

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Busilvex 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 (sterile concentrate).

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Busilvex 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.

Busilvex 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.

Busilvex 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

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

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

Posology

Busilvex 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 Busilvex (see section 4.5).

Paediatric population (0 to 17 years)

The recommended dose of Busilvex is as follows:

<u>Actual body weight (kg)</u>	<u>Busilvex dose (mg/kg)</u>
< 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 Busilvex.(see section 4.5).

Busilvex 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 Busilvex without dose-adjustment. However, for the safe use of Busilvex 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.

Busilvex 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.
- Busilvex 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)/(m²) > 30 kg/m² 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

Busilvex 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

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

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

Busilvex 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 Busilvex to 24 h after the last dose of Busilvex.

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 Busilvex 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 Busilvex 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 $< 0.5 \times 10^9/l$ at a median of 4 days post transplant occurred in 100% of patients and recovered at median day 10 and 13 days following autologous and allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively). Thrombocytopenia ($< 25 \times 10^9/l$ 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 $< 0.5 \times 10^9/l$ 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 ($< 25 \times 10^9/l$ 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 Busilvex should be used with caution in this type of patients.

Hepatic impairment

Busilvex as well as busulfan has not been studied in patients with hepatic impairment. Since busulfan is mainly metabolized through the liver, caution should be observed when Busilvex 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 Busilvex. 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 Busilvex 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 Busilvex. However cardiac function should be monitored regularly in patients receiving Busilvex (see section 4.8).

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in Busilvex 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 Busilvex (see section 4.8).

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of Busilvex to patients with a history of seizures. Patients should receive adequate anticonvulsant prophylaxis. In adults and children studies, data with Busilvex 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 Busilvex 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 Busilvex. 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 Venous 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.

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 Busilvex 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-HT₃ antiemetics such as ondansetron or granisetron.

4.6 Fertility, pregnancy and lactation

Pregnancy

HPCT is contraindicated in pregnant women; therefore, Busilvex 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

Busilvex in combination with cyclophosphamide or melphalan

In adults

Adverse events information is derived from two clinical trials (n=103) of Busilvex.

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 Busilvex 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 allogeneic transplant respectively. VOD observed were neither fatal nor severe and resolved in all cases.

Busilvex in combination with fludarabine (FB)

In adults

The safety profile of Busilvex 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 ($\geq 1/10$), common ($\geq 1/100, < 1/10$), uncommon ($\geq 1/1,000, < 1/100$) 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”.

Busilvex in combination with cyclophosphamide or melphalan

Adverse reactions reported both in adults and paediatric patients as more than an isolated case are listed below, by system organ class and by frequency. Within each frequency grouping, adverse events are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Not known
Infections and infestations	Rhinitis Pharyngitis			
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Febrile neutropenia Anaemia Pancytopenia			
Immune system disorders	Allergic reaction			
Endocrine disorders				Hypogonadism **
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypocalcaemia Hypokalaemia Hypomagnesaemia Hypophosphatemia	Hyponatraemia		
Psychiatric disorders	Anxiety Depression Insomnia	Confusion	Delirium Nervousness Hallucination Agitation	

Nervous system disorders	Headache Dizziness		Seizure Encephalopathy Cerebral haemorrhage	
Eye disorders				Cataract Corneal thinning Lens disorders ***
Cardiac-disorders	Tachycardia	Arrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis	Ventricular extrasystoles Bradycardia	
Vascular disorders	Hypertension Hypotension Thrombosis Vasodilatation		Femoral artery thrombosis Capillary leak syndrome	
Respiratory thoracic and mediastinal disorders	Dyspnoea Epistaxis Cough Hiccup	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia	Interstitial lung disease**
Gastrointestinal disorders	Stomatitis 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			
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

Busilvex 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

Vascular disorders		Hyper-tension	
Respiratory thoracic and mediastinal disorders		Pulmonary haemorrhage	Respiratory failure
Gastro-intestinal disorders	Nausea Vomiting Diarrhoea Stomatitis		Gastro-intestinal haemorrhage Tooth hypoplasia*
Hepato-biliary disorders	Veno occlusive liver disease		Jaundice Liver disorders
Skin and subcutaneous tissue disorders		Rash	
Renal and urinary disorders	Haemorrhagic cystitis**	Renal disorder	Oliguria
General disorders and 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 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 Busilvex other than haematopoietic progenitor cell transplantation. In the absence of haematopoietic progenitor cell transplantation, the recommended dose of Busilvex 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 Busilvex 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

Busilvex in combination with cyclophosphamide

In adults

Documentation on the safety and efficacy of Busilvex 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 myelogenous 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 Busilvex. No patients were discontinued from treatment due to adverse reactions related to Busilvex.

All patients experienced a profound myelosuppression. The time to Absolute Neutrophil Count (ANC) greater than $0.5 \times 10^9 / l$ was 13 days (range 9-29 days) in allogeneic 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 Busilvex 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 $0.5 \times 10^9 / l$ was 21 days (range 12-47 days) in allogeneic 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.

Busilvex in combination with fludarabine (FB)

In adults

Documentation on the safety and efficacy of Busilvex 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 Busilvex) 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 Busilvex 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 inpatient 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 $\mu\text{mol/L}\cdot\text{minute}$ per administration (equivalent to a daily exposure between 3600 and 6000 $\mu\text{mol/L}\cdot\text{minute}$). 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 $\mu\text{mol/L}\cdot\text{minute}$) and at least 80% were within the targeted therapeutic window (900-1500 $\mu\text{mol/L}\cdot\text{minute}$). Similar targeting rate is achieved within the daily exposure of 3600 - 6000 $\mu\text{mol/L}\cdot\text{minute}$ following the administration of intravenous busulfan 3.2 mg/kg once daily.

Special populations

Hepatic or renal impairment

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

Paediatric population

A continuous variation of clearance ranging from 2.49 to 3.92 ml/minute/kg has been established in children from < 6 months up to 17 years old. The terminal half life ranged from 2.26 to 2.52 h. Inter and intra patient variabilities in plasma exposure were lower than 20% and 10%, respectively. A population pharmacokinetic analysis has been performed in a cohort of 205 children adequately distributed with respect to bodyweight (3.5 to 62.5 kg), biological and diseases (malignant and non-malignant) characteristics, thus representative of the high heterogeneity of children undergoing HPCT. This study demonstrated that bodyweight was the predominant covariate to explain the busulfan pharmacokinetic variability in children over body surface area or age. 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 $\mu\text{mol/L}\cdot\text{minute}$). However a higher variability was observed in children < 9 kg leading to 60% of children achieving the therapeutic window (900-1500 $\mu\text{mol/L}\cdot\text{minute}$). 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 $\mu\text{mol/L}\cdot\text{min}$ 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 histopathological 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 arteriosus and no ductus arteriosus, 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 Busilvex.

6.3 Shelf life

Vials: 3 years

Diluted solution:

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

- 8 hours (including infusion time) after dilution when stored at 20 °C ± 5 °C
- 12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °C (including infusion time).

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than the above mentioned conditions when dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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 a butyl rubber stopper covered by a purple flip-off aluminium seal cap.

Multipack containing 8 (2 packs of 4) vials.

6.6 Special precautions for disposal and other handling

Preparation of Busilvex

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 Busilvex solution:

- The use of gloves and protective clothing is recommended.
- If Busilvex or diluted Busilvex solution contacts the skin or mucosa, wash them thoroughly with water immediately.

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

Busilvex 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 Busilvex ensuring the final concentration of busulfan remains at approximately 0.5 mg/ml. By example:

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

- Quantity of Busilvex:

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

Y: body weight of the patient in kg

D: dose of Busilvex (see section 4.2)

- Quantity of diluent:

$(A \text{ ml Busilvex}) \times (10) = B \text{ ml of diluent}$

To prepare the final solution for infusion, add (A) ml of Busilvex 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

- Busilvex must be prepared by a healthcare professional using sterile transfer techniques. Using a non polycarbonate syringe fitted with a needle:
 - the calculated volume of Busilvex 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. Busilvex must always be added to the diluent, not the diluent to Busilvex. Busilvex 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 Busilvex 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 Busilvex has not been tested and is not recommended.

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

Busilvex must not be infused concomitantly with another intravenous solution.

Polycarbonate syringes must not be used with Busilvex.

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

Pierre Fabre Médicament
45, Place Abel Gance
F-92654 Boulogne Billancourt Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/03/254/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 July, 2003
Date of latest renewal: 08 July, 2008

10 DATE OF REVISION OF THE TEXT

MM/YYYY

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 responsible for batch release

Pierre Fabre Médicament Production
Site Aquitaine Pharm International
Avenue du Béarn -Idron
F-64320
France

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**

The requirements for submission of periodic safety update reports 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)**

Not applicable

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING WITH BLUE BOX

{Box containing 8 vials of 10ml}

1. NAME OF THE MEDICINAL PRODUCT

Busilvex 6 mg/ml concentrate for solution for infusion
busulfan

2. STATEMENT OF ACTIVE SUBSTANCE

One ml of concentrate contains 6 mg of busulfan and provides 0.5 mg/ml of busulfan after dilution

3. LIST OF EXCIPIENTS

Each vial contains Dimethylacetamide and Macrogol 400

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
Multipack: 8 (2 packs of 4) vials of 10 ml
60 mg per vial

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use (IV)
Must be diluted before use
Read the package leaflet before use

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: handle with caution.

8. EXPIRY DATE

EXP:
Read the leaflet for the shelf life of diluted medicine

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pierre Fabre Médicament
45, place Abel Gance
F-92654 Boulogne Billancourt cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/254/002

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: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING WITHOUT BLUE BOX

{ box containing 4 vials of 10ml}

1. NAME OF THE MEDICINAL PRODUCT

Busilvex 6 mg/ml
busulfan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

60 mg

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate
4 vials of 10ml. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use (IV)
Must be diluted before use
Read the package leaflet before use

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C)

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/254/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{10ml type I glass vial}

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

Busilvex 6 mg/ml sterile concentrate
IV

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

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Busilvex 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.

What is in this leaflet:

1. What Busilvex is and what it is used for
2. What you need to know before you use Busilvex
3. How to use Busilvex
4. Possible side effects
5. How to store Busilvex
6. Contents of the pack and other information

1. What Busilvex is and what it is used for

Busilvex contains the active substance busulfan, which belongs to a group of medicines called alkylating agents. Busilvex destroys the original bone marrow before the transplant.

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

In adults Busilvex is used in combination with cyclophosphamide or fludarabine.

In new-born infants, children and adolescents, Busilvex 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 Busilvex

Do not use Busilvex:

- if you are allergic to busulfan or any of the other ingredients of Busilvex listed in section 6,
- if you are pregnant, or think you may be pregnant.

Warnings and precautions

Busilvex 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 Busilvex 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 Busilvex

Tell your doctor if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription. Busilvex may interact with other medicines.

Particular caution should be taken if you use itraconazole and metronidazole (used for certain types of infections) or ketobemidone (used to treat pain), because this may increase the side-effects.

The use of paracetamol during the 72 hours prior to or with Busilvex 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 Busilvex. Women must not be pregnant during treatment with Busilvex and up to 6 months after treatment.

Women must stop breast-feeding before starting their treatment with Busilvex.

Adequate contraceptive precautions should be used when either partner is receiving Busilvex.

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

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

3. How to use Busilvex

Dose and administration:

The dose of Busilvex will be calculated according to your body weight.

In adults:

Busilvex in combination with cyclophosphamide:

- The recommended dose of Busilvex is 0.8 mg/kg
- Each infusion will last 2 hours
- Busilvex will be administered every 6 hours during 4 consecutive days prior to transplant.

Busilvex in combination with fludarabine

- The recommended dose of Busilvex is 3.2 mg/kg
- Each infusion will last 3 hours
- Busilvex 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 Busilvex in combination with cyclophosphamide or melphalan is based on your body weight varying between 0.8 and 1.2 mg/kg.

- Each infusion will last 2 hours
- Busilvex will be administered every 6 hours during 4 consecutive days prior to transplant.

Medicines before you receive Busilvex:

Before receiving Busilvex, 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, this medicine can cause side effects, although not everybody gets them.

Serious side effects:

The most serious side effects of Busilvex 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. 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, 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.

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 Busilvex

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) after dilution when stored at 20 °C ± 5 °C or 12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °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 Busilvex contains

- The active substance is busulfan. One ml of concentrate contains 6 mg busulfan (60 mg in the vial). After dilution: one ml of solution contains approximately 0.5 mg of busulfan.
- The other ingredients are dimethylacetamide and macrogol 400.

What Busilvex looks like and contents of the pack

Busilvex consists of a concentrate for solution for infusion and is supplied in colourless glass vials, each vial containing 60 mg of busulfan.

Busilvex is available in multipacks comprising 2 packs, each containing 4 vials.

When diluted Busilvex is a clear colourless solution.

Marketing Authorisation Holder

Pierre Fabre Médicament
45, place Abel Gance
F-92654 Boulogne-Billancourt cedex
France

Manufacturer

Pierre Fabre Médicament Production, site Aquitaine Pharm International
Avenue du béarn
F-64320 Idron
France

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 medical or healthcare professionals only

PREPARATION GUIDE

Busilvex 6 mg/ml concentrate for solution for infusion

Busulfan

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

1. PRESENTATION

Busilvex is supplied as a clear colourless solution in 10 ml clear glass vials (type I). Busilvex 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 Busilvex solution:

- The use of gloves and protective clothing is recommended.
- If Busilvex or diluted Busilvex solution contacts the skin or mucosa, wash them thoroughly with water immediately.

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

Busilvex 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 Busilvex ensuring the final concentration of busulfan remains at approximately 0.5 mg/ml.

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

- Quantity of Busilvex:

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

Y: body weight of the patient in kg

D: dose of Busilvex (see SPC section 4.2)

- Quantity of diluent:

$(A \text{ ml Busilvex}) \times (10) = B \text{ ml of diluent}$

To prepare the final solution for infusion, add (A) ml of Busilvex 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

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

- Using a non polycarbonate syringe fitted with a needle:
 - the calculated volume of Busilvex 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. Busilvex must always be added to the diluent, not the diluent to Busilvex. Busilvex 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 Busilvex 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 Busilvex has not been tested and is not recommended.

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

Busilvex must not be infused concomitantly with another intravenous solution.

Polycarbonate syringes must not be used with Busilvex.

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) after dilution when stored at 20 °C ± 5 °C or 12 hours after dilution when stored at 2 °C-8 °C followed by 3 hours stored at 20 °C ± 5 °C (including infusion time).

For a microbiological point of view, the diluted solution should be used immediately.

3. PROCEDURE FOR PROPER DISPOSAL

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

Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for busulfan, the scientific conclusions of CHMP are as follows:

In view of the data presented in the reviewed PSUR, the PRAC considered that changes to the product information of medicinal products containing busulfan were warranted.

Seven literature reports have been published cumulatively concerning disturbance in dental development. In one article it was studied the role of busulfan in juvenile rats resulting in abnormal root development; a review of two cases of immunodeficiency disorders treated with busulfan and cyclophosphamide in which dental orthodontic treatment was provided; additional 2 case report of hypoplasia of permanent tooth germ is presented; one review assessed the long term effects of cytotoxic therapy concluding that tooth agenesis was more prevalent in patients treated with busulfan and cyclophosphamide; a study of 81 patients concluded that busulfan is as toxic as total body irradiation in causing disturbances in dental development; finally, a study of risk factors of tooth formation anomalies in paediatric cancers concluded that the high risk group of tooth agenesis was the subject with high dose chemotherapy under 4 years old. From the assessment of these articles, the causality of busulfan in the development of tooth hypoplasia is confirmed. Therefore, “tooth hypoplasia” should be added to the product information for both pharmaceutical forms.

Interaction between busulfan and metronidazol has been reported in literature reviews and post marketing cases. It is of particular interest the study of this interaction in three groups of patients in which higher plasma levels of busulfan were observed in the group receiving metronidazol prophylaxis during busulfan treatment than in those without metronidazoles. Therefore, this interaction should be included in the product information for both pharmaceutical forms.

The signal concerning interaction with deferasirox is refuted and it can be closed. This signal was open based on an isolated case from the literature and no additional cases have been reported. No pharmacokinetic explanation justifies this interaction. The signals concerning busulfan oral formulations and hepatic veno-occlusive disease risk in patients who have received prior radiation therapy /chemotherapy /HSCT, sterility, overdose treatment can be closed. These risks are assessed in the corresponding national procedures.

The MAH of Busilvex has responded to the question of “Thrombotic microangiopathy” (TMA) after hematopoietic cell transplantation (HCT) requested as supplementary information. A cumulative review of the literature and safety database has been performed. The occurrence of TMA is multifactorial and busulfan IV by itself cannot be considered as a main factor in the development of this reaction. Mainly studies from literature have shown that high busulfan *i.v.* doses in combination with other drugs in conditioning treatment previous HCT could be an important role in the development of TMA. As a conclusion, busulfan could be one risk factor of development TMA and a warning in section 4.4 of the Busilvex SmPC is considered warranted.

The warning for TMA after HCT only applies to one pharmaceutical form: the intravenous. Cases of TMA after high doses of busulfan *i.v.* in combination with other medicine as a conditioning treatment previous HCT have been seen after reviewing the literature and the cases retrieved in the safety database of the company. There are no cases with oral busulfan.

The benefit risk profile of the product remains favourable in the approved indications.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for busulfan the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing busulfan is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.

The CHMP agrees with the scientific conclusions made by the PRAC.