1. NAME OF THE MEDICINAL PRODUCT

Bufatas (Busulfan concentrate for solution for infusion 6 mg/ml, 10ml vial)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Busulfan Ph.Eur. 6 mg

After dilution, 1 mL of solution contains 0.5 mg of busulfan.

Dimethylacetamide and Macrogol 400.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Busulfan concentrate for solution for infusion 6 mg/ml, 10 ml vial is a clear, colourless solution free from visible particles in a clear glass vial with flip-off seal. This medicinal product is supplied in vials as a sterile, concentrated injection containing 60 mg/10 mL of busulfan.
Diluted Busulfan Injection is a clear colourless solution free from foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

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

4.2 Posology and Method of 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 16th 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+0.91x (height in cm -152)

Women: IBW (kg)=45+0.91x (height in cm -152)

- For obese or severely obese patients, base Busulfan dosing on adjusted ideal body weight (AIBW):

AIBW= IBW +0.25x (actual weight -IBW).

Pediatrics: The effectiveness of Busulfan in the treatment of CML has not been specifically studied in pediatric patients.

Method of administration

Intravenous infusion

4.3 Contraindications and reproductive safety

Busulfan is contraindicated in patients with a history of hypersensitivity to any of its components.

Pregnancy

Haematopoietic progenitor cell transplantation (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

4.4 Special Warnings and Precautions for Use

The following warnings pertain to different physiologic effects of busulfan in the setting of allogeneic transplantation.

Myelosuppression

The most frequent serious consequence of treatment with Busulfan at the recommended dose and schedule is prolonged myelosuppression, occurring in all patients (100%). Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Hematopoietic progenitor cell transplantation is required to prevent potentially fatal complications of the prolonged myelosuppression. Monitor complete blood counts, including white blood cell differentials, and quantitative platelet counts daily during treatment and until engraftment is demonstrated. Absolute neutrophil counts dropped below 0.5x109/L at a median of 4 days post-transplant in 100% of patients treated in the Busulfan clinical trial. The absolute neutrophil count recovered at a median of 13 days following allogeneic transplantation when prophylactic G-CSF was used in the majority of patients. Thrombocytopenia (<25,000/mm3 or requiring platelet transfusion) occurred at a median of 5-6 days in 98% of patients. Anemia (hemoglobin < 8.0 g/dL) occurred in 69% of patients. Use antibiotic therapy and platelet and red blood cell support when medically indicated.

Seizures

Seizures have been reported in patients receiving high-dose oral busulfan at doses producing plasma drug levels similar to those achieved following the recommended dosage of busulfan. Despite prophylactic therapy with phenytoin, one seizure (1/42 patients) was reported during an autologous transplantation clinical trial of busulfan. This episode occurred during the cyclophosphamide portion of the conditioning regimen, 36 hours after the last busulfan dose. Initiate phenytoin therapy or any other alternative anti-convulsant prophylactic therapy (e.g., benzodiazepines, valproic acid or levetiracetam) prior to busulfan treatment. Use caution when administering the recommended dose of busulfan to patients with a history of a seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs.

Hepatic Veno-Occlusive Disease (HVOD)

Current literature suggests that high busulfan area under the plasma concentration versus time curve (AUC) values (>1,500 μM•min) may be associated with an increased risk of developing HVOD. 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 HVOD with the recommended busulfan dose and regimen. Based on clinical examination and laboratory findings, HVOD was diagnosed in 8% (5/61) of patients treated with busulfan in the setting of allogeneic transplantation, was fatal in 2/5 cases (40%), and yielded an overall mortality from HVOD in the entire study population of 2/61 (3%). Three of the five patients diagnosed with HVOD were retrospectively found to meet the Jones' criteria. The incidence of HVOD reported in the literature from the randomized, controlled trials was 7.7%-12%. Monitor serum transaminases, alkaline phosphatase, and bilirubin daily through BMT Day +28 to detect hepatotoxicity, which may herald the onset of HVOD.

Embryo-fetal Toxicity
Busulfan can cause fetal harm when administered to a pregnant woman based on animal data. Busulfan was teratogenic in mice, rats, and rabbits. The solvent, DMA, may also cause fetal harm when administered to a pregnant woman based on findings in animals. Advise pregnant women of the potential risk to a fetus. Advise females and males of reproductive potential to use effective contraception during and after treatment with Busulfan.

Cardiac Tamponade
Cardiac tamponade has been reported in pediatric patients with thalassemia (8/400 or 2% in one series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children died and two were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. Monitor for signs and symptoms, promptly evaluate and treat if cardiac tamponade is suspected.

Bronchopulmonary Dysplasia
Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).

Cellular Dysplasia
Busulfan may cause cellular dysplasia in many organs. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes, pancreas, thyroid, adrenal glands, liver, lungs and bone marrow. This cytologic dysplasia may be severe enough to cause difficulty in the interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix.

Infections
Bone marrow suppression often results in opportunistic infection that can be lethal. Patients should be monitored for signs of local or systemic infection or bleeding. Their hematologic status should be evaluated appropriately. Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for the prevention and management of infections during the neutropenic period.

4.5 Interaction of Other Medicaments

Itraconazole decreases busulfan clearance by up to 25% and may produce an AUC >1500 μM•min in some patients. Fluconazole (200 mg) has been used with Busulfan.

Phenytoin increases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione-S-transferase. Since the pharmacokinetics of Busulfan were studied in patients treated with phenytoin, the clearance of Busulfan at the recommended dose may be lower and exposure (AUC) higher in patients not treated with phenytoin.

Because busulfan is eliminated from the body via conjugation with glutathione, use of acetaminophen prior to (<72 hours) or concurrent with Busulfan may result in reduced busulfan

clearance based upon the known property of acetaminophen to decrease glutathione levels in the blood and tissues.

Metronidazole increases plasma levels of Busulfan, which may lead to treatment-related toxicities.

4.6 Fertility, pregnancy and lactation

Pregnancy
Haematopoietic progenitor cell transplantation (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

4.7 Effects on Ability to Drive and Use Machines
Not relevant

4.8 Undesirable Effects

Summary of the safety profile

Busulfan in combination with cyclophosphamide or melphalan
In adults
Adverse events information is derived from two clinical trials (n=103) of busulfan. Serious toxicities involving the haematologic, hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process. These include infection and Graft-versus host disease (GVHD) which although not directly related, were the major causes of morbidity and mortality, especially in allogeneic HPCT.

Blood and lymphatic system disorders:
Myelo-suppression and immuno-suppression were the desired therapeutic effects of the conditioning regimen. Therefore all patients experienced profound cytopenia: leucopenia 96%, thrombocytopenia 94%, and anemia 88%. The median time to neutropenia was 4 days for both autologous and allogeneic patients. The median duration of neutropenia was 6 days and 9 days for autologous and allogeneic patients.

Immune system disorders:
The incidence of acute graft versus host disease (a-GVHD) data was collected in OMC-BUS-4 study (allogeneic)(n=61). A total of 11 patients (18%) experienced a- GVHD. The incidence of a-GVHD grades I-II was 13% (8/61), while the incidence of grade III-IV was 5% (3/61). Acute GVHD was rated as serious in 3 patients. Chronic GVHD (c-GVHD) was reported if serious or the cause of death and was reported as the cause of death in 3 patients.

Infections and infestations:
39% of patients (40/103) experienced one or more episodes of infection, of which 83% (33/40) were rated as mild or moderate. Pneumonia was fatal in 1% (1/103) and life-threatening in 3% of patients. Other infections were considered severe in 3% of patients. Fever was reported in 87% of patients and graded as mild/moderate in 84% and severe in 3%. 47% of patients experienced chills which were mild/moderate in 46% and severe in 1%.

Hepato-biliary disorders:
15% of SAEs involved liver toxicity. HVOD is a recognized potential complication of conditioning therapy post-transplant. Six of 103 patients (6%) experienced HVOD. HVOD occurred in: 8.2% (5/61) allogeneic patients (fatal in 2 patients) and 2.5% (1/42) of autologous patients. Elevated bilirubin (n=3) and elevated AST (n=1) were also observed. Two of the above four patients with serious serum hepatotoxicity were among patients with diagnosed HVOD.

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 in the busulfan studies.

Paediatric population
Adverse events information are derived from the clinical study in paediatrics (n=55). Serious toxicities involving the hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process.

Immune system disorders:
The incidence of acute graft versus host disease (a-GVHD) data was collected in allogeneic patients (n=28). A total of 14 patients (50%) experienced a-GVHD. The incidence of a-GVHD grades I-II was 46.4% (13/28), while the incidence of grade IIIIV was 3.6% (1/28). Chronic GVHD was reported only if it is the cause of death: one patient died 13 months post-transplant.

Infections and infestations:
Infections (documented and non documented febrile neutropenia) were experienced in 89% of patients (49/55). Mild/moderate fever was reported in 76% of patients.

Hepato-biliary disorders:
Grade 3 elevated transaminases were reported in 24% of patients.
Veno occlusive disease (VOD) was reported in 15% (4/27) and 7% (2/28) of the autologous and allogenic transplant respectively. VOD observed were neither fatal nor severe and resolved in all cases.

Busulfan in combination with fludarabine (FB)
In adults
The safety profile of busulfan combined with fludarabine (FB) has been examined through a review of adverse events reported in published data from clinical trials in RIC regimen. In these studies, a total of 1574 patients received FB as a reduced intensity conditioning (RIC) regimen prior to haematopoietic progenitor cell transplantation.

Myelo-suppression and immuno-suppression were the desired therapeutic effects of the conditioning regimen and consequently were not considered undesirable effects.

Infections and infestations:
The occurrence of infectious episodes or reactivation of opportunistic infectious agents mainly reflects the immune status of the patient receiving a conditioning regimen.

The most frequent infectious adverse reactions were Cytomegalovirus (CMV reactivation [range: 30.7% - 80.0%], Epstein-Barr Virus (EBV) reactivation [range: 2.3% - 61%], bacterial infections [range: 32.0% - 38.9%] and viral infections [range: 1.3% - 17.2%].

Gastrointestinal disorders:
The highest frequency of nausea and vomiting was 59.1% and the highest frequency of stomatitis was 11%.

Renal and urinary disorders:
It has been suggested that conditioning regimens containing fludarabine were associated with higher incidence of opportunistic infections after transplantation because of the immunosuppressive effect of fludarabine. Late haemorrhagic cystitis occurring 2 weeks post-transplant are likely related to viral infection / reactivation. Haemorrhagic cystitis including haemorrhagic cystitis induced by viral infection was reported in a range between 16% and 18.1%.

Hepato-biliary disorders:
VOD was reported with a range between 3.9% and 15.4%.

The treatment-related mortality/non-relapse mortality (TRM/NRM) reported until day+100 post-transplant has also been examined through a review of published data from clinical trials. It was considered as deaths that could be attributable to secondary side effects after HPCT and not related to the relapse/progression of the underlying haematological malignancies.

The most frequent causes of reported TRM/NRMs were infection/sepsis, GVHD, pulmonary disorders and organ failure.

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

System organ class	Very common	Common	Uncommon	Not known
				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	
Respiratory thoracic and mediastinal disorders	Dyspnoea Epistaxis Cough Hiccup	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia	Interstitial lung disease**
Gastrointestinal disorders	Stomatitis Diarrhea 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	Rash Pruritus Alopecia	Skin desquamation Erythema Pigmentation disorder		
Musculoskeletal and connective tissue disorders	Myalgia Back pain Arthralgia			
Renal and	Dysuria	Hematuria		

System organ class	Very common	Common	Uncommon	Not known
urinary disorders	Oliguria	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			
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			Febrile neutropenia

System organ class	Very common	Common	Not known*
lymphatic system disorders			
Metabolism and nutrition disorders	Hypoalbuminemia 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		Hyper-tension	
Respiratory thoracic and mediastinal disorders		Pulmonary haemorrhage	Respiratory failure
Gastro-intestinal disorders	Nausea Vomiting Diarrhea 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 Bilirubin 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

4.9 Overdose and Treatment

There is no known antidote to Busulfan other than hematopoietic progenitor cell transplantation. In the absence of hematopoietic progenitor cell transplantation, the recommended dosage for Busulfan would constitute an overdose of busulfan. The principal toxic effect is profound bone marrow hypoplasia/aplasia and pancytopenia, but the central nervous system, liver, lungs, and gastrointestinal tract may be affected. Monitor hematologic status closely and institute vigorous supportive measures as medically indicated.

Survival after a single 140 mg dose of Tablets in an 18 kg, 4-year old child has been reported. Inadvertent administration of a greater than normal dose of oral busulfan (2.1 mg/kg; total dose of 23.3 mg/kg) occurred in a 2-year old child prior to a scheduled bone marrow transplant without sequelae. An acute dose of 2.4 g was fatal in a 10-year old boy. There is one report that busulfan is dialyzable, thus dialysis should be considered in the case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Alkyl sulfonates, ATC code: L01AB01.

Mechanism of action
Busulfan is a bifunctional alkylating agent in which two labile methanesulfonate groups are attached to opposite ends of a four-carbon alkyl chain. In aqueous media, busulfan hydrolyzes to release the methanesulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is thought to be responsible for much of the cytotoxicity of busulfan.

5.2 Pharmacokinetic properties

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

The pharmacokinetics of Busulfan Injection were studied in 59 patients participating in a prospective trial of a Busulfan Injection-cyclophosphamide preparatory regimen prior to allogeneic hematopoietic progenitor stem cell transplantation. Patients received 0.8 mg/kg Busulfan Injection every six hours, for a total of 16 doses over four days. Fifty-five of fifty-nine patients (93%) administered Busulfan Injection maintained AUC values below the target value (<1500 μM•min).

Table: Steady State Pharmacokinetic Parameters Following Busulfan Injection Infusion (0.8 mg per kg; N=59)

	Mean	CV (%)	Range
Cmax (ng/mL)	1222	18	496 – 1684
AUC (μM.min)	1167	20	556-1673
CL (mL/min/kg)[1]	2.52	25	1.49-4.31

[1] Clearance normalized to actual body weight for all patients.

Busulfan Injection pharmacokinetics showed consistency between dose 9 and dose 13 as demonstrated by reproducibility of steady state Cmax and a low coefficient of variation for this parameter.

Distribution
Busulfan achieves concentrations in the cerebrospinal fluid approximately equal to those in plasma. Busulfan primarily binds to albumin (Mean ± standard deviation=32.4 ± 2.2%).

Metabolism
Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione S-transferase (GST) catalysis. This conjugate undergoes extensive oxidative metabolism in the liver.

Excretion
Following administration of 14C-labeled busulfan to humans, approximately 30% of the radioactivity was excreted into the urine over 48 hours; negligible amounts were recovered in feces.

Special populations

Paediatric population
In a pharmacokinetic study of Busulfan Injection in 24 pediatric patients, the population pharmacokinetic (PPK) estimates of Busulfan Injection for clearance (CL) and volume of distribution (V) were determined. For actual body weight, PPK estimates of CL and V were 4.04 L/hr/20 kg (3.37 mL/min/kg; interpatient variability 23%); and 12.8 L/20 kg (0.64 L/kg; interpatient variability 11%).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Dimethylacetamide
Macrogol 400.

6.2 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.

6.3 Shelf life

Unopened vials: 24 months

Diluted solution:

8 hours (including infusion time) after dilution when stored at 20 °C ± 5 °C.

12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °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 and would normally not be longer than the above-mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Keep vial in outer carton in order to protect from light.

Unopened vials of Busulfan Injection must be stored under refrigerated conditions between 2°C to 8°C. Discard unused portion.

Diluted solution:
8 hours (including infusion time) after dilution when stored at 20 °C ± 5 °C.

12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °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 and would normally not be longer than the above-mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Busulfan concentrate for solution for infusion 6 mg/ml is available in 10 ml clear glass vial closed with a grey westar rubber stopper and purple aluminium flip off seal or purple aluminium flip off plain seal.

Pack size: 1 x 1 Vial pack

Primary packaging material
1. 10 ml, 13 mm clear glass vial (type I).
Transparent flat bottom tubular glass vials

2. 13 mm Tef 2, 4405/50 grey Westar rubber stopper.
Grey colored siliconised rubber stoppers with teflon film on plug surface.

Secondary packing material

1. 13 mm Purple aluminium flip off seal OR 13 mm Purple aluminium flip off plain seal Aluminium seal with a purple coloured flip off top embossed with "FLIP OFF".

Carton: Printed folding box with both sides flaps open/bottom lock.

6.6 Special Precautions for Handling and 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 Injection 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

Y (kg) x D (mg/kg)

---------- = A ml of Busulfan Injection to be diluted
6 (mg/ml)

Y: body weight of the patient in kg

- Calculate ideal body weight (IBW) as follows (height in cm, and weight in kg):

Men: IBW (kg)=50+0.91x (height in cm -152)

Women: IBW (kg)=45+0.91x (height in cm -152)

- For obese or severely obese patients, base Busulfan dosing on adjusted ideal body weight (AIBW):

AIBW= IBW +0.25x (actual weight -IBW).

Pediatrics: The effectiveness of Busulfan in the treatment of CML has not been specifically studied in pediatric patients.

D: dose of busulfan

- 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%)

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

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
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.

7. Name and address of Product Registration Holder & Manufacturer

Product Registration Holder:
Accord Healthcare Sdn Bhd (1035160 D)

Suite 12A-15, Level 12A, Wisma Zelan
No 1 Jalan Tasik Permaisuri 2
Bandar Tun Razak,
56000 Kuala Lumpur, Malaysia

Manufactured by:
Intas Pharmaceuticals Limited
Plot Numbers 457 458 & 191/218P
Sarkhej- Bavla Highway Matoda Sanand
Ahmedabad Gujarat IN-382210 India

8. DATE OF REVISION OF THE TEXT
October 2026.