**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Busulfan Fresenius Kabi 6 mg/ml concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate contains 6 mg of busulfan.

One 10 ml vial contains 60 mg of busulfan.
One 40 ml vial contains 240 mg of busulfan.

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 (sterile concentrate).
Clear, colourless viscous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

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

Posology

*Busulfan 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 (see section 4.5).

*Paediatric population (0 to 17 years)*
The recommended dose of busulfan is as follows:

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

followed by:
- 4 cycles of 50 mg/kg body weight (BW) cyclophosphamide (BuCy4) or
- one administration of 140 mg/m² melphalan (BuMel)

initiated for at least 24 hours following the 16th dose of busulfan (see section 4.5).

Busulfan 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 without dose-adjustment. However, for the safe use of busulfan 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 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/m² for 5 consecutive days or 40 mg/m² for 4 consecutive days.
- Busulfan 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 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

Busulfan is for intravenous use.

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

For instructions on dilution of the medicinal product before administration, see section 6.6.

Busulfan should not be given by rapid intravenous, *bolus* or peripheral injection.
All patients should be pre-medicated with anticonvulsant medicinal products to prevent seizures reported with the use of high dose busulfan.

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

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 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.

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 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. 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 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 (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 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 are advised not to father a child during and up to 6 months after treatment and to seek advice on cryo-conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with busulfan.
Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in pre-menopausal patients. Busulfan treatment in a pre-adolescent girl prevented the onset of puberty due to ovarian failure. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. The solvent dimethylacetamide (DMA) may also impair fertility. DMA decreases fertility in male and female rodents (see sections 4.6 and 5.3).

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

## 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. Patients who are concurrently treated with busulfan and itraconazole or metronidazole should be closely monitored for signs of busulfan toxicity.
No interaction was observed when busulfan was combined with fluconazole (antifungal agent).

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

In adults, for the BuCy2 regimen it has been reported that the time interval between the last oral busulfan administration and the first cyclophosphamide administration may influence the development of toxicities. A reduced incidence of Hepatic Veno Occlusive Disease (HVOD) and other regimen-related toxicity have been observed in patients when the lag time between the last dose of oral busulfan and the first dose of cyclophosphamide is > 24 hours.

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

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

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

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

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

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

## 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
HPCT is contraindicated in pregnant women; therefore, busulfan 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.

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

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

## 4.8 Undesirable effects

Summary of the safety profile

*Busulfan in combination with cyclophosphamide or melphalan*
*In adults*
Adverse reactions 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 reactions 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.

*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 reactions 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 lists 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 reactions are presented in order of decreasing seriousness.

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

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

| System organ class | Very common | Common | Uncommon | Not known |
|---|---|---|---|---|
| Investigations | Transaminases increased<br>Bilirubin increased<br>GGT increased<br>Alkaline phosphatases increased<br>Weight increased<br>Abnormal breath sounds<br>Creatinine elevated | Bun increase<br>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<br>CMV reactivation<br>EBV reactivation<br>Bacterial infection | Invasive fungal infection<br>Pulmonary infection | Brain abscess<br>Cellulitis<br>Sepsis |
| Blood and lymphatic system disorders | | | Febrile neutropenia |
| Metabolism and nutrition disorders | Hypoalbuminaemia<br>Electrolyte disturbance<br>Hyperglycaemia | | Anorexia |
| Psychiatric disorders | | | Agitation<br>Confusional state<br>Hallucination |
| Nervous system disorders | | Headache<br>Nervous system disorders [Not Elsewhere Classified] | Cerebral haemorrhage<br>Encephalo-pathy |
| Cardiac disorders | | | Atrial fibrillation |
| Vascular disorders | | Hyper-tension | |
| Respiratory thoracic and mediastinal | | Pulmonary haemorrhage | Respiratory failure |

| System organ class | Very common | Common | Not known* |
|---|---|---|---|
| disorders | | | |
| Gastro-intestinal disorders | Nausea<br>Vomiting<br>Diarrhoea<br>Stomatitis | | Gastro-intestinal haemorrhage<br>Tooth hypoplasia* |
| Hepato-biliary disorders | Veno occlusive liver disease | | Jaundice<br>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<br>Oedema<br>Pain |
| Investigations | Transaminases increased<br>Bilirubine increased<br>Alkaline phosphatases increased | Creatinine elevated | Blood lactate dehydrogenase increased<br>Blood uric acid increased<br>Blood urea increased<br>GGT increased<br>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 national reporting system listed in Appendix V.

## 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 would constitute an overdose of busulfan. The haematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated.
There have been two reports that busulfan is dialyzable, thus dialysis should be considered in the case of an overdose. Since, busulfan is metabolized through conjugation with glutathione, administration of glutathione might be considered.

It must be considered that overdose of busulfan will also increase exposure to DMA. In human the principal toxic effects were hepatotoxicity and central nervous system (CNS) effects. CNS

changes precede any of the more severe side effects. No specific antidote for DMA overdose is known.
In case of overdose, management would include general supportive care.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

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

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

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

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

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

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

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

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

regimen-related death through the first 100-day post-transplant and up to one year post-transplant.

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

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

Data from a recently completed prospective multicentre phase 2 study including 80 patients, aged 18 to 65 years old, diagnosed with different hematologic malignancies who underwent allo-HCT with an FB (3 days of busulfan) reduced intensity conditioning regimen became available. In this study, all, but one, patients engrafted, at a median of 15 (range, 10-23) days after allo-HCT. The cumulative incidence of neutrophil recovery at day 28 was 98.8% (95%CI, 85.7-99.9%). Platelet engraftment occurred at a median of 9 (range, 1-16) days after allo-HCT.
The 2-year OS rate was 61.9% (95%CI, 51.1-72.7%)]. At 2 years, the cumulative incidence of NRM was 11.3% (95%CI, 5.5-19.3%), and that of relapse or progression from allo-HCT was 43.8% (95CI, 31.1-55.7%). The Kaplan-Meier estimate of DFS at 2 years was 49.9% (95%CI, 32.6-72.7).

## 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 drug accumulation and a wash out period (without circulating busulfan concentration) between consecutive administrations. The review of the literature allows a comparison of PK series performed either within the same study or between studies and demonstrated unchanged dose-independent PK parameters regardless the dosage or the schedule of administration. It seems that the recommended intravenous busulfan dose administered either as an individual infusion (3.2 mg/kg) or into 4 divided infusions (0.8 mg/kg) provided equivalent daily plasma exposure with similar both inter-and intrapatient variability. As a result, the control of intravenous busulfan AUC within the therapeutic windows is not modified and a similar targeting performance between the two schedules was illustrated.

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

Special populations
*Hepatic or renal impairment*
The effects of renal dysfunction on intravenous busulfan disposition have not been assessed.
The effects of hepatic dysfunction on intravenous busulfan disposition have not been assessed. Nevertheless the risk of liver toxicity may be increased in this population.
No age effect on busulfan clearance was evidenced from available intravenous busulfan data in patients over 60 years.

*Paediatric population*
A continuous variation of clearance ranging from 2.52 to 3.97 ml/minute/kg has been established in children from < 6 months up to 17 years old. The terminal half life ranged from 2.24 to 2.5 h. Inter and intra patient variabilities in plasma exposure were lower than 20% and 10%, respectively.
A population pharmacokinetic analysis has been performed in a cohort of 205 children adequately distributed with respect to bodyweight (3.5 to 62.5 kg), biological and diseases (malignant and non-malignant) characteristics, thus representative of the high heterogeneity of children undergoing HPCT. This study demonstrated that bodyweight was the predominant covariate to explain the busulfan pharmacokinetic variability in children over body surface area or age.
The recommended posology for children as detailed in section 4.2 enabled over 70% up to 90% of children ≥ 9kg in achieving the therapeutic window (900 - 1500 µmol/L.minute). However a higher variability was observed in children < 9 kg leading to 60% of children

achieving the therapeutic window (900 - 1500 µmol/L.minute). For the 40% of children < 9 kg outside the target, the AUC was evenly distributed either below or above the targeted limits*; i.e*. 20% each < 900 and > 1500 µmol/L.min following 1 mg/kg. In this regard, for children < 9 kg, a monitoring of the plasma concentrations of busulfan (therapeutic drug monitoring) for dose-adjustment may improve the busulfan targeting performance, especially in extremely young children and neonates.

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

### 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.

Due to incompatibility, do not use any infusion components containing polycarbonate with busulfan.

## 6.3 Shelf life

Vials
2 years.

After opening and before dilution - 240 mg/ 40 ml vial
Chemical and physical in-use stability has been demonstrated for 28 days at 5°C ± 3°C following multiple needle entries and product withdrawal. Other in-use storage time and conditions are the responsibility of the user.

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) when stored at 25°C ± 2°C

- 12 hours 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 the diluted solution.
For storage conditions after dilution of the medicinal product see section 6.3.

## 6.5 Nature and contents of container

Clear colourless glass vials (type I) with teflon faced rubber stopper and sealed with aluminium flip-off seal containing either 10mL or 40mL of concentrate. Each vial is sleeved with shrinkable plastic film.

Pack sizes
One pack contains 8 vials of 10 ml each.
One pack contains one vial of 40 ml.

## 6.6 Special precautions for disposal and other handling

*Preparation of Busulfan Fresenius Kabi*
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.

Following multiple needle entries and product withdrawal, the 40 ml vials maintain microbial, chemical, and physical stability for up to 28 days at 5C ± 3°C. Other in-use storage time and conditions are the responsibility of the user.

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

Busulfan must be diluted prior to use with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%.
The quantity of the diluent must be 10 times the volume of the concentrate ensuring the final concentration of busulfan remains at approximately 0.5 mg/ml. By example:

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

- Quantity of busulfan:

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

Y: body weight of the patient in kg
D: dose of busulfan (see section 4.2)

- Quantity of diluent:

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

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

Preparation of the solution for infusion

- Busulfan must be prepared by a healthcare professional using sterile transfer techniques. Using a non polycarbonate syringe fitted with a needle:
  - the calculated volume of concentrate must be removed from the vial.
  - the contents of the syringe must be dispensed into an intravenous bag (or syringe) which already contains the calculated amount of the selected diluent. Busulfan must always be added to the diluent, not the diluent to the concentrate. Busulfan must not be put into an intravenous bag that does not contain sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection 5%.
- The diluted solution must be mixed thoroughly by inverting several times.

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

Diluted concentrate is a clear colourless solution.

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

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

The entire prescribed busulfan dose should be delivered over two 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 infusion and then flushed with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.
Busulfan must not be infused concomitantly with another intravenous solution.

No infusion components containing polycarbonate must be used with busulfan.
Only a clear solution without any particles should be used.

Busulfan 10 ml vial is for single use only while 40 ml vial is a multidose vial.

It is recommended that healthcare professionals and end-users follow best practices such as piercing perpendicular to stopper surface and within target ring to avoid hitting the stopper legs, piercing at appropriate speeds, and limit reuse of needles to help reduce stopper coring and fragmentation risks.

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

## 7 MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

## 8 MARKETING AUTHORISATION NUMBER(S)

EU/1/14/951/001
EU/1/14/951/002

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 September 2014
Date of latest renewal: 20 June 2019

## 10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of European Medicinal Agency http://www.ema/europa.eu

# ANNEX II

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg
Germany

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

## A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON containing 8 vials**

## 1. NAME OF THE MEDICINAL PRODUCT

Busulfan Fresenius Kabi 6 mg/ml concentrate for solution for infusion
busulfan

## 2. STATEMENT OF ACTIVE SUBSTANCE

One ml of concentrate contains 6 mg of busulfan (0.5 mg/ml after dilution).

## 3. LIST OF EXCIPIENTS

Excipients: Dimethylacetamide and Macrogol 400

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

8 vials of 10 ml

60 mg/ 10 ml

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Intravenous use after dilution.
For single use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING IF NECESSARY

Cytotoxic

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/951/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**CARTON containing 1 vial**

## 1. NAME OF THE MEDICINAL PRODUCT

Busulfan Fresenius Kabi 6 mg/ml concentrate for solution for infusion
busulfan

## 2. STATEMENT OF ACTIVE SUBSTANCE

One ml of concentrate contains 6 mg of busulfan (0.5 mg/ml after dilution).

## 3. LIST OF EXCIPIENTS

Excipients: Dimethylacetamide and Macrogol 400

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 vial of 10 ml.

60 mg/ 10 ml

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use
Intravenous use after dilution.
For single use only.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING IF NECESSARY

Cytotoxic

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/951/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Busulfan Fresenius Kabi 6 mg/ml sterile concentrate
busulfan
IV after dilution

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

60 mg/10 ml

## 6. OTHER

Cytotoxic

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

Busulfan Fresenius Kabi 6 mg/ml concentrate for solution for infusion
busulfan

## 2. STATEMENT OF ACTIVE SUBSTANCE

One ml of concentrate contains 6 mg of busulfan (0.5 mg/ml after dilution).

## 3. LIST OF EXCIPIENTS

Excipients: Dimethylacetamide and Macrogol 400

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

Multidose vial: 1 vial of 40 ml

240 mg/ 40 ml

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after dilution.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING IF NECESSARY

Cytotoxic

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/951/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL**

## 1. NAME OF THE MEDICINAL PRODUCT

Busulfan Fresenius Kabi 6 mg/ml sterile concentrate
busulfan

## 2. STATEMENT OF ACTIVE SUBSTANCE

One ml of concentrate contains 6 mg of busulfan (0.5 mg/ml after dilution)

## 3. LIST OF EXCIPIENTS

Excipients: Dimethylacetamide and Macrogol 400

## 4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

Multidose vial

240 mg/40 ml

## 5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
IV use after dilution.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING IF NECESSARY

Cytotoxic

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Fresenius Kabi Deutschland GmbH

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/951/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to restricted medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

# B. PACKAGE LEAFLET

**Package leaflet: Information for the user**

**Busulfan Fresenius Kabi 6 mg/ml concentrate for solution for infusion**
busulfan

**Read all of this leaflet carefully before you start using this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet:**



## 1. What Busulfan Fresenius Kabi is and what it is used for

This medicine contains the active substance busulfan, which belongs to a group of medicines called alkylating agents. Busulfan Fresenius Kabi destroys the original bone marrow before the transplant.

Busulfan Fresenius Kabi is used in adults, new-born infants, children and adolescents as a **treatment prior to transplantation.**

In adults Busulfan Fresenius Kabi is used in combination with cyclophosphamide or fludarabine.

In new-born infants, children and adolescents, this medicine is used in combination with cyclophosphamide or melphalan.

You will receive this preparative medicine before receiving a transplant of either bone marrow or haematopoietic progenitor cell.

## 2. What you need to know before you use Busulfan Fresenius Kabi

**Do not use Busulfan Fresenius Kabi:**
- if you are allergic to busulfan or any of the other ingredients of this medicine listed in section 6.
- if you are pregnant, or think you may be pregnant.

**Warnings and precautions**
Busulfan Fresenius Kabi is a potent cytotoxic medicine that results in profound decrease of blood cells. At the recommended dose, this is the desired effect. Therefore careful monitoring will be performed.

It is possible that use of Busulfan Fresenius Kabi may increase the risk of suffering another malignancy in the future. You should tell your doctor:
- if you have a liver, kidney, heart or lung problem,
- if you have a history of seizures,
- if you are currently taking other medicines.

**Cases of formation of blood clots in the small blood vessels may appear after hematopoietic cell transplantation (HCT) with high-dose of your treatment in combination with other medicines.**

**Other medicines and Busulfan Fresenius Kabi**
Tell your doctor if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. Busulfan Fresenius Kabi may interact with other medicines.

Particular caution should be taken if you use itraconazol and metronidazole (used for certain types of infections) or ketobemidone (used to treat pain) or deferasirox (a medicine used to remove excess iron from your body), because this may increase the side-effects.

The use of paracetamol during the 72 hours prior to or with Busulfan Fresenius Kabi administration should be used with caution.

**Pregnancy, breast-feeding and fertility**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor before you receive treatment with Busulfan Fresenius Kabi. Women must not be pregnant during treatment with Busulfan Fresenius Kabi and up to 6 months after treatment. Women must stop breast-feeding before starting their treatment with Busulfan Fresenius Kabi.

Adequate contraceptive precautions should be used when either partner is receiving Busulfan Fresenius Kabi.

It may no longer be possible for you to achieve a pregnancy (infertility) after treatment with Busulfan Fresenius Kabi. If you are concerned about having children, you should discuss this with your doctor before treatment. Busulfan Fresenius Kabi can also produce symptoms of menopause and in pre-adolescent girls it can prevent the onset of puberty.

Men treated with Busulfan Fresenius Kabi are advised not to father child during and up to 6 months after treatment.

## 3. How to use Busulfan Fresenius Kabi

**Dose and administration**
The dose of busulfan will be calculated according to your body weight.

In adults:
*Busulfan Fresenius Kabi in combination with cyclophosphamide*:
- The recommended dose of Busulfan Fresenius Kabi is 0.8 mg/kg
  – Each infusion will last 2 hours
  – Busulfan will be administered every 6 hours during 4 consecutive days prior to transplant.

*Busulfan Fresenius Kabi in combination with fludarabine*
  – The recommended dose of busulfan is 3.2 mg/kg
  – Each infusion will last 3 hours
  – Busulfan will be administered once daily during 2 or 3 consecutive days prior to transplant.

In new-born infants, children and adolescents (0 to 17 years):
The recommended dose of Busulfan Fresenius Kabi in combination with cyclophosphamide or melphalan is based on your body weight varying between 0.8 and 1.2 mg/kg.

**Medicines before you receive Busulfan Fresenius Kabi:**
Before receiving Busulfan Fresenius Kabi, you will be medicated with
- anticonvulsive medicines to prevent seizures (phenytoin or benzodiazepines) and
- antiemetic medicines to prevent vomiting.

## 4. Possible side effects

Like all medicines, Busulfan Fresenius Kabi can cause side effects, although not everybody gets them.

**Serious side effects:**
The most serious side effects of busulfan therapy or the transplant procedure may include decrease in circulating blood cell counts (intended effect of the medicine to prepare you for your transplant infusion), infection, liver disorders including blocking of a liver vein, graft versus host disease (the graft attacks your body) and pulmonary complications. Contact your doctor immediately if you get any of the following symptoms. Your doctor will monitor your blood counts and liver enzymes regularly to detect and manage these events.

**Other side effects may include:**
**Very common (may affect more than 1 in 10 people):**
**Blood:** decrease of blood circulating cells (red and white) and platelets. **Infections. Nervous system:** insomnia, anxiety, dizziness, and depression. **Nutrition:** loss of appetite, decrease in magnesium, calcium, potassium, phosphate, albumine in blood, and increase in blood sugar. **Cardiac:** increase in heart rate, increase or decrease of blood pressure, vasodilatation (a state of increased calibre of the blood vessels), and blood clots. **Respiratory:** shortness of breath, nasal secretion (rhinitis), sore throat, cough, hiccup, nosebleeds, abnormal breath sounds. **Gastro-intestinal:** nausea, inflammation of the mucosa of the mouth, vomiting, abdominal pain, diarrhoea, constipation, heart burn, anus discomfort, liquid in the abdomen. **Hepatic:** enlarged liver, jaundice**,** blocking of a liver vein. **Skin:** rash, itching, loss of hairs. **Muscle and bone:** back, muscle and joint pain. **Renal:** increase in creatinine elimination, discomfort in urination, and decrease in urine output and bloody urine. **General:** fever, headache, weakness, chills, pain, allergic reaction, oedema, general pain or inflammation at injection site, chest pain, inflammation of the mucosa. **Investigations**: elevated liver enzymes and weight increased.

**Common (may affect up to 1 in 10 people):**
**Nervous system:** confusion, nervous system disorders. **Nutrition:** low blood sodium. **Cardiac:** changes and abnormalities in heart rhythm, fluid retention or inflammation around the heart, decrease heart output. **Respiratory:** increase in breath rhythm, respiratory failure, alveolar haemorrhages, asthma, collapse of small portions of the lung, fluid around the lung. **Gastro-intestinal:** inflammation of the mucosa of oesophagus, paralysis of the gut, vomiting blood. **Skin**: Skin colour disorder, redness of the skin, skin desquamation. **Renal:** increase in the amount of nitrogen components in the blood stream, moderate renal insufficiency, renal disorder.

**Uncommon (may affect up to 1 in 100 people):**
**Nervous system:** delirium, nervousness, hallucination, agitation, abnormal brain function, cerebral haemorrhage, and seizure. **Cardiac:** clotting of femoral artery, extra heart beats, decrease in heart rate, diffuse leak of fluid from the capillaries (small blood vessels). **Respiratory:** decrease in blood oxygen. **Gastro-intestinal:** bleeding in the stomach and/or the gut.

**Not known (frequency cannot be estimated from the available data)**
Sex glands dysfunction
Lens disorders including clouding of the lens of the eye (cataract), and blurred vision (corneal thinning)
Menopausal symptoms and female infertility.
Brain abscess, Inflammation of the skin, generalised infection.
Liver disorders.
Increase of lactate dehydrogenase in the blood.
Increase of uric acid and urea in the blood.
Incomplete development of teeth
Increased blood pressure in the blood vessels of the lungs (pulmonary hypertension)

**Reporting of side effects**
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this

leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Busulfan Fresenius Kabi

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the vial label and the carton after EXP.

*Unopened vials:*
Store in a refrigerator (2°C - 8°C).

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

Do not throw away any medicine via wastewater or household waste. Ask your pharmacist how to throw away medicine you no longer use. These measures will help protect environment.

## 6. Contents of the pack and other information

**What Busulfan Fresenius Kabi contains**
- The active substance is busulfan. One ml of concentrate contains 6 mg busulfan (60 mg in 10 ml vial and 240 mg in 40 ml vial). After dilution: one ml of solution contains approximately 0.5 mg of busulfan.
- The other ingredients are dimethylacetamide and macrogol 400.

**What Busulfan Fresenius Kabi looks like and contents of the pack**
Busulfan Fresenius Kabi consists of a concentrate for solution for infusion. When diluted Busulfan Fresenius Kabi is a clear colourless viscous solution.

Busulfan Fresenius Kabi is supplied in colourless glass vials, each vial sleeved with shrinkable plastic film.

Each vial contains either 10 ml or 40 ml of concentrate.

One pack contain 8 vials of 10 ml each or one vial of 40 ml.

**Marketing Authorisation Holder**

Fresenius Kabi Deutschland GmbH
Else-Kröner-Straße 1,
61352 Bad Homburg v.d.Höhe
Germany

**Manufacturer**
Fresenius Kabi Deutschland GmbH
Pfingstweide 53
61169 Friedberg
Germany

For any information about this medicine, please contact the Marketing Authorisation Holder

**This leaflet was last revised in** {MM/YYYY}

**Other sources of information**
Detailed information on this product is available on the website of European Medicinal Agency http://www.ema/europa.eu

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The following information is intended for healthcare professionals only:

**PREPARATION GUIDE**

**Busulfan Fresenius Kabi 6 mg/ml concentrate for solution for infusion**
Busulfan

Read this guide prior to the preparation and administration of busulfan.

## 1. PRESENTATION

Busulfan is supplied as a clear colourless viscous solution in 10 ml and 40 ml clear, colourless glass vials (type I). Busulfan must be diluted prior to administration.

## 2. RECOMMENDATION FOR SAFE HANDLING

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.

Following multiple needle entries and product withdrawal, the 40 ml vials maintain microbial, chemical, and physical stability for up to 28 days at 5°C ±3°C. Other in-use storage time and conditions are the responsibility of the user.

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

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

The quantity of the diluent must be 10 times the volume of concentrate ensuring the final concentration of busulfan remains at approximately 0.5 mg/ml.

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

- Quantity of busulfan:

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

Y: body weight of the patient in kg
D: dose of busulfan (see SPC section 4.2)

- Quantity of diluent:

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

To prepare the final solution for infusion, add (A) ml of busulfan to (B) ml of diluent (sodium chloride 9 mg/ml (0.9%) solution for injection or glucose solution for injection5%).

Preparation of the solution for infusion

Busulfan must be prepared by a healthcare professional using sterile transfer techniques.

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

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

Diluted concentrate is a clear colourless solution

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

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

The entire prescribed busulfan dose should be delivered over two or three hours depending on the conditioning regimen.

Small volumes may be administered over 2 hours using electric syringes. In that case infusion sets with minimal priming space should be used (i.e 0.3-0.6 ml), primed with medicinal product solution prior to beginning the actual busulfan infusion and then flushed with sodium chloride 9 mg/ml (0.9%) solution for injection or glucose (5%) solution for injection.

Busulfan must not be infused concomitantly with another intravenous solution.

Due to incompatibility, do not use infusion components containing polycarbonate with busulfan.

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

Storage conditions
*Unopened vials:*
Store in a refrigerator (2°C – 8°C).

*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) when stored at 25°C ± 2°C or 12 hours 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 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.

Do not freeze the diluted solution.

It is recommended that healthcare professionals and end-users follow best practices such as piercing perpendicular to stopper surface and within target ring to avoid hitting the stopper legs, piercing at appropriate speeds, and limit reuse of needles to help reduce stopper coring and fragmentation risks.

## 3. PROCEDURE FOR PROPER DISPOSAL

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