SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Busulfan 6 mg/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 6 mg of busulfan (60 mg in 10 ml).

After dilution: 1 ml of solution contains 0.5 mg of busulfan

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear, colourless solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 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 4.5).

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/m^2 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 (n=23) 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 5.2) 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 4.8 and 5.2).

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 4.4).

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 6.6.

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 Injection to 24 h after the last dose of Busulfan Injection.

In adult and paediatric studies, patients received either phenytoin or benzodiazepines as seizure prophylaxis treatment. (see sections 4.4 and 4.5).

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy (see section 4.6).

4.4 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.
Patients who are concurrently treated with the conventional dose of busulfan and itraconazole or metronidazole should be closely monitored for signs of busulfan toxicity. At concomitant use of these agents with busulfan weekly blood counts are recommended (see section 4.5)

In adults, absolute neutrophil counts < $0.5x10^9$/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 (< $25x10^9$/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.

In paediatric population, absolute neutrophil counts < $0.5x10^9$/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 (< $25x10^9$/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 5.2).

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

Busulfan has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolized through the liver, caution should be observed when busulfan is used in patients with pre-existing impairment of liver function, especially in those with severe hepatic impairment. It is recommended when treating these patients that serum transaminase, alkaline phosphatase, and bilirubin should be monitored regularly 28 days following transplant for early detection of hepatotoxicity.

Hepatic veno-occlusive disease is a major complication that can occur during treatment with Busulfan 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 4.8).

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 4.5).

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 4.8).

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 4.8).

Periodic monitoring of renal function should be considered during therapy with Busulfan Injection (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 Injection 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 agents 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 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. 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 medicinal products and other forms of interaction

No specific clinical trial was carried out to assess drug-drug interaction between intravenous busulfan and itraconazole or metronidazole. From published studies in adults, administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance. Also, there are published case reports of increased plasma levels of busulfan after administration of metronidazole.

In combination with metronidazole (1200 mg, given as 400 mg three times daily) busulfan values are increased in approximately 80% (see section 4.4).
Patients who are concurrently treated with busulfan and itraconazole or metronidazole should be
closely monitored for signs of busulfan toxicity.
No interaction was observed when busulfan was combined with fluconazole (antifungal agent)
Published studies in adults described that ketobemidone (analgesic) might be associated with high levels of plasma busulfan. Therefore special care is recommended when combining these two compounds.

In adults, for the BuCy2 regimen it has been reported that the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the development of toxicities. A reduced incidence of Hepatic Veno Occlusive Disease (HVOD) and other regimen related toxicity have been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 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 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.

Increases in busulfan exposure have been observed at concomitant administration of busulfan and deferasirox. The mechanism behind the interaction is not fully elucidated. It is recommended to regularly monitor busulfan plasma concentrations and, if necessary, adjust the busulfan dose in patients who are or have recently been treated with deferasirox.

4.6 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). (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.

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 4.4).

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 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.

<u>Busulfan in combination with fludarabine (FB)</u>
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	Neutropenia			

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

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

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

* veno occlusive liver disease is more frequent in paediatric population.
** reported in post marketing with IV busulfan
*** reported in post marketing with oral Busulfan

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

System organ class	Very common	Common	Not known*
Infections and infestations	Viral infection CMV reactivation EBV reactivation Bacterial infection	Invasive fungal infection Pulmonary infection	Brain abscess Cellulitis Sepsis
Blood and lymphatic system disorders			Febrile neutropenia
Metabolism and nutrition disorders	Hypoalbuminaemia Electrolyte disturbance Hyperglycaemia		Anorexia
Psychiatric disorders			Agitation Confusional state Hallucination
Nervous system disorders		Headache Nervous system disorders [Not Elsewhere Classified]	Cerebral haemorrhage Encephalo-pathy
Cardiac disorders			Atrial fibrillation

System organ class	Very common	Common	Not known*
Vascular disorders		Hyper-tension	
Respiratory thoracic and mediastinal disorders		Pulmonary haemorrhage	Respiratory failure Pulmonary hypertension
Gastro-intestinal disorders	Nausea Vomiting Diarrhoea Stomatitis		Gastro-intestinal haemorrhage Tooth hypoplasia*
Hepato-biliary disorders	Veno occlusive liver disease		Jaundice Liver disorders
Skin and subcutaneous tissue disorders		Rash	
Renal and urinary disorders	Haemorrhagic cystitis**	Renal disorder	Oliguria
General disorders and administration site conditions	Mucositis		Asthenia Oedema Pain
Investigations	Transaminases increased Bilirubine increased Alkaline phosphatases increased	Creatinine elevated	Blood lactate dehydrogenase increased Blood uric acid increased Blood urea increased GGT increased Weight increased

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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).

Two prospective, single arm, open-label, uncontrolled phase II studies were conducted in patients with haematological disease, the majority of whom had advanced disease.

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

Patients received doses of 0.8 mg/kg busulfan every 6 hours infusion for a total 16 doses followed by cyclophosphamide at 60 mg/kg once per day for two days (BuCy2 regimen).

The primary efficacy parameters in these studies were myeloablation, engraftment, relapse, and survival.

In both studies, all patients received a 16/16 dose regimen of busulfan. No patients were discontinued from treatment due to adverse reactions related to busulfan.

All patients experienced a profound myelosuppression. The time to Absolute Neutrophil Count (ANC) greater than $0.5x10^9$/l was 13 days (range 9-29 days) in allogenic patients (OMC-BUS 4), and 10 days (range 8-19 days) in autologous patients (OMC-BUS 3). All evaluable patients engrafted. There is no primary or secondary graft rejection. Overall mortality and non- relapse mortality at more than 100 days post-transplant was (8/61) 13% and (6/61) 10% in allotransplanted patients, respectively. During the same period there was no death in autologous recipients.

Paediatric population

Documentation of the safety and efficacy of busulfan in combination with cyclophosphamide in the BuCy4 or with melphalan in the BuMel regimen prior to conventional allogeneic and/or autologous HPCT derives from clinical trial F60002 IN 101 G0.

The patients received the dosing mentioned in section 4.2.

All patients experienced a profound myelosuppression. The time to Absolute Neutrophil Count (ANC) greater than $0.5x10^9$/l was 21 days (range 12-47 days) in allogenic patients, and 11 days (range 10-15 days) in autologous patients. All children engrafted. There is no primary or secondary graft rejection. 93% of allogeneic patients showed complete chimerism. There was no regimen-related death through the first 100-day post-transplant and up to one year post-transplant.

Busulfan in combination with fludarabine (FB)

In adults

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

Patients received a conditioning regimen based on the administration of fludarabine immediately followed by single daily dose of 3.2 mg/kg busulfan over 2 or 3 consecutive days. Total dose of busulfan per patient was between 6.4 mg/kg and 9.6 mg/kg.

The FB combination allowed sufficient myeloablation modulated by the intensity of conditioning regimen through the variation of number of days of busulfan infusion. Fast and complete engraftment rates in 80-100% of patients were reported in the majority of studies. A majority of publications reported a complete donor chimerism at day+30 for 90-100% of patients. The long-term outcomes confirmed that the efficacy was maintained without unexpected effects.

Data from a recently completed prospective multicentre phase 2 study including 80 patients, aged 18 to 65 years old, diagnosed with different hematologic malignancies who underwent allo-HCT with an FB (3 days of busulfan) reduced intensity conditioning regimen became available. In this study, all, but one, patients engrafted, at a median of 15 (range, 10-23) days after allo-HCT. The cumulative incidence of neutrophil recovery at day 28 was 98.8% (95%CI, 85.7-99.9%). Platelet engraftment occurred at a median of 9 (range, 1-16) days after allo-HCT.

The 2-year OS rate was 61.9% (95%CI, 51.1-72.7%)]. At 2 years, the cumulative incidence of NRM was 11.3% (95%CI, 5.5-19.3%), and that of relapse or progression from allo-HCT was 43.8% (95CI, 31.1-55.7%). The Kaplan-Meier estimate of DFS at 2 years was 49.9% (95%CI, 32.6-72.7).

5 PHARMACOLOGICAL PROPERTIES

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-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.

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 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 AUC_S 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 2.52 to 3.97 ml/minute/kg has been established in children from < 6 months up to 17 years old. The terminal half life ranged from 2.24 to 2.5 h. Inter and intra patient variabilities in plasma exposure were lower than 20% and 10%, respectively. A population pharmacokinetic analysis has been performed in a cohort of 205 children adequately distributed with respect to bodyweight (3.5 to 62.5 kg), biological and diseases (malignant and non-malignant) characteristics, thus representative of the high heterogeneity of children undergoing HPCT. This study demonstrated that bodyweight was the predominant covariate to explain the busulfan pharmacokinetic variability in children over body surface area or age.
The recommended posology for children as detailed in section 4.2 enabled over 70% up to 90% of children ≥ 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.

5.3 Preclinical safety data

Busulfan is mutagenic and clastogenic. Busulfan was mutagenic in *Salmonella typhimurium, Drosophila melanogaster* and barley. Busulfan induced chromosomal aberrations *in vitro* (rodent and human cell) and *in vivo* (rodents and humans). Various chromosome aberrations have been observed in cells from patients receiving oral busulfan.

Busulfan belongs to a class of substances which are potentially carcinogenic based on their mechanism of action. On the basis of human data, busulfan has been classified by the IARC as a human carcinogen. WHO has concluded that there is a causal relationship between busulfan exposure and cancer. The available data in animals support the carcinogenic potential of busulfan. Intravenous administration of busulfan to mice significantly increased the incidences of thymic and ovarian tumours.

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.

DMA is teratogenic in rats. Doses of 400 mg/kg/day DMA administered during organogenesis caused significant developmental anomalies. The malformations included serious heart and/or major vessels anomalies: a common truncus arteriosis and no ductus arteriosis, coarctation of the pulmonary trunk and the pulmonary arteries, intraventricular defects of the heart. Other frequent anomalies included cleft palate, anasarca and skeletal anomalies of the vertebrae and ribs. DMA decreases fertility in male and female rodents. A single s.c. dose of 2.2 g/kg administered on gestation day 4 terminated pregnancy in 100% of tested hamster. In rats, a DMA daily dose of 450 mg/kg given to rats for nine days caused inactive spermatogenesis.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylacetamide

Macrogol 400.

6.2 Incompatibilities

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

Do not use polycarbonate syringes with Busulfan Injection.

6.3 Shelf life

Vials: 18 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.

6.4 Special precautions for storage

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 6.3.

6.5 Nature and contents of container

10 ml of concentrate for solution for infusion in clear glass vials (type I) with teflon faced rubber stopper and sealed with aluminium flip-off purple seal.

Pack size

Pack containing 1 vial or 8 vials of 10 ml concentrate for solution for infusion.

Not all pack sizes may be marketed.

6.6 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 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:

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

$$\frac{\text{(mg/kg)}}{\text{6 (mg/ml)}}$$ diluted

Y: body weight of the patient in kg

D: dose of busulfan (see section 4.2)

- 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 Injection 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.

7 MARKETING AUTHORISATION HOLDER

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