PRODUCT INFORMATION

BUSULFEX (BUSULFAN) INJECTION

1 NAME OF THE MEDICINE

BUSULFEX

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mL vial of Busulfex contains 60 mg (6 mg/mL) of busulfan.

Busulfan, the active ingredient of Busulfex, is a white crystalline solid that is only very slightly soluble in water, sparingly soluble in acetone and slightly soluble in ethanol.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection.

Busulfex is supplied as a sterile solution in 10 mL single-use clear glass vials each containing 60 mg of busulfan at a concentration of 6 mg/mL for intravenous use.

Busulfex (Busulfan) injection is a potent cytotoxic drug that results in profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in the use of cancer chemotherapeutic agents and in the management of patients with severe pancytopenia. Appropriate management of therapy and complications is only possible when adequate diagnostic and treatment facilities are readily available.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Busulfex (busulfan) Injection is indicated for use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation**.**

4.2 DOSE AND METHOD OF ADMINISTRATION

Busulfex should be administered intravenously via a central venous catheter as a two-hour infusion every 6 hours x 4 consecutive days for a total of 16 doses. All patients should be premedicated with appropriate anti-convulsant therapy (e.g. phenytoin, benzodiazepines) to prevent seizures, as busulfan is known to cross the blood brain barrier. Antiemetics of the 5-HT3 class should be administered prior to the first dose of Busulfex and continued on a fixed schedule through administration of Busulfex or considered through completion of the preparative regimen.

The usual adult dose of Busulfex in combination with cyclophosphamide as a preparative regimen prior to bone marrow or peripheral blood progenitor cell replacement support is 0.8 mg/kg of ideal body weight or actual body weight, whichever is lower. For obese, or severely obese patients, dosing based on adjusted ideal body weight could be considered. Ideal body weight (IBW) should be calculated as follows: (height in cm, and weight in kg): IBW (kg; men) = 50 + 0.91 × (height -152); IBW (kg;

women) = 45 + 0.91 × (height - 152). Adjusted ideal body weight (AIBW) should be calculated as follows: AIBW = IBW + 0.25 × (actual weight - IBW). Cyclophosphamide in combination with Busulfex was given on each of two days as a one-hour infusion at 60 mg/kg beginning on BMT day -3, six hours following the 16th dose of Busulfex.

Busulfex must be diluted prior to administration.
For instructions on dilution of the product before administration, see section 6.6.

4.3 CONTRAINDICATIONS

Busulfex is contraindicated in patients with hypersensitivity to the active substance busulfan or to any of the excipients.

Busulfex is contraindicated in women who are pregnant and/or lactating.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The consequence of treatment with Busulfex 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. To detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase and bilirubin should be evaluated daily until transplant day 28. 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 G-CSF, should be employed as medically indicated. Documentation on Precautions with Busulfex use is derived from two uncontrolled clinical trials in adults (trials OMC-BUS-3 and 4) and one uncontrolled clinical trial in children (trial F60002 IN 1 01 G0).

Myelosuppression

In adults, absolute neutrophil counts <0.5 x 10^9/L at a median of 4 days post-transplant occurred in 100% of patients and recovered at median day 10 and 13 days following autologous and allogeneic transplant respectively (median neutropenic period of 6 and 9 days respectively). Thrombocytopenia (<25 x 10^9/L or requiring platelet transfusion) occurred at a median of 5-6 days in 98% of patients. Anaemia (haemoglobin <80 g/L) occurred in 69% of patients.

In children, absolute neutrophil counts < 0.5 x 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 x 10^9/L or requiring platelet transfusion) occurred in 100% of patients. Anaemia (haemoglobin <80 g/L) occurred in 100% of patients.

Infection

In adults, 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%.

In children, infections (documented and non-documented febrile neutropenia) were experienced in 89% of patients (49/55). Mild/moderate fever was reported in 76% of patients.

Fanconi anaemia

The Fanconi anaemia cells have hypersensitivity to cross-linking agents. There is limited clinical experience of the use of busulfan as component of conditioning regimen prior to HSCT in children with Fanconi anaemia. Therefore, Busulfex should be used with caution in this type of patients.

Graft versus host disease

In adults, 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.

In children, 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.

Liver toxicity

In adults, 15% of serious adverse events 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. Patients who have received prior radiation therapy, greater than or equal to three cycles of chemotherapy, or prior stem cell transplant may be at an increased risk (see Section 4.8 ADVERSE EFFECTS).

In children grade 3 elevated transaminases were reported in 24% of patients. HVOD was reported in 15% (4/27) and 7% (2/28) of the autologous and allogenic transplant respectively. HVOD observed were neither fatal nor severe and resolved in all cases.

Repeated doses of the solvent, 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.

Cardiac toxicity

Cardiac tamponade has been reported in children with thalassemia (8/400 or 2% in one series) who received high doses of oral busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation. Six of the eight children died and two were saved by rapid pericardiocentesis. Abdominal pain and vomiting preceded the tamponade in most patients. No patients treated in the Busulfex clinical trials experienced cardiac tamponade or other specific cardiac toxicities related to Busulfex. However cardiac function should be monitored regularly in patients receiving Busulfex (see Section 4.8 ADVERSE EFFECTS).

Pulmonary toxicity

Occurrence of acute respiratory distress syndrome with subsequent respiratory failure associated with interstitial pulmonary fibrosis was reported in Adverse Effects studies in one patient who

died, although, no clear etiology 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 ADVERSE EFFECTS).

Seizures

Seizures have been reported with high dose busulfan treatment. Special caution should be exercised when administering the recommended dose of Busulfex to patients with a history of seizures. Patients should receive adequate anticonvulsant prophylaxis. In adults all data with Busulfex have been obtained using phenytoin. There are no data available on the use of other anticonvulsant agents such as benzodiazepines, therefore the effect of other agents on busulfan pharmacokinetics is not known. In paediatric patients data have been obtained using benzodiazepines and phenytoin.

High-risk patients

HSCT is generally not recommended in high-risk patients because of poorer outcomes. High- risk patients include those of age >50 years and those with prior myeloablative transplants, organ dysfunction, poor performance status or extensive prior chemotherapy. Careful consideration of the risks and benefits of Busulfex is necessary in these patients. Non-myeloablative conditioning regimens, with a reduced dose or reduced duration of Busulfex, have demonstrated a low rate of regimen related toxicity in high-risk patients but can lead to an increase in the incidence of disease relapse (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Use in hepatic impairment

Busulfex 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 Busulfex 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.

Use in 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.

Caution is recommended. In a Phase I study conducted in patients with metastatic renal carcinoma, all of whom had only one functioning kidney, a conditioning regimen of once-daily Busulfex in combination with fludarabine gave a high incidence of regimen related toxicity.

Use in the elderly

Patients older than 50 years of age have been successfully treated with Busulfex. Refer to Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials for information on the use of Busulfex in elderly patients in non-myeloablative conditioning regimens. Only limited information is available for the safe use of Busulfex in patients older than 60 years.

Paediatric use

Data on the use of Busulfex in children are limited (see Section 5.1 PHARMACODYNAMIC

PROPERTIES, Clinical Trials) and there have been no studies in juvenile animals. The level of DMA in Busulfex is higher than in other products and this may represent a particular risk to children. Pulmonary thrombosis and vasculitis were seen with DMA alone in clinical trials in adults and hepatoxicity and neurotoxic effects have been reported with DMA in the literature.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No specific clinical trial was carried out to assess drug-drug interaction between IV busulfan and antifungal agents. From published studies in adults, administration of itraconazole to patients receiving high-dose busulfan may result in reduced busulfan clearance. Patients should be monitored for signs of busulfan toxicity when itraconazole is used as an antifungal prophylaxis with IV busulfan.

No interaction was observed when busulfan was combined with fluconazole (antifungal agent) or 5 -HT3 antiemetics such as ondansetron or granisetron.

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

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

It has been reported that when using the BuCy2 regimen in adults 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.

It has also been reported that when using the BuMel regimen in paediatric patients 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. Caution should be exercised when using paracetamol prior to (less than 72 hours) or concurrently with Busulfex due to a possible decrease in the metabolism of busulfan.

Phenytoin or benzodiazepines were administered for seizure prophylaxis in all patients in the clinical trials conducted with IV busulfan. The concomitant systemic administration of phenytoin to patients receiving high-dose busulfan has been reported to increase busulfan clearance, due to induction of glutathion-S-transferase. However, no evidence of this effect has been seen in IV data.

No interaction has been reported when benzodiazepines such as diazepam, clonazepam or lorazepam have been used to prevent seizures with high-dose busulfan. Periodic monitoring of renal function should be considered during therapy with Busulfex (see Section 4.8 ADVERSE EFFECTS).

Iron chelating agents

Decreased clearance of busulfan has been observed with deferasirox. The mechanism of this interaction is not fully elucidated. Iron chelating agents should be discontinued well in advance of administration of busulfan to avoid increased exposure to busulfan.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Busulfan can impair fertility. Impotence, sterility, azoospermia, and testicular atrophy have been reported in male patients. Therefore, men treated with Busulfex 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 Busulfex. 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. Busulfan may cause temporary or permanent infertility in females.

Busulfan disrupted spermatogenesis in rats, guinea-pigs, rabbits and monkeys, depleted oocytes and impaired fertility in female mice, and induced sterility in male rats and male hamsters. The solvent dimethylacetamide (DMA) was found to impair fertility in studies with male and female rodents.

Use in pregnancy – Category D

Busulfex is contraindicated during pregnancy. Busulfan and DMA reduced fetal weight and caused embryofetal lethality and malformations in various animal species in pre-clinical studies. For busulfan, terata were observed in the musculoskeletal system of mice, rats and rabbits, while DMA-induced malformations occurred in the heart, major vessels and oral cavity in the rat. Administration of busulfan to pregnant rats caused sterility in male and female offspring due to the destruction of germinal cells in the testes and ovaries.

There are no adequate and well-controlled studies of either 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 drug, and third trimester exposure may be associated with impaired intrauterine growth.

Women of childbearing potential must use effective contraception during and up to 6 months after treatment.

Use in lactation

Patients who are taking Busulfex must be advised not to breast-feed. It is not known whether busulfan and DMA are excreted in human milk. Because of the potential for severe adverse effects, including tumourigenicity, breast-feeding should be discontinued at the start of therapy.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No relevant effects have been noted.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse event information is derived from two trials in adults in 103 patients (OMC-BUS 3 and 4) and one trial in children in 55 patients (F60002 IN 1 01) in which Busulfex was used in a four times daily regimen for 4 days in combination with cyclophosphamide or melphalan.

Adverse reactions reported as more than an isolated case are listed in Table 1. See 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for more information on serious adverse reactions. Serious toxicities involving the haematological, hepatic and respiratory systems were considered as expected consequences of the conditioning regimen and transplant process. These include infection and graft-versus-host disease which were the major causes of morbidity and mortality. The safety profile for Busulfex in once daily and twice daily regimens and in combination with fludarabine appears similar to four times daily in combination with cyclophosphamide or melphalan; however, the data are very limited and in small numbers of patients.

Table 1 Adverse Reactions Reported both in Adults and Children
(Very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100))

System Organ Class	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Leukopenia Neutropenia Thrombocytopenia Anaemia Pancytopenia Febrile neutropenia		
Immune system disorders	Acute graft-versus-host disease	Chronic graft-versus-host disease	
Infections and infestations	Infection Fever Chills	Pneumonia	
Nervous system disorders	Insomnia Dizziness Depression	Confusion	Delerium Nervousness Hallucination Agitation Encephalopathy Cerebral haemorrhage Seizure
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypomagnesaemia Hypokalaemia Hypocalcaemia Hypophosphataemia Oedema	Hyponatraemia	
Psychiatric disorders	Anxiety		
Cardiac disorders	Tachycardia Hypertension Hypotension Vasodilatation Thrombosis	Arrhythmia Atrial fibrillation Cardiomegaly Pericardial effusion Pericarditis Decrease ejection fraction	Femoral artery thrombosis Ventricular extrasystoles Bradycardia Capillary leak syndrome

Respiratory thoracic and mediastinal disorders	Dyspnoea Rhinitis Pharyngitis Cough Hiccup Epistaxis Abnormal breath sounds	Hyperventilation Respiratory failure Alveolar haemorrhages Asthma Atelectasis Pleural effusion	Hypoxia
Gastrointestinal disorders	Nausea Stomatitis Vomiting Diarrhoea Constipation Dyspepsia Anus discomfort Abdominal pain Ascites	Oesophagitis Ileus Haematemesis	Gastrointestinal haemorrhage
Hepato-biliary disorders	Hepatomegaly Jaundice	Hepatic veno-occlusive disease	
Skin and subcutaneous tissue disorders	Rash Pruritis Alopecia	Erythema Pigmentation disorder Skin desquamation	
Musculoskeletal and connective tissue disorders	Back pain Myalgia Arthralgia		
Renal and urinary disorders	Creatinine elevated Dysuria Oliguria	BUN increase Haematuria Moderate renal insufficiency	
General disorders and administration site conditions	Headache Asthenia Pain Allergic reaction Oedema general Pain or inflammation at injection site Chest pain Mucositis		
Investigations	Transaminases increased Bilirubin increased GGT increased Weight increased Alkaline phosphatases increased		

Note: One patient in the Busulfex trials experienced a fatal case of acute respiratory distress syndrome with subsequent respiratory failure associated with intestinal pulmonary fibrosis. Cardiac tamponade and alterations of cornea and lens of the eye have been reported with oral busulfan.

Post-Marketing Experience

The following adverse reactions (reported as MedDRA terms) have been identified during post-approval use of Busulfex (busulfan) Injection: febrile neutropenia, tumor lysis syndrome,

thrombotic micro-angiopathy (TMA), severe bacterial, viral (eg, cytomegalovirus viraemia) and fungal infections, sepsis and tooth hypoplasia. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure.

Reporting 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/.

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 Busulfex other than haematopoietic stem cell transplantation. In the absence of haematopoietic progenitor cell transplantation, the recommended dosage of Busulfex 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 Busulfex will also increase exposure to DMA. In human the principal toxic effects were hepatotoxicity and central nervous system 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: Cytotoxic agents (alkylating agents). 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 trials

Clinical trials in adults

Documentation of the safety and efficacy of Busulfex in combination with cyclophosphamide in myeloablation prior to autologous or allogeneic haematopoietic stem cell transplantation (HSCT) in adults is derived from two uncontrolled clinical trials (trials OMC-BUS 3 and 4 respectively).

The trials 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. The age of patients was 18-63 years and 60% were male. Patients received 0.8 mg/kg Busulfex every 6 hours by intravenous (IV) infusion for 4 days from day 7 to day 4 before HSCT. Cyclophosphamide 60 mg/kg/day once daily IV was given for 2 days from day 3 to 2 before HSCT (BuCy2 regimen).

The primary efficacy parameters in these studies were myeloablation, engraftment, relapse, and survival. Busulfex with cyclophosphamide was effective in inducing myeloablation and engraftment. Relapse-free and overall survival were similar in the two trials (Table 2).

Table 2. Busulfex *qid*/Cyclophosphamide – HSCT Conditioning Efficacy in Adults

	OMC-BUS 3 (n=42)	**OMC-BUS-4 (n=61)**
Myeloablation[1] %	100	100
Median time to neutropenia (range) *days*	4 (-7, 6)	4 (-7, 5)
Median duration of neutropenia (range) *days*	6 (2, 13)	9 (1, 28)
Engraftment[2] %	100	98[3]
Median time to engraftment (range) *days*	10 (8, 19)	13 (9, 29)
Relapse-free Kaplan-Meier estimate % at 1 yr [95% CI]	56 [40, 72]	51 [35, 67]
Survival Kaplan-Meier estimate % at 1 yr [95% CI]	70 [52, 88]	67 [54, 80]

[1]Absolute neutrophil count (ANC) < 0.5 x 10^9/L, absolute lymphocyte count <0.1 x 10^9/L or platelet count <20 x 10^9/L or bleeding requiring platelet transfusion.
[2]ANC >0.5 x 10^9/L within 100 days of HSCT.
[3]One patient died before engraftment could be determined.

Uncontrolled (Fernandez) and non-randomised controlled trials (Mamlouk) in adults with haematological malignancies showed comparable incidences of engraftment for once daily and twice daily Busulfex 3.2 mg/kg/day regimens in combination with cyclophosphamide 60 mg/kg/day compared with the four times daily regimen. Short-term survival was above 80% (Table 3). Reproducible busulfan pharmacokinetic parameters were demonstrated for once daily Busulfex.

Table 3. Busulfex *od* or *bd*/Cyclophosphamide – HSCT Conditioning Efficacy in Adults

	Fernandez (n=12)	**Mamlouk**		
Busulfex/oral busulfan schedule	*od* (n=6) or *bd* (n=6), days -7 to -4[1]	*od* IV 4d (n=20)	*qid* IV 4d (n=11)	*qid po* 4d (n=25)
Cyclophosphamide schedule	daily, days -3 to -2	2 days, start 27 h after Busulfex	2 days, start 18 h after Busulfex	2 days, start 18 h after busulfan
Engraftment[2]%	92[3]	100	100	100
Median time to engraftment[3] (range) *days*	11 (10, 20)	12 (11, 17)	14 (12, 18)	13 (10, 26)
Relapse-free at 100 days post-HSCT %	67	90	100	88
Survival at 100 days post-HSCT %	83	95	82	84

[1] Before HSCT.
[2] ANC > 0.5 x 10^9/L.
[3] One patient died before engraftment could be determined.

Two uncontrolled trials in adults with haematological malignancies (Russell, de Lima) showed comparable incidences of engraftment for once daily Busulfex 3.2-3.3 mg/kg in combination with fludarabine compared with the four times daily Busulfex with cyclophosphamide regimen. Two-year survival was 37-88% depending on risk (Table 4). Reproducible busulfan pharmacokinetic parameters were demonstrated for Busulfex.

Table 4. Busulfex *od* or *bd*/Fludarabine – HSCT Conditioning Efficacy in Adults

	Russell (n=70)	**de Lima (n=96)**
Busulfex schedule	3.2 mg/kg *od*, days -5 to -2[1]	130 mg/m^2 *od* ≡ 3.3 mg/kg, days -6 to -3[1]
Fludarabine schedule	50 mg/m^2/d days -6 to -2[1]	40 mg/m^2/d days -6 to -3[1]
Engraftment[2] %	94[3]	99
Medium time to engraftment[2] (range) *days*	18 (12, 42)	12 (9, 25)
Relapse-free %	26-74 (depending on risk) (2 yr est)	66
Survival %	37-88 (depending on risk) (2 yr est)	65 (1 yr est)

[1]Before HSCT.
[2]ANC > 0.5 x 10^9/L.
[3]Two patients failed engraftment because of persistent leukaemia and two died before engraftment could be determined. In unrelated or mismatched donor, anti- thymocyte globulin (ATG) was used.

In a retrospective analysis (Alyea) comparing the outcomes of allogeneic transplant in patients aged >50 years with haematological malignancies, who received either a non- myeloablative conditioning regimen of once-daily Busulfex 0.8 mg/kg for 4 days in combination with fludarabine 30 mg/m^2 for 4 days or a myeloablative conditioning regimen of total body irradiation (TBI)/cyclophosphamide or oral busulfan/cyclophosphamide, improved 100-day treatment-related mortality rates and non- relapse mortality rates were noted in patients receiving the non-myeloablative Busulfex-fludarabine conditioning regimen (Table 5). Although the cumulative incidence of disease relapse was higher in patients receiving the non- myeloablative conditioning regimen, overall survival and progression-free survival were not adversely affected by the reduction in intensity of the conditioning regimen.

Table 5. Busulfex/Fludarabine – Comparison of Myeloablative and Non-Myeloablative HSCT Conditioning Efficacy in Adults – Alyea

	Non-Myeloablative (n=71)	**Myeloablative (n=81)**
Myeloablative/non-myeloablative schedule	Busulfex 0.8 mg/kg/d, fludarabine 30 mg/m^2/d days -6 to -3[1]	Cyclophosphamine/ TBI or oral busulfan/ cyclophosphamine[2]
Treatment related mortality (100 day)	6%	30%
Non-relapse mortality	32%	50%
Cumulative relapse rate	46%	30%
Kaplan-Meier overall survival	39% (2 yr est)	29% (2 yr est)
Kaplan-Meier progression-free survival	27% (2 yr est)	25% (2yr est)

[1] Before HSCT.
[2] 94% received Cytarabine 1800 mg/m^2/d for 2 days and TBI (total body irradiation) 1400cGy in 7 fractions over 4

days. 6% received oral busulfan 16 mg/kg divided over 4 days and cyclophosphamide.

Clinical trials in Children

Documentation of the safety and efficacy of Busulfex in combination with cyclophosphamide or melphalan in myeloablation prior to autologous or allogeneic HSCT in children is derived from one uncontrolled clinical trial (trial F60002 IN 1 01 G0). The age of patients was 0.3-17.2 years and 53% were male. The dose of Busulfex ranged from 3.2-4.8 mg/kg/day depending on weight group. The Busulfex dose was based on body weight as detailed in Section 4.2 DOSE AND METHOD OF ADMINISTRATION and given in four divided doses daily for 4 days.

In autologous HSCT, Busulfex was given from day 6 to day 3 before HSCT and melphalan 140 mg/m^2 IV on the day before HSCT (BuMel regimen). In allogeneic HSCT, Busulfex was given from day 9 to day 6 before HSCT and cyclophosphamide 50 mg/kg IV for 4 days from day 5 to 2 before HSCT (BuCy4 regimen). All patients achieved myeloablation and engraftment. The estimated 2-year survival was almost 80% (Table 6).

Table 6. Busulfex *qid*/Melphalan (Bu/Mel) or Cyclophosphamide (Bu/Cy) – HSCT Conditioning Efficacy in Children – Trial F60002 IN 1 01

	Bu/Mel (n=27)	**Bu/Cy (n=28)**
Myeloablation[1] %	100	100
Median time to neutropenia (range) *days*	5 (3, 8)	5 (3, 8)
Median duration of neutropenia (range) *days*	5 (3, 10)	5 (3, 10)
Engraftment[2] %	100	100
Median time to engraftment (range) *days*	11 (10, 15)	21 (12, 47)
Median follow-up (range) *mths*	16.9 (5.4, 26.9)	13.5 (3.4, 23.5)
Relapse-free Kaplan-Meier estimate % at 2 yrs [95% CI]	72 [66, 73]	88 [84, 91]
Survival Kaplan-Meier estimate % at 2 yrs [95% CI]	77 [73, 82]	79 [73, 85]

[1]Absolute neutrophil count (ANC) < 0.5 x 10^9/L, absolute lymphocyte count <0.1 x 10^9/L or platelet count <20 x 10^9/L or bleeding requiring platelet transfusion.
[2]ANC >0.5 x 10^9/L within 100 days of HSCT.

Four uncontrolled trials in children (Table 7) with malignant and non-malignant conditions showed comparable incidences of engraftment for once daily Busulfex 4 mg/kg/day for 4 days (Grigull) or with Busulfex targeted to a steady-state concentration of 900 ng/mL four times daily (approx 3.2 mg/kg/day) for 4 days (Horn) in combination with fludarabine 30- 40 mg/m^2/day, compared with four times daily Busulfex with cyclophosphamide or melphalan. Lower incidences of engraftment were obtained for reduced intensity conditioning regimens using a reduced dose or reduced duration of Busulfex (Kletzel, Horn, Jacobsohn). The reduced intensity conditioning was associated with lower incidences of treatment related toxicity.

Table 7. Busulfex *od* or *bd*/Fludarabine – HSCT Conditioning Efficacy in Children

	Grigull (n=5)	**Horn (n=19)**	**Kletzel (n=30)**	**Jacobsohn (n=13)**
Busulfex schedule[†]	4 mg/kg/d *od*, days -8 to -5	Target C_{ss} 600 ng/mL (n=16), 900 ng/mL (n=3) *qid,* days -9 to -6	3.2 mg/kg/d *od*, target 3200-4800 µmol.min days -5 to -4[1]	0.8 mg/kg *qid*, target 3800-4200 µmol.min days -5 to -4

Fludarabine schedule	30 mg/m^2/d days -10 to -5	40 mg/m^2/d days -5 to -2	30 mg/m^2/d days -5 to -2	30 mg/m^2/d days -10 to -5
Engraftment[2] %	100	75% (C_{ss} 600 mg/mL) 100% (C_{ss} 900 mg/mL)	87	72
Med time to engraft (range) *days*	16	20 (16, 28)	not stated	18 (14, 25)
Relapse-free %	100	74	63	23
Survival %	100 (med 32 mth F/U)	89 (med 2 yr KM)	60 (2 yr KM)	69 (2 yr KM)

[1]Before HSCT.
[2]ANC >0.5 x 10^9/L within 100 days of HSCT. KM – Kaplan-Meier.
[†]Rabbit or equine ATG was also used.

5.2 PHARMACOKINETIC PROPERTIES

Absorption and distribution pharmacokinetics of IV busulfan has been investigated. The information presented on metabolism and elimination is based on oral busulfan.

Absorption

The pharmacokinetics of IV 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 patients receiving 1 mg/kg oral and 0.8 mg/kg IV busulfan. Low inter (CV=21%) and intra (CV=12%) patient variability on drug exposure was demonstrated through a population pharmacokinetic analysis with IV busulfan, performed on 102 patients.

Distribution

Terminal volume of distribution Vz 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%.

Metabolism

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.

Excretion

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 drug. Elimination in faeces is negligible. Irreversible protein binding

may explain the incomplete recovery. Contribution of long- lasting metabolites is not excluded.

Pharmacokinetic linearity

The dose proportional increase of drug exposure was demonstrated following intravenous busulfan up to 1 mg/kg.

Pharmacokinetic/ pharmacodynamics Relationships

The literature on oral busulfan when used in myeloablative conditioning regimens every six hours for four days suggests a therapeutic window between 900 and 1500 µMol-minute for AUC. During clinical trials with IV busulfan administered in this way, 90% of patients AUCs were below the upper AUC limit (1500 µMol-minute) and at least 80 % were within the targeted therapeutic window (900 - 1500 µMol-minute).

Special populations

The effects of renal dysfunction on IV busulfan disposition have not been thoroughly assessed. However, Busulfex was not well tolerated in a Phase I study conducted in patients with metastatic renal carcinoma where all patients had only one functioning kidney.

The effects of hepatic dysfunction on IV 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 IV busulfan data in patients over 60 years.

Pharmacokinetics in children

A continuous variation of clearance ranging from 2.49 to 3.92 mL/minute/kg was established in children from < 6 months up to 17 years old. The terminal half life ranged from 2.26 to 2.52 h. The described dosing based on body weight allows achievement of a similar targeted AUC whatever the child's age, comparable with adult plasma exposure. Inter and intra patient variabilities in plasma exposure were lower than 20% and lower than 10%, respectively.

The successful engraftment achieved in all paediatric patients during the phase II clinical trial suggests the appropriateness of the targeted AUCs of 900 to 1500 µMol-minute. Occurrence of hepatic veno-occlusive disease (HVOD) was not related to overexposure. A pharmacokinetic/pharmacodynamic 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

Genotoxicity

Busulfan was mutagenic in bacterial (*Salmonella typhimurium* and *E. coli*), insect (*Drosophila melanogaster*) and mammalian (mouse, hamster and human) cells. Busulfan induced chromosomal aberrations *in vitro* (mouse, hamster and human cells) and *in vivo* (mouse, rat, hamster and human).

Carcinogenicity

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 International Agency for Research on Cancer (IARC) as a human carcinogen. The World Health Organisation (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.

The increased risk of a second malignancy should be explained to the patient. Leukaemia patients treated with busulfan developed many different cytological abnormalities, and some developed carcinomas. Busulfan is thought to be leukemogenic.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are polyethylene glycol 400 (macrogol 400) and dimethylacetamide (DMA).

The drug product Busulfex is intended for dilution with 0.9% sodium chloride solution for injection or 5% dextrose solution for injection.

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, Busulfex must not be mixed with other medicinal products except those mentioned in Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.3 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials of Busulfex Injection must be stored at 2°-8°C in a refrigerator (Do not freeze).

Busulfex diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is stable at room temperature (25°C) for up to 8 hours but the infusion must be completed within that time. Busulfex diluted in 0.9% Sodium Chloride Injection, USP is stable at refrigerated conditions (2°-8°C) for up to 12 hours but the infusion must be completed within that time.

Freezing of diluted preparations of Busulfex is not recommended.

6.5 NATURE AND CONTENTS OF CONTAINER

Busulfex (busulfan) Injection is supplied as a sterile solution in 10 mL single-use clear glass vials each containing 60 mg of busulfan at a concentration of 6 mg/mL for intravenous use.
Busulfex is provided in packages of one or eight clear Type I glass vials.
Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING OF THE PRODUCT

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

Instruction for handling and disposal

Procedures for proper handling and disposal of anticancer drugs 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 Busulfex solution:

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

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

Busulfex must be diluted prior to use with either sodium chloride (0.9%) solution for injection or dextrose (5%) solution for injection. The quantity of the diluent must be 10 times the volume of Busulfex ensuring the final concentration of busulfan remains at approximately 0.5 mg/mL.

For example, the amount of Busulfex and diluent to be administered would be calculated as follows for a patient with a Y kg body weight receiving Z mg/kg busulfan:

- Quantity of Busulfex:

  $$\frac{Y\ (kg) \times Z\ (mg/kg)}{6\ (mg/mL)} = A\ mL\ of\ Busulfex\ to\ be\ diluted$$

  Y: body weight of the patient in kg
  Z: dose on a mg/kg basis

- Quantity of diluent:

  (A mL Busulfex) x (10) = B mL of diluent

To prepare the final solution for infusion, add (A) mL of Busulfex to (B) mL of diluent (sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose solution for injection 5%).

Intravenous Injection

1) 0.9% Sodium Chloride Injection USP

Vial Size (mL)	Volume of Diluent to be Added (mL) (for a 70 kg patient)	Approximate Available Volume (mL) (for a 70 kg patient)	Nominal Concentration per mL
10	93	102	0.5 mg

2) 5% Dextrose Injection, USP

Vial Size (mL)	Volume of Diluent to be Added (mL) (for a 70 kg patient)	Approximate Available Volume (mL) (for a 70 kg patient)	Nominal Concentration per mL
10	93	102	0.5 mg

By way of example, for a 70 kg patient, the amount of drug to be administered would be calculated as follows:

(70 kg patient) × (0.8 mg/kg) / (6 mg/mL) = 9.3 mL Busulfex (56 mg total dose).
To prepare the final solution for infusion, add 9.3 mL of Busulfex to 93 mL of diluent (normal saline or D5W) as calculated below:

(9.3 mL Busulfex) × (10) = 93 mL of either diluent plus the 9.3 mL of Busulfex to yield a final concentration of busulfan of 0.54 mg/mL (9.3 mL × 6 mg/mL / 102.3 mL = 0.54 mg/mL).

Preparation of the solution for infusion

Due to incompatibility, do not use any infusion components containing polycarbonate with Busulfex.
Using a non polycarbonate syringe fitted with a needle:

- Remove the calculated volume of Busulfex from the vial.
- Dispense the contents of the syringe into an intravenous bag (or syringe) which already contains the calculated amount of the selected diluent. Always add Busulfex to the diluent, not the diluent to Busulfex. Do not put Busulfex into an intravenous bag that does not contain sodium chloride (0.9%) solution for injection or dextrose (5%) solution for injection.
- Mix thoroughly by inverting several times.

After dilution, 1 mL of solution for infusion contains 0.5 mg of busulfan. Diluted Busulfex 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 (0.9%) solution for injection or dextrose(5%) solution for injection.

Do not flush residual drug in the administration tubing as rapid infusion of Busulfex has not been tested and is not recommended.

The entire prescribed Busulfex dose should be delivered over two hours.

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 drug solution prior to beginning the actual Busulfex infusion and then flushed with sodium chloride (0.9%) solution for injection or dextrose (5%) solution for injection.

A nylon or polyester filter should be used if Busulfex is administered via an in-line filter or a filter fitted with an infusion set.

Do not infuse concomitantly with another intravenous solution.

Busulfex contains no antimicrobial agent. Product is for single use in one patient only. Only a clear solution without any particles should be used. Opened vials should be used immediately to assure sterility. Discard any residue.

Busulfex should not be given by rapid intravenous, *bolus* or peripheral injection.

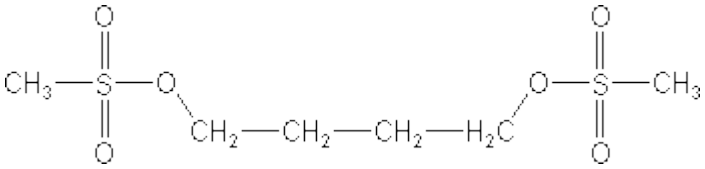
6.7 PHYSICOCHEMICAL PROPERTIES

Busulfan, 1,4-butanediol dimethanesulfonate

Molecular Formula: $C_6H_{14}O_6S_2$

Molecular Weight: 246.31

Chemical structure



CAS number

CAS Registry Number: 55-98-1

7 MARKETING AUTHORISATION HOLDER

Tzamal Bio-Pharma LTD., 20 Hamagshimim st., Petah-Tikva, Israel

8 MANUFACTURER

Otsuka Pharmaceutical Development & Commercialization, Inc., USA
Maryland, USA

9 MARKETING AUTHORISATION NUMBER

117 29 29837

Revised in July 2023 according to MOHs guidelines.

BUS_PI_TZ_072023