, administration of glutathione might be considered.

It must be considered that overdose of Busulfan will also increase exposure to DMA. In human the principal toxic effects were hepatotoxicity and central nervous system (CNS) effects. CNS changes precede any of the more severe side effects. No specific antidote for DMA overdose is known.

In case of overdose, management would include general supportive care.

Store in a refrigerator (2°C-8°C).
Do not freeze the diluted solution.

Diluted solution

- Busulfan Kabi Injection diluted in 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, is stable at room temperature (25°C) for up to 8 hours but the infusion must be completed within that time.

- Busulfan Kabi Injection diluted in 0.9% Sodium Chloride Injection, is stable at refrigerated conditions (2°C to 8°C) for up to 12 hours but the infusion must be completed within that time.

From a microbiological point of view, the product should be used immediately after dilution.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than the above-mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

INCOMPATIBILITIES:

Busulfan must be diluted prior to use with either 0.9% Sodium Chloride Injection (normal

saline) or 5% Dextrose Injection. Busulfan should not be mixed with other medicinal products. Polycarbonate syringes must not be used with Busulfan.

PRESENTATION:

Busulfan Kabi Injection 6 mg/ml Concentrate for Solution for Infusion is packaged as a sterile solution in 10 ml single-use clear glass vials each containing 60 mg of busulfan at a concentration of 6 mg/ml for intravenous use.

Pack size: 1 x 10 ml vial, 8 x 10 ml vials

MANUFACTURER INFORMATION:

Manufactured in India by:
Fresenius Kabi Oncology Ltd.
Village Kishanpura,
Baddi,
Tehsil Nalagarh,
District Solan,
Himachal Pradesh,
174101 INDIA

Product Registration Holder/Importer:
Fresenius Kabi Malaysia Sdn Bhd
3-1 & 3-2, Axis Technology Centre,
Lot 13, Jalan 51A/225,
46100 Petaling Jaya
Selangor

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