PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1 NAME OF THE MEDICINE

BUSULFAN 6 mg/mL FRESENIUS

Pharmaceutical form

Concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL concentrate contains 6 mg Busulfan

Sugar free

BUSULFAN FRESENIUS contains the solvent, dimethylacetamide (DMA) (see sections 4.4, 4.6 and 5.3)

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless, viscous solution free from visible particles

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

BUSULFAN 6 mg/mL FRESENIUS should not be given by rapid IV injection or bolus.

BUSULFAN 6 mg/mL FRESENIUS should be administered under the supervision of a qualified

medical practitioner who is experienced in conditioning treatment prior to haematopoeietic progenitor cell transplantation, in the use of cancer chemotherapeutic medicines and in the management of patients with
severe pancytopenia.
It is recommended to use actual body weight for dosing.
All patients should be premedicated with anticonvulsant medicine to prevent seizures reported with the use of high dose busulfan. Antiemetics should be administered prior to the first dose and continued on a fixed schedule through its administration.
The recommended dosage and regimen is 0,8 mg/kg body weight of BUSULFAN FRESENIUS 6 mg/mL as a two-hour infusion every 6 hours over 4 consecutive days, for a total of 16 doses prior to haematopoietic progenitor cell transplantation.
Obese patients: For obese or severely obese patients, dosing based on adjusted ideal body weight could be considered. Ideal body weight (IBW) should be calculated as follows (height in cm and weight in kg):
IBW (kg; men) = 50 + 0,91 X (height - 152); IBW (kg; women) = 45 + 0,91 X (height-152).
Adjusted ideal body weight (AIBW) should be calculated as follows:
AIBW = IBW + 0,25 X (actual body weight - IBW)

Paediatric population
The safety and efficacy of BUSULFAN 6 mg/mL FRESENIUS in children has not been established.

Administration:
BUSULFAN 6 mg/mL FRESENIUS must be diluted before administration. A final concentration of approximately 0,5 mg/mL busulfan should be achieved (see section 6.6). BUSULFAN 6 mg/mL FRESENIUS should be administered by IV infusion via central venous catheter.
For instructions on dilution of the product before administration, (see section 6.6.)

4.3 Contraindication

Hypersensitivity to busulfan or to any of the excipients of BUSULFAN FRESENIUS.

Pregnancy and lactation (see section 4.6).

Hepatic insufficiency.

4.4 Special warnings and precautions for use

The consequence of treatment with BUSULFAN 6 mg/mL FRESENIUS 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 medicine (G-CSF), should be employed as medically indicated.

In adults, absolute neutrophil counts < 0,5 x 10^9/l at a median of 4 days post transplant occurred in 100 % of patients and recovered at median day 10 and 13 days following autologous and allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively). Thrombocytopenia (<25 x10^9/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.

Hepatic impairment

Busulfan has not been studied in patients with hepatic impairment.

Since busulfan is mainly metabolised through the liver, exposure to BUSULFAN 6 mg/mL FRESENIUS is expected to increase if liver function is impaired, and the use of BUSULFAN 6 mg/mL FRESENIUS in hepatic impaired populations is contraindicated (see section 4.3).
Caution should be observed when BUSULFAN 6 mg/mL FRESENIUS is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. It is recommended when treating patients with BUSULFAN 6 mg/mL FRESENIUS 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 6 mg/mL FRESENIUS. 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 4.8).

Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with BUSULFAN 6 mg/mL FRESENIUS due to a possible decrease in the metabolism of busulfan (See section 4.5).

As documented in clinical studies, no treated patients experienced cardiac tamponade or other specific cardiac toxicities related to BUSULFAN 6 mg/mL FRESENIUS.
However cardiac function should be monitored regularly in patients receiving BUSULFAN 6 mg/mL FRESENIUS (see section 4.8).

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in BUSULFAN 6 mg/mL FRESENIUS 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 medicines. Therefore, attention should be paid to this pulmonary issue in patients with prior history of mediastinal or pulmonary radiation (see section 4.8).
Periodic monitoring of renal function should be considered during therapy with BUSULFAN 6 mg/mL FRESENIUS (see section 4.8).

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of BUSULFAN 6 mg/mL FRESENIUS to patients with a history of seizures. Patients should receive adequate anticonvulsant prophylaxis.
In adults and children
studies,data with busulfan were obtained when using concomitant administration of either phenytoin or benzodiazepines for seizure prophylaxis.
The effect of those anticonvulsant medicines on busulfan pharmacokinetics was investigated in a phase II study (see section 4.5).

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 leukaemogenic.

Fertility
Busulfan can impair fertility. Therefore, men treated with BUSULFAN 6 mg/mL FRESENIUS 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 6 mg/mL FRESENIUS.
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.

4.5 Interaction with other medicines and other forms of interaction

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 6 mg/mL FRESENIUS and 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 medicine).

Ketobemidone (analgesic) may 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 has been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24 hours.

Paracetamol is described to decrease glutathione levels in blood and tissues, and may

therefore decrease busulfan clearance when used in combination (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.

4.6 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

BUSULFAN 6 mg/mL FRESENIUS is contraindicated during pregnancy. Studies in animals have shown reproductive toxicity (embryo-foetal lethality and malformations). (see section 5.3) 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.

Breastfeeding

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, breastfeeding 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 4.4).

4.7 Effects on ability to drive and use machines

Since adverse reactions such as dizziness, seizures and lens disorders have been reported in patients receiving BUSULFAN 6 mg/mL FRESENIUS, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that BUSULFAN 6 mg/mL FRESENIUS does not adversely
affect their ability to do so (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Busulfan in combination with cyclophosphamide

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: leukopenia 96 %, thrombocytopenia 94 %, and anaemia 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 reactions information is derived from the clinical study in paediatrics. 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 III-IV 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.

Combination of BUSULFAN 6 mg/mL FRESENIUS and fludarabine is not indicated.

Tabulated list of adverse reactions

Frequencies are defined as: frequent, less frequent, not known. Undesirable effects coming from post-marketing survey have been implemented in the tables with the incidence “not known”.

Busulfan in combination with cyclophosphamide

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	**Frequent**		**Less Frequent**	**Not known**
	(≥ 1/10)	**(≥ 1/100, < 1/10)**	**(≥ 1/1,000, < 1/100)**	
Infections and infestations	Rhinitis Pharyngitis			
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Febrile			

System organ class	**Frequent**		**Less Frequent**	**Not known**
	(≥ 1/10)	**(≥ 1/100, < 1/10)**	**(≥ 1/1,000, < 1/100)**	
	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	Frequent		Less Frequent	Not known
	(≥ 1/10)	(≥ 1/100, < 1/10)	(≥ 1/1,000, < 1/100)	
				Corneal thinning Lens disorders ***
Cardiac disorders	Tachycardia	Arrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis	Ventricular extrasystoles Bradycardia	
Vascular disorders	Hypertension Hypotension Thrombosis		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 Diarrhoea Abdominal pain	Haematemesis Ileus Oesophagitis	Gastrointestinal haemorrhage	Tooth hypoplasia**

System organ class	Frequent		Less Frequent	Not known
	(≥ 1/10)	(≥ 1/100, < 1/10)	(≥ 1/1,000, < 1/100)	
	Nausea Vomiting Dyspepsia Ascites Constipation Anus discomfort			
Hepato-biliary disorders	Hepatomegaly Jaundice	Veno occlusive liver disease *		
Skin and subcutaneous tissue disorders	Rash Pruritis Alopecia	Skin desquamation Erythema Pigmentation disorder		
Musculoskeletal and connective tissue disorders	Myalgia Back pain Arthralgia			
Renal and urinary disorders	Dysuria Oliguria	Haematuria Moderate renal Insufficiency		
Reproductive system				Premature menopause

System organ class	Frequent		Less Frequent	Not known
	(≥ 1/10)	(≥ 1/100, < 1/10)	(≥ 1/1,000, < 1/100)	
and breast disorders				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	Bun increase Decrease ejection fraction		

System organ class	Frequent		Less Frequent	Not known
	(≥ 1/10)	(≥ 1/100, < 1/10)	(≥ 1/1,000, < 1/100)	
	Abnormal breath sounds Creatinine elevated			

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

** reported in post marketing with IV busulfan

*** reported in post marketing with oral busulfan

System organ class	Frequent		Not known*
	(≥ 1/10)	(≥ 1/100, < 1/10)	
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

System organ class	Frequent		Not known*
	(≥ 1/10)	(≥ 1/100, < 1/10)	
			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	Mucositis		Asthenia Oedema

System organ class	Frequent		Not known*
	(≥ 1/10)	(≥ 1/100, < 1/10)	
administration site conditions			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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Healthcare providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

4.9 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 other than haematopoietic progenitor cell transplantation. In the absence of haematopoietic progenitor cell transplantation, the recommended dose of BUSULFAN 6 mg/mL FRESENIUS would constitute an overdose of busulfan. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.
Dialysis should be considered in the case of an overdose. Since, busulfan is metabolised 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 humans, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 26 Cytostatic agents

Pharmacotherapeutic group: Alkyl sulfonates

ATC code: L01AB01.

Mechanism of action

Busulfan is a cytotoxic medicine and a bifunctional alkylating medicine in which two labile methanesulphonate groups are attached to the opposite end of a four-carbon alkyl chain.

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.

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.

5.2 Pharmacokinetic properties

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

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 oral and 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 V_z 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.

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 medicine 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.

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.

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.

5.3 Preclinical safety data

Busulfan is mutagenic and clastogenic. Busulfan induced chromosomal aberrations *in vitro* (rodent and human cell) and *in vivo* (rodents and humans).

Busulfan belongs to a class of substances which are potentially carcinogenic based on their mechanism of action.

Busulfan is a teratogen in rats, mice and rabbits. Malformations and anomalies included

significant alterations in the musculoskeletal system, body weight gain, and size. In pregnant rats, busulfan produced sterility in both male and female offspring due to the absence of germinal cells in testes and ovaries. Busulfan was shown to cause sterility in rodents. Busulfan depleted oocytes of female rats, and induced sterility in male rats and hamster.

Repeated doses of DMA produced signs of liver toxicity, the first being increases in serum clinical enzymes followed by histopatological changes in the hepatocytes. Higher doses can produce hepatic necrosis and liver damage can be seen following single high exposures.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylacetamide, Macrogol 400

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines except those mentioned in section 6.6.

Do not use polycarbonate syringes with BUSULFAN 6 mg/mL FRESENIUS.

6.3 Shelf life

Vials: 2 years.

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:

- 8 hours (including infusion time) after dilution when stored at 25 °C ± 2 °C
- 12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 25 °C ± 2 °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). Do not freeze.

Do not freeze the diluted solution.

For storage conditions after dilution of the medicine see section 6.3

6.5 Nature and contents of container

Type I, clear, colourless, tubular glass vials of 10 mL with Teflon faced chlorobutyl Grey rubber closure and sealed with an aluminium flip-off Green overseal.

Pack sizes: 1 and 8 vials.

Each vial may be shrink wrapped along with a plastic bottom.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of BUSULFAN 6 mg/mL FRESENIUS

Procedures for proper handling and disposal of anticancer medicine 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 6 mg/mL FRESENIUS solution:

- The use of gloves and protective clothing is recommended.

- If BUSULFAN 6 mg/mL FRESENIUS or diluted BUSULFAN 6 mg/mL FRESENIUS solution contacts the skin or mucosa, wash them thoroughly with water immediately.

Calculation of the quantity of BUSULFAN FRESENIUS 6 mg/mL to be diluted and of the diluent

BUSULFAN 6 mg/mL FRESENIUS must be diluted with 0,9 % sodium chloride or 5 % glucose solution for injection. The quantity of the diluent must be 10 times the volume of BUSULFAN 6 mg/mL FRESENIUS to ensure the final concentration of busulfan remains at approximately 0,5 mg/mL.

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

(70 kg patient) X (0,8 mg/kg)/ 6 mg/mL) = 9,3 mL BUSULFAN 6 mg/mL FRESENIUS (56 mg total dose).

To prepare the final solution for infusion, add 9,3 mL of BUSULFAN 6 mg/mL FRESENIUS to 93 mL of diluent 0,9 % sodium chloride or 5 % dextrose solution for injection) as calculated below:

9,3 mL BUSULFAN 6 mg/mL FRESENIUS X (10) = 93 mL of either diluent plus the 9,3 mL BUSULFAN 6 mg/mL FRESENIUS to yield a final concentration of BUSULFAN of 0,5 mg/mL **(9,3 mL X 6 mg/mL/ 102,3 mL = 0,5 mg/mL).**

Preparation of the solution for infusion

- BUSULFAN 6 mg/mL FRESENIUS 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 6 mg/mL FRESENIUS 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 6 mg/mL FRESENIUS must always be added to the diluent, not the diluent to BUSULFAN 6 mg/mL FRESENIUS. BUSULFAN 6 mg/mL FRESENIUS must not be

put into an intravenous bag that does not contain sodium chloride 9 mg/mL (0,9 %)

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 6 mg/mL FRESENIUS 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 medicine must not be flushed in the administration tubing as rapid infusion of BUSULFAN 6 mg/mL FRESENIUS has not been tested and is not recommended.

The entire prescribed BUSULFAN 6 mg/mL FRESENIUS 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 medicine solution prior to beginning the actual BUSULFAN 6 mg/mL FRESENIUS infusion and then flushed with sodium chloride 9 mg/mL (0,9 %) solution for injection or glucose (5 %) solution for injection.

BUSULFAN 6 mg/mL FRESENIUS must not be infused concomitantly with another intravenous solution.

Polycarbonate syringes must not be used with BUSULFAN 6 mg/mL FRESENIUS.

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

Any unused medicine or waste material should be disposed of in accordance with local requirements for cytotoxic medicine.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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10 DATE OF REVISION OF THE TEXT