# PRESCRIBING INFORMATION

*(For the use of a registered medical practitioner or a hospital or a laboratory only)*

**BUFATAS**
**Busulfan concentrate for solution for infusion 6 mg/mL, 10 mL**

## 1. PRODUCT NAME:

BUFATAS
Busulfan concentrate for solution for infusion 6 mg/mL, 10 mL.

## 2. NAME AND STRENGTH OF ACTIVE INGREDIENT (S):

Busulfan:
Each mL contains:
Busulfan 6 mg (Busulfan Ph. Eur.)

## 3. PRODUCT DESCRIPTION:

Clear, colourless solution free from visible particles.

## 4. PHARMACODYNAMICS/PHARMACOKINETICS:

## 4.1 PHARMACODYNAMICS:

Pharmacotherapeutic group: 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).

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.

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 Posology and method of administration

All patients experienced a profound myelosuppression. The time to Absolute Neutrophil Count (ANC) greater than 0.5x109/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.

## 4.2 PHARMACOKINETICS

The pharmacokinetics of busulfan has been investigated. The information presented on biotransformation and elimination is based on oral busulfan.

*Pharmacokinetics in adults*

Absorption
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 oral and intravenous busulfan at 1 mg/kg and 0.8 mg/kg respectively.

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-Stransferase 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.

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.

Linearity
The dose proportional increase of busulfan exposure was demonstrated following intravenous busulfan up to 1 mg/kg.

Compared to the four times a day regimen, the once-daily regimen is characterized by a higher peak concentration, no drug accumulation and a wash out period (without circulating busulfan concentration) between consecutive administrations. The review of the literature allows a comparison of PK series performed either within the same study or between studies and demonstrated unchanged dose-independent PK parameters regardless the dosage or the schedule of administration. It seems that the recommended intravenous busulfan dose administered either as an individual infusion (3.2 mg/kg) or into 4 divided infusions (0.8 mg/kg) provided equivalent daily plasma exposure with similar both inter-and intrapatient variability. As a result, the control of intravenous busulfan AUC within the therapeutic windows is not modified and a similar targeting performance between the two schedules was illustrated.

Pharmacokinetic/pharmacodynamic relationships
The literature on busulfan suggests a therapeutic AUC window between 900 and 1500 µmol/L. minute per administration (equivalent to a daily exposure between 3600 and 6000 µmol/L. minute). During clinical trials with intravenous busulfan administered as 0.80 mg/kg four-times daily, 90% of patients AUCS were below the upper AUC limit (1500 µmol/L. minute) and at least 80% were within the targeted therapeutic window (900-1500 µmol/L. minute). Similar targeting rate is achieved within the daily exposure of 3600 - 6000 µmol/L. minute following the administration of intravenous busulfan 3.2 mg/kg once daily.

**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 2.49 to 3.92 ml/minute/kg has been established in children from < 6 months up to 17 years old. The terminal half-life ranged from 2.26 to 2.52 h. Inter and intra patient variabilities in plasma exposure were lower than 20% and 10%, respectively.

The recommended posology for children as detailed in section 4.2 enabled over 70% up to 90% of children ≥ 9 kg 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 $AUC_S$. Occurrence of VOD was not related to overexposure. PK/PD relationship was observed between stomatitis and $AUC_S$ in autologous patients and between bilirubin increase and $AUC_S$ in a combined autologous and allogeneic patient analysis.

## 5. INDICATIONS:

Busulfan Injection followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option.

Busulfan Injection following fludarabine (FB) is indicated as conditioning treatment prior to haematopoietic progenitor cell transplantation (HPCT) in adult patients who are candidates for a reduced-intensity conditioning (RIC) regimen.

Busulfan Injection followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.

## 6. POSOLOGY AND METHOD OF ADMINISTRATION:

Busulfan Injection administration should be supervised by a physician experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation.

Busulfan Injection is administered prior to the haematopoietic progenitor cell transplantation (HPCT).

*Posology*
Busulfan Injection in combination with cyclophosphamide or melphalan.

In adults
The recommended dose and schedule of administration is:
- 0.8 mg/kg body weight (BW) of busulfan as a two-hour infusion every 6 hours over 4 consecutive days for a total of 16 doses,

- followed by cyclophosphamide at 60 mg/kg/day over 2 days initiated for at least 24 hours following the 16th dose of Busulfan Injection (see section Interaction with other medicinal products).

Paediatric population (0 to 17 years)

The recommended dose of Busulfan Injection is as follows:

| **Actual body weight (kg)** | **Busulfan Injection dose (mg/kg)** |
|---|---|
| < 9 | 1.0 |
| 9 to < 16 | 1.2 |
| 16 to 23 | 1.1 |
| > 23 to 34 | 0.95 |
| > 34 | 0.8 |

followed by:
- 4 cycles of 50 mg/kg body weight (BW) cyclophosphamide (BuCy4) or

- one administration of 140 mg/m2 melphalan (BuMel) initiated for at least 24 hours following the 16th dose of Busulfan Injection. (See section 4.5).

Busulfan Injection is administered as a two-hour infusion every 6 hours over 4 consecutive days for a total of 16 doses prior to cyclophosphamide or melphalan and haematopoietic progenitor cell transplantation (HPCT).

Elderly patients
Patients older than 50 years of age have been successfully treated with Busulfan Injection without dose adjustment. However, for the safe use of Busulfan Injection in patients older than 60 years

only limited information is available. Same dose (see section Pharmacokinetic) for elderly patients as for adults (< 50 years old) should be used.

Busulfan Injection in combination with fludarabine (FB)
In adults

The recommended dose and schedule of administration is:
- fludarabine administered as a single daily one-hour infusion at 30 mg/m$^2$ for 5 consecutive days or 40 mg/m$^2$ for 4 consecutive days.

- Busulfan Injection will be administered at 3.2 mg/kg as a single daily three-hour infusion immediately after fludarabine for 2 or 3 consecutive days.

Paediatric population (0 to 17 years)

The safety and efficacy of FB in pediatric population has not been established.

Elderly patients
The administration of FB regimen has not been specifically investigated in elderly patients. However, more than 500 patients aged ≥ 55 years were reported in publications with FB conditioning regimens, yielding efficacy outcomes similar to younger patients. No dose adjustment was deemed necessary.

*Obese patients*
In adults
For obese patients, dosing based on adjusted ideal body weight (AIBW) should be considered.
Ideal body weight (IBW) is calculated as follows:

IBW men (kg) = 50 + 0.91x (height in cm-152);
IBW women (kg) = 45 + 0.91x (height in cm-152).

Adjusted ideal body weight (AIBW) is calculated as follows:
AIBW= IBW+0.25x (actual body weight - IBW).

In paediatric population
The medicinal product is not recommended in obese children and adolescents with body mass index Weight (kg)/(m$^2$) >30 kg/m$^2$ until further data become available.

Patients with renal impairment
Studies in renally impaired patients have not been conducted, however, as busulfan is moderately excreted in the urine, dose modification is not recommended in these patients.

However, caution is recommended (see sections Undesirable effects and Pharmacokinetic).

Patients with hepatic impairment

Busulfan Injection as well as busulfan has not been studied in patients with hepatic impairment. Caution is recommended, particularly in those patients with severe hepatic impairment (see section Special warnings and precautions for use).

**Method of administration**

*Precautions to be taken before handling or administering the medicinal product*

Busulfan Injection must be diluted prior to administration. A final concentration of approximately 0.5 mg/mL busulfan should be achieved. Busulfan Injection should be administered by intravenous infusion via central venous catheter.

For instructions on dilution of the medicinal product before administration, see section Special precautions for disposal.

Busulfan Injection 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 concentrate for solution for infusion to 24 h after the last dose of Busulfan concentrate for solution for infusion.

In adult and paediatric studies, patients received either phenytoin or benzodiazepines as seizure prophylaxis treatment. (See sections Special warnings & precautions for use and Interaction with other medicinal products).

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

## 7. CONTRA-INDICATIONS:

Hypersensitivity to the active substance or to any of the excipients listed in section List of excipients.

Pregnancy (see section Fertility, pregnancy and lactation).

## 8. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

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.

In adults, absolute neutrophil counts < 0.5x109/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 allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively). Thrombocytopenia (< 25x109/l 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.

In paediatric population, absolute neutrophil counts < 0.5x109/l at a median of 3 days post transplant occurred in 100% of patients and lasted 5 and 18.5 days in autologous and allogeneic transplant respectively. In children, thrombocytopenia (< 25x109/l or requiring platelet transfusion) occurred in 100% of patients. Anaemia (haemoglobin<8.0 g/dl) occurred in 100% of patients.

In children < 9 kg, a therapeutic drug monitoring may be justified on a case by case basis, in particular in extremely young children and neonates (see section Pharmacokinetic).

The Fanconi anaemia cells have hypersensitivity to cross-linking agents. There is limited clinical experience of the use of busulfan as a component of a conditioning regimen prior to HSCT in children with Fanconi's anaemia. Therefore Busulfan Injection should be used with caution in this type of patients.

**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 Injection. 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 (see section Undesirable effects).

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with Busulfan Injection due to a possible decrease in the metabolism of busulfan (See section Interaction with other medicinal products).

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 (see section Undesirable effects).

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 (see section Undesirable effects).

Periodic monitoring of renal function should be considered during therapy with Busulfan Injection (see section Undesirable effects).

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of Busulfan Injection 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 Injection 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 Injection. 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.

## 9. INTERACTIONS WITH OTHER MEDICINAL PRODUCTS:

No specific clinical trial was carried out to assess drug-drug interaction between intravenous busulfan and itraconazole.

From published studies in adults, 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 intravenous busulfan.

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 > 24hours.

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.

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

Either phenytoin or benzodiazepines were administered for seizure prophylaxis in patients participating to the clinical trials conducted with intravenous busulfan (see section Posology and method of administrationand Special warnings and precautions for use). 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.

No interaction was observed when busulfan was combined with fluconazole (antifungal agent) or 5 HT3 antiemetics such as ondansetron or granisetron.

## 10. FERTILITY, PREGNANCY AND LACTATION:

Pregnancy

HPCT is contraindicated in pregnant women; therefore, Busulfan Injection is contraindicated during pregnancy. Studies in animals have shown reproductive toxicity (embryo-fetal 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.

Women of childbearing potential

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

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 (see section Special warnings and precautions for use).

## 11. EFFECTS ON ABILITY TO DRIVE AND OPERATE MACHINE:

Not relevant.

## 12. UNDESIRABLE EFFECTS:

Summary of the safety profile:

*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.

*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 |
|---|---|---|---|
| Infections and infestations | Rhinitis, Pharyngitis | | |
| Blood and lymphatic system disorders | Neutropenia, Thrombocytopenia, Febrile neutropenia, Anaemia, Pancytopenia. | | |
| Immune system disorders | Allergic reaction | | |
| Endocrine disorders | | | |
| 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 | | | |
| 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. |
| Respiratory thoracic and mediastinal disorders | Dyspnoea, Epistaxis, Cough, Hiccup | Hyperventilation, Respiratory failure, Alveolar haemorrhages, Asthma, Atelectasis, Pleural effusion. | Hypoxia |
| Gastrointestinal disorders | Stomatitis, Diarrhoea, Abdominal pain, Nausea, Vomiting, Dyspepsia, Ascites, Constipation, Anus discomfort. | Haematemesis, Ileus, Oesophagitis. | Gastrointestinal haemorrhage |
| Hepato-biliary disorders | Hepatomegaly, Jaundice | Veno occlusive liver disease * | |
| Skin and subcutaneous tissue | Rash, Pruritis | Skin desquamation, Erythema, | |
| | Alopecia | Pigmentation | |
| Musculoskeletal and connective tissue disorders | Myalgia, Back pain, Arthralgia | | |
| Renal and urinary disorders | Dysuria, Oligurea | Haematuria<br><br>Moderate renal insufficiency | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|---|---|---|
| General disorders and administration site conditions | Asthenia, Chills, Fever, Chest pain, Oedema, Oedema general Pain, Pain or inflammation at injection site, Mucositis | | |
| 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.

*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** |
|---|---|---|
| Infections and infestations | Viral infection, CMV reactivation | Invasive fungal infection, Pulmonary infection |
| | EBV reactivation, Bacterial infection | |
| Blood and lymphatic system disorders | | |
| Metabolism and nutrition disorders | Hypoalbuminaemia, Electrolyte disturbance, Hyperglycaemia | |
| Psychiatric disorders | | |
| Nervous system disorders | | Headache<br>Nervous system disorders [Not Elsewhere Classified] |
| Cardiac disorders | | |
| Vascular disorders | | Hyper-tension |
| Respiratory thoracic and mediastinal disorders | | Pulmonary haemorrhage |

| | | |
|---|---|---|
| Gastro-intestinal disorders | Nausea, Vomiting, Diarrhoea, Stomatitis | |
| Hepato-biliary disorders | Veno occlusive liver disease | |
| Skin and subcutaneous tissue disorders | | Rash |
| Renal and urinary disorders | Haemorrhagic cystitis** | Renal disorder |
| General disorders and administration site conditions | Mucositis | |
| Investigations | Transaminases increased, Bilirubine increased, Alkaline phosphatases increased. | Creatinine elevated |

** include haemorrhagic cystitis induced by viral infection.

## 13. OVERDOSE AND TREATMENT:

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 Injection 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 Injection 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.

## 14. INCOMPATIBILITIES:

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal.

**Do not use polycarbonate syringes with Busulfan concentrate for solution for infusion.**

## 15. SPECIAL PRECAUTIONS FOR DISPOSAL:

*Preparation of Busulfan Injection*
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 concentrate for solution for infusion to be diluted and of the diluent

Busulfan Injection 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 Busulfan Injection ensuring the final concentration of busulfan remains at approximately 0.5 mg/mL.

By example:

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

- Quantity of Busulfan Injection:

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

Y: body weight of the patient in kg
D: dose of busulfan (see section Posology and method of administration)

- Quantity of diluent:
(A ml Busulfan Injection) x (10) = B mL of diluents

To prepare the final solution for infusion, add (A) ml of Busulfan Injection 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 Injection must be prepared by a healthcare professional using sterile transfer techniques. Using a non polycarbonate syringe fitted with a needle:

- the calculated volume of Busulfan Injection 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 Injection must always be added to the diluent, not the diluent to Busulfan Injection. Busulfan Injection 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 Injection 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 Injection dose should be delivered over two or three hours depending of the conditioning regimen.

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 concentrate for solution for infusion and then flushed with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

Busulfan Injection must not be infused concomitantly with another intravenous solution.
Polycarbonate syringes must not be used with Busulfan Injection.

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.

## 16. STORAGE CONDITION:

Store in a refrigerator (2°C - 8°C).
Do not freeze the diluted solution.
For storage conditions after dilution of the medicinal product see section Shelf life.

## 17. LIST OF EXCIPIENTS:

Dimethylacetamide,
Macrogol 400.

## 18. DOSAGE FORMS AND PACKAGING AVAILABLE:

Busulfan concentrate for solution for infusion 6 mg/mL is available in type I clear glass vial and one such vial in one box pack.

## 19. SHELF LIFE:

Vials: 24 months.

Diluted solution:
Chemical and physical in-use stability after dilution in glucose 5% or sodium chloride 9 mg/mL (0.9%) solution for injection has been demonstrated for:

- 4 hours (including infusion time) after dilution when stored at 20 °C - 25 °C.

- 15 hours after dilution when stored at 2 °C – 8 °C followed by 3 hours stored at 20 °C - 25 °C (including infusion 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.

## 20. MANUFACTURED BY:

**Intas Pharmaceuticals Limited**
Plot no.: 457-458, Village-Matoda,
Bavla Road, Dist.: Ahmedabad,
Gujarat, India.

**Importer & Product License Holder:**
DKSH (Thailand) Limited.

## 21. DATE OF REVISION OF PACKAGE INSERT:

Jan 2019