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Antineoplastic

Caution: Must be diluted prior to use.

BUSULFEX[®] (busulfan) injection
6 mg/mL

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 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.

ACTIONS AND CLINICAL PHARMACOLOGY

Busulfan is a potent cytotoxic agent and a bifunctional alkylating agent. In aqueous media, release of the methanesulfonate group produces carbonium ions, which can alkylate DNA, thought to be an important biological mechanism for its cytotoxic effect. Current literature suggests that high AUC values (>1,500 $\mu\text{Mol}\cdot\text{min}$) may be associated with an increased risk of developing hepatic veno-occlusive disease and/or seizures.

Mean C_{max} , AUC, $T_{1/2}$ and plasma clearance are provided below for oral busulfan and BUSULFEX (busulfan) (See PHARMACOLOGY).

Parameter	Oral Busulfan	BUSULFEX
C_{max} (ng/mL) (range) (CV%)	870 (30%)	1,167 (12%)
AUC ($\mu\text{Mol}\cdot\text{min}$) (CV%)	1,396 (24%)	1,156 (14%)
$T_{1/2}$ (hr) (CV%)	3.55 (33%)	3.11 (10%)
Plasma Clearance (ml/min) (CV%)	195 (27%)	182 (16%)

Intravenous BUSULFEX had a more consistent pharmacokinetic profile than oral busulfan among patients.

Busulfan achieves concentrations in the cerebrospinal fluid approximately equal to those in plasma. Irreversible binding to plasma elements, primarily albumin, has been estimated to be $32.4 \pm 2.2\%$ which is consistent with the reactive electrophilic properties of this alkylator.

Busulfan is predominantly metabolized through conjugation with glutathione, both spontaneously and through glutathione S-transferase (GST).

INDICATIONS AND CLINICAL USAGE

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.

CONTRAINDICATIONS

BUSULFEX (busulfan) Injection is contraindicated in patients who are sensitive, allergic or intolerant of the drug or its vehicle.

WARNINGS

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 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. The most frequent serious consequence of treatment with BUSULFEX at the recommended dose and schedule is profound myelosuppression, occurring in all patients. Severe granulocytopenia, thrombocytopenia, anemia, or any combination thereof may develop. Frequent complete blood counts, including white blood cell differentials, and quantitative platelet counts should be monitored during treatment and until recovery is achieved. 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 following transplant (median neutropenic period of 6 days). Prophylactic or empiric use of anti-infectives (bacterial, fungal, viral) should be considered for prevention and management of infections during the neutropenic period. Thrombocytopenia ($<25,000$ /mm or requiring platelet transfusion) at a median of 5-6 days occurred in 98% of patients. Anemia (hemoglobin <8.0 g/dL) occurred in 69% of patients. Platelet and red blood cell support should be employed as medically indicated. Busulfan may be a human carcinogen. Several cases of leukemia have occurred 5-8 years following oral busulfan treatment.

Ovarian suppression and amenorrhea commonly occur in premenopausal women undergoing chronic, low-dose busulfan therapy for chronic myelogenous leukemia. Sterility, azoospermia, and testicular atrophy have been reported in male patients. Bronchopulmonary dysplasia with pulmonary fibrosis is a rare complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).

Pregnancy: Busulfan can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If BUSULFEX is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for busulfan in human and animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Hepatic Insufficiency: BUSULFEX has not been administered to patients with hepatic insufficiency. Patients who have received prior radiation therapy, greater than three cycles of chemotherapy, or a prior progenitor cell transplant may be at an increased risk of developing hepatic veno-occlusive disease with the recommended BUSULFEX dose and regimen.

PRECAUTIONS

General: At the recommended dosage of BUSULFEX (busulfan), profound myelosuppression is universal, and can manifest as neutropenia, thrombocytopenia, anemia, or a combination thereof. The patient should be monitored for signs of local or systemic infection or bleeding and their hematologic status should be evaluated frequently.

Caution should be exercised when administering the recommended dose of BUSULFEX to patients with a history of seizure disorder, head trauma, or receiving other potentially epileptogenic drugs. It is recommended that appropriate anti-convulsant therapy (e.g. phenytoin, benzodiazepines) be administered prophylactically to such patients. Seizures have been reported with high dose oral busulfan treatment.

Information for Patients: The increased risk of a second malignancy should be explained to the patient.

Monitoring: Patients receiving BUSULFEX should be monitored daily with a complete blood count, including differential count and quantitative platelet count, until engraftment has been demonstrated.

To detect hepatotoxicity, which may herald the onset of hepatic veno-occlusive disease, serum transaminases, alkaline phosphatase, and bilirubin should be evaluated daily through transplant day 28.

Drug Interactions: There are no known or manifest interactions with the antifungal agent fluconazole, however, itraconazole decreases busulfan clearance by up to 25%, and may produce an AUC > 1500 µMol/min in some patients. Metronidazole significantly increases plasma levels of busulfan, which may lead to treatment-related toxicities.

It has been reported that phenytoin increases the clearance of busulfan by 10% or more, possibly due to the induction of GST. Since virtually all patients are empirically treated with anticonvulsants (phenytoin, clonazepam), the dose of BUSULFEX should be adjusted to account for enhanced clearance (see DOSAGE AND ADMINISTRATION).

Busulfan is eliminated from the body via conjugation with glutathione. Since acetaminophen may decrease glutathione levels in blood and tissues, concurrent or prior use (<72 hours) may result in modified busulfan clearance.

Pediatric: BUSULFEX conditioning regimen above has been used in pediatric patients as young as 5 months of age. The use of BUSULFEX has not been fully investigated in the pediatric population.

Older patients: Patients older than 50 years of age (n=23) have been successfully treated with BUSULFEX as measured by myeloablation and engraftment and which was well tolerated in these patients.

Gender/Race: Dosing with BUSULFEX does not need adjustment for gender or race.

Renal Insufficiency: Studies in renally impaired patients have not been conducted; however, busulfan is not significantly metabolized by the kidney or excreted in the urine.

ADVERSE REACTIONS

Treatment with BUSULFEX (busulfan) at the recommended dose and schedule will result in profound myelosuppression in 100% of patients, including granulocytopenia, thrombocytopenia, anemia, or a combined loss of formed elements

of the blood. All patients received 0.8 mg/kg BUSULFEX as a two-hour infusion every 6 hours for 16 doses over four days. Ninety percent (90%) of patients receiving this dose of BUSULFEX maintained AUCs less than 1,500 $\mu\text{Mol}\cdot\text{min}$ which has generally been considered efficacious in terms of myelosuppression, engraftment and relapse prevention, and safe with respect to minimizing the risk of HVOD, acute infection and other causes of morbidity.

Patients undergoing high-dose busulfan therapy followed by hematopoietic progenitor cell transplantation experience a wide range of adverse experiences. These may result from their disease, prior therapy, concomitant cytotoxic drugs or other medications, as well as from busulfan.

Hepatic veno-occlusive disease developed in 5.8% (6/103) (1 of 42 autologous and 5 of 61 allogeneic patients) of patients treated with BUSULFEX in these studies and was fatal in 1.9% (2/103) (2 of 61 allogeneic patients, one of which had a prior transplant). Of the two mortalities, one patient was heavily pre-treated and had undergone a prior transplant. Of the six patients identified by site investigators, four met the Jones' Criteria, including the two mortalities and two of the other identified cases, which both resolved. Therefore, the incidence of HVOD per the Jones' Criteria was 3.8% (4/103). Hepatic veno-occlusive disease was reported in 17% of patients treated with high-dose oral busulfan in the transplant setting; 5-6% of patients died. Serum transaminases, alkaline phosphatase, and bilirubin should be monitored regularly for early detection of hepatotoxicity.

As reported in the literature, HVOD is recognized as a common complication of pretransplant preparative regimens, and various preparative regimens have been implicated. Both oral and IV busulfan have been associated with the occurrence of HVOD. The incidences of HVOD were compared in patients undergoing allogeneic transplantation using an oral or IV busulfan /cyclophosphamide (BuCy2) conditioning regimen (see Table 1 below).

Table 1. Incidences of HVOD in Patients Undergoing Allogeneic Transplantation: IV Bu vs. Oral Bu

Publication	Population	Conditioning regimen	N		HVOD incidence (%)		HVOD criteria
			IV Bu	Oral Bu	IV Bu	Oral Bu	
Kashyap	CML, acute leukemia, MDS, NHL, MM	BuCy2	61	30	8	33	Clinical
					5	20	Baltimore
Lee	AML, CML, ALL, MDS, other	BuCy2	55	186	18.5	41.7	Seattle

BuCy2: IV Busulfan was administered at 0.8 mg/kg over 2 hours every 6 hours for 16 doses (days -7 to -4). Oral busulfan was administered at a fixed dose of 1 mg/kg adjusted ideal body weight every 6 hours for a total of 16 dose (days -7 to -4). Cyclophosphamide was then given at 60 mg/kg IV over 1 hour daily for 2 doses (days -3 and -2).

Although not seen with BUSULFEX, cardiac tamponade (often fatal) frequently preceded by abdominal pain and vomiting, has been reported in thalassemia patients who received high doses of oral busulfan and cyclophosphamide.

Clinical Trial and Literature Database Adverse Drug Reactions:

Adverse reaction information is primarily derived from two clinical studies (N=103) of BUSULFEX (Tables 2 and 3) and the literature database (Table 4). The BUSULFEX studies prospectively identified events to be recorded and adverse experience incidence rates were calculated. All patients received 0.8 mg/kg BUSULFEX as a two-hour infusion every six hours for 16 doses over four days. Information from the literature database is limited to those events selected by the authors for reporting. Incidence is approximated by considering the number of patients (N) equal to the sum of the patients included in those studies, which reported a particular event. Seventy-seven percent (77%) of the patients in the literature database received a total busulfan dose of 16 mg/kg. Other than the expected bone marrow suppression often resulting in opportunistic infections, which can be lethal, the most clinically relevant adverse events are for the liver, lung and brain.

Table 2: Summary of the Incidence ($\geq 20\%$) of Hematologic Adverse Events in Patients who Received BUSULFEX Prior to Autologous or Allogeneic Hematopoietic Progenitor Cell Transplantation (n=103)

HEMATOLOGICAL ADVERSE EVENTS	PERCENT INCIDENCE (# Patients)	
	Anemia	Grade 3 (65-79 g/L) Grade 4 (<65 g/L)
Leukopenia	Grade 3 ($1.0 \times 10^9 - 1.9 \times 10^9$ cells/L) Grade 4 (< 1.0×10^9 cells/L)	0 (0) 96 (99)
Thrombocytopenia	Grade 3 ($25 \times 10^9 - 49 \times 10^9$ cells/L) Grade 4 (< 25×10^9 cells/L)	2 (2) 91 (94)
Median No. Platelet transfusions per patient Autologous (N=41) Allogeneic (N=60)	3 6	
Median No. Red Blood Cells transfusions per patient Autologous (N=37) Allogeneic (N=53)	3 4	

Table 3: Summary of the Incidence ($\geq 20\%$) of Non-Hematologic Adverse Events in Patients who Received BUSULFEX prior to Autologous or Allogeneic Hematopoietic Progenitor Cell Transplantation (n=103) through Blood and Marrow Transplant (BMT) Day +28

NON- HEMATOLOGIC ADVERSE EVENTS*	PERCENT INCIDENCE
BODY AS A WHOLE	
Fever	87
Headache	69
Abdominal Pain	62
Asthenia	56
Chills	47
Pain	41
Allergic Reaction	32
Edema General	27
Inflammation at Injection site	23
Chest pain	22
CARDIOVASCULAR SYSTEM	
Tachycardia	50
Thrombosis	27
Hypertension	25
Vasodilation	23
DIGESTIVE SYSTEM	
Nausea	97
Stomatitis (Mucositis)	96
Vomiting	91
Anorexia	80
Diarrhea	80
Dyspepsia	40
Constipation	31
Rectal Disorder	24
METABOLIC AND NUTRITIONAL SYSTEM	
Hypomagnesemia	64
Hypokalemia	58
Hyperglycemia	57
Hypocalcemia	43
Hyperbilirubinemia	37
Edema	37
SGPT Elevation	25
Hypophosphatema	21
NERVOUS SYSTEM	
Insomnia	80
Anxiety	65
Dizziness	26
Depression	20
RESPIRATORY SYSTEM	
Rhinitis	44
Cough	36
Lung Disorder	34
Pharyngitis	27
Epistaxis	23
Dyspnea	23

SKIN AND APPENDAGES	
Rash	50
Pruritus	29

*All reported adverse events regardless of severity (toxicity grades 1-4)

Safety assessment of high dose oral busulfan-based regimens prior to hematopoietic progenitor cell transplantation as reported from the literature is limited by the information selected for inclusion into published reports. Available adverse events information is derived from the Subset Literature Database and from the Overall Literature Database when it was provided. The denominator for incidence reporting is the sum of the patients in those studies, which reported that event. The reported non-hematologic general toxicities are noted in Table 4.

Table 4: Percent Incidence of Non-hematologic Adverse Events Reported in a Review of 43 Publications Using High-Dose Oral Busulfan as a Conditioning Regimen Prior to Hematopoietic Progenitor Cell Transplant

NON- HEMATOLOGIC ADVERSE EVENTS	PERCENT INCIDENCE (# Patients)
Mucositis/Stomatitis	85 (483/571)
Fever	83 (379/457)
Nausea/Vomiting	72 (52/72)
Rash	67 (38/57)
Diarrhea	58 (28/48)
Acute GVHD	45 (187/413)
Chronic GVHD	35 (301/848)
Infection	31 (128/407)
Hemorrhagic cystitis	15 (149/968)
Hepatic veno-occlusive disease	13 (153/1196)
Interstitial pneumonitis	11 (45/415)
Seizures	3 (15/482)

Acute graft-versus-host disease (GVHD) incidence was 26% (1153/4367 patients) in the Overall Literature Database. Chronic graft versus host disease of all grades was 28% (793/2846 patients) in the Overall Literature Database and 35% (301/848 patients) in the Subset Literature Database. The incidence of infection was 43% (911/2099 patients) in the Overall Literature Database and 31% (128/407 patients) in the Subset Literature Database. Allogeneic transplants were associated with a higher incidence of infection than autologous transplants (38% versus 22% respectively). The reported incidence of hepatic veno-occlusive disease (HVOD) was 17% (960/5798) in the Overall Literature Database and 13% (153/1196) in the Subset Literature Database [14% (43/316) for autologous and 12% (106/856) for allogeneic transplantation]. At least one publication reported that patients whose initial area under the plasma busulfan curve (AUC) >1,500 µMol-min were at an increased risk of developing VOD. Interstitial pneumonitis was reported at an incidence of 10% (262/2633) in the Overall Literature Database and 11% (45/415) in the Subset Literature Database. The incidence among allogeneic transplants was 11% (39/348) compared with 12% (4/34) for autologous transplants. Seizures were reported at an incidence of 7.4% (170/2303 patients) in the Overall Literature Database and 3.1% (15/482 patients) in the Subset Literature Database. For patients who received prophylactic anticonvulsant therapy, there was a 1.7% (1/60) incidence of seizure.

The following sections describe clinically significant events occurring in the two BUSULFEX clinical trials regardless of an attribution.

Hematologic: At the indicated dose and schedule, BUSULFEX produced profound myelosuppression in 100% of patients. Severe leukopenia occurred in 92% of patients, thrombocytopenia in 86%, and anemia in 50%. Following hematopoietic progenitor cell infusion, recovery of neutrophil counts to ≥ 500 cells/mm³ occurred at median day 10 and 13, for autologous and allogeneic patients, respectively.

Gastrointestinal: Gastrointestinal toxicities were frequent and generally considered to be related to the drug. Few were categorized as serious. Mild/moderate nausea occurred in 93% of patients and mild/moderate vomiting occurred in 91% through blood and marrow transplant (BMT) day 28; nausea was severe in 4%. The incidence of vomiting during BUSULFEX administration (BMT Day -7 to -4) was 38% (39/103). Stomatitis was severe in 13% of the patients and mild/moderate in 83%; 6% of patients developed mild/moderate esophagitis. Severe anorexia occurred in 16% of patients and was mild/moderate in 64%. Diarrhea was severe in 6% of patients and mild/moderate in 74%. Mild/moderate constipation occurred in 31% of patients; ileus developed in 7% and was severe in 2%. Forty percent (40%) of patients reported mild/moderate dyspepsia. Two percent (2%) of patients experienced mild hematemesis. Mild/moderate rectal discomfort occurred in 24% of patients. One patient (1%) developed gastrointestinal bleeding, which was severe and considered serious.

Hepatic: Hyperbilirubinemia was observed in 37% of patients; it was considered life threatening in 3% and associated with veno-occlusive disease, severe in 8%, and mild/moderate in 26%. It was associated with graft-versus-host disease in six patients. Severe serum glutamic pyruvic transaminase (SGPT) elevations occurred in 2% of patients. There were mild/moderate increases in SGPT in 23% and serum glutamic oxaloacetic transaminase (SGOT) in 10%. Alkaline phosphatase increases were mild/moderate in 12% of patients. Mild/moderate jaundice developed in 8% of patients; it was associated with graft-versus-host disease or hepatic veno-occlusive disease in 4%. Mild/moderate hepatomegaly developed in 5% of patients.

Hepatic veno-occlusive disease: Hepatic veno-occlusive disease (HVOD) is a recognized potential complication of conditioning therapy prior to transplant. Six of 103 patients (6%) experienced HVOD; it was fatal in 2%, severe in 2% and moderate in 2%.

Graft Versus-Host Disease: Graft-versus-host disease developed in 15% of patients (9/61) receiving allogeneic transplants; it was severe in 2%, and mild/moderate in 13%. After BMT day +28, an additional 3% developed GVHD, which was considered serious.

Edema: Seventy-one percent (71%) of patients exhibited some form of edema, hypervolemia, or weight increase; all events were reported as mild/moderate. One patient (<1%) developed moderate capillary leak syndrome.

Infection/Fever: Although 39% of patients (40/103) experienced one or more episodes of infection, 83% (33/40) were rated as mild/moderate. Pneumonia was fatal in 1% and life threatening in 3% of patients. Other infections were considered severe in 3% of patients. Fever was reported in 87% of patients; it was mild/moderate in 84% and severe in 3%. Forty-seven percent (47%) of patients experienced chills which were mild/moderate in 46% and severe in 1%.

Cardiovascular: Mild/moderate tachycardia was reported in 50% of patients. Other rhythm abnormalities, which were all mild/moderate, included arrhythmia (3%), atrial fibrillation (2%), ventricular extrasystoles (1%), and bradycardia (1%). Mild/moderate thrombosis occurred in 27% of patients, usually associated with the central venous catheter. One patient (1%) experienced a severe femoral artery thrombosis, which was controlled with coagulation therapy. Hypertension was reported in 25% of patients and was severe in 1%. Hypotension occurred in 17% of patients and was severe in 2%. Mild vasodilation was reported in 23% of patients. Other cardiovascular events included mild cardiomegaly, mild ECG abnormality, moderate pericardial effusion, moderately decreased ejection fraction, and moderate pericarditis; all were reported at an incidence of $\leq 3\%$ and mainly in the post-cyclophosphamide phase.

Pulmonary: Mild/moderate dyspnea occurred in 22% of patients and was severe in 2%. One patient (1%) experienced severe hyperventilation; and in 4 (4%) additional patients, it was mild/moderate. Respiratory failure occurred in two patients (2%), either in conjunction with VOD and cerebral hemorrhage or pneumonia. Mild/moderate rhinitis and cough were reported in 44% and 36% of patients, respectively; most events were mild. Epistaxis events were mild in 22% of patients and moderate in 1%. Alveolar hemorrhages were severe in 1% and life-threatening in 1% of patients. Other pulmonary events that were mild/moderate included abnormal breath sounds (34%), pharyngitis (27%), hiccup (17%), asthma (7%), atelectasis (3%), pleural effusion (3%), and hypoxia (1%).

Neurologic: The most commonly reported events involved nonspecific, global disturbances of the central nervous system; insomnia (80%), anxiety (65%), dizziness (26%), and depression (20%). Severity was mild/moderate except for one patient (1%) who experienced severe insomnia. One patient (1%) developed a life-threatening cerebral hemorrhage and a coma as a terminal event following multi-organ failure after HVD. Other events considered severe included delirium (1%), nervousness (1%), confusion (2%), hallucination (1%), agitation (1%), and encephalopathy (1%). One patient (1%) experienced a mild seizure while receiving cyclophosphamide, however 99% of patients were prophylactically treated with phenytoin.

Renal: Creatinine was mildly or moderately elevated in 17% of patients. BUN was increased in 2% of patients and to a severe degree in 1%. Thirteen percent (13%) of patients experienced dysuria, 11% oliguria, and 9% hematuria; all were mild/moderate except for 1% severe hematuria. Moderate renal insufficiency was reported in 2% of patients.

Skin: Mild/moderate rash (50%) and pruritus (29%) were reported; both conditions were predominantly mild. Alopecia was mild in 12% of patients and moderate in 3%. Mild vesicular rash was reported in 8% of patients and mild/moderate maculopapular rash in 7%.

Metabolic: Hyperglycemia was observed in 57% of patients and was severe in 5%. More than half of the patients experienced some electrolyte disturbance, usually a decrease, and none were considered serious. Hypomagnesemia was mild/moderate in 64% of patients; hypokalemia was mild/moderate in 57% and severe in 1%; hypocalcemia was mild/moderate in 40% and severe in 3%; hypophosphatemia was mild/moderate in 21%; and hyponatremia was mild/moderate in 3%.

Other: Other events reported include: headache (mild/moderate 65%, severe 4%), abdominal pain (mild/moderate 61%, severe 2%), asthenia (mild/moderate 56%, severe 1%), unspecified pain (mild/moderate 40%, severe 1%), allergic reaction (mild/moderate 31%, severe 1%), injection site inflammation (mild/moderate 23%), injection site pain (mild/moderate 17%), chest pain (mild/moderate 23%), back pain (mild/moderate 18%), myalgia (mild/moderate 17%) and arthralgia (mild/moderate 13%).

Post-Marketing Adverse Drug Reactions:

The following additional adverse events have been spontaneously reported during the post-marketing use of Busulfex: febrile neutropenia; tumor lysis syndrome; thrombotic micro-angiopathy (TMA); severe bacterial, viral (e.g., cytomegalovirus viraemia) and fungal infections; and sepsis. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In addition, premature menopause, ovarian failure and hypogonadism were reported with unknown frequency.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The principal toxic effect is profound bone marrow hypoplasia/aplasia and pancytopenia, but the central nervous system, liver, lungs, and gastrointestinal tract may be affected.

There is no known antidote to busulfan overdose other than hematopoietic progenitor cell transplantation. The hematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated. In the absence of hematopoietic progenitor cell transplantation, the recommended dosage for BUSULFEX would constitute an overdose of busulfan. Survival after a single 140 mg dose of Myleran® Tablets in an 18 kg, 4-year old child has been reported. Inadvertent administration of a greater than normal dose of oral busulfan (2.1 mg/kg; total dose of 23.3 mg/kg) occurred in a 2-year old child prior to a scheduled bone marrow transplant without sequelae. An acute dose of 2.4 g was fatal in a 10-year old boy. There has been one report that busulfan is dialyzable, thus dialysis should be considered in the case of overdose. Busulfan is metabolized by conjugation with glutathione, thus administration of glutathione may be considered.

DOSAGE AND 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.

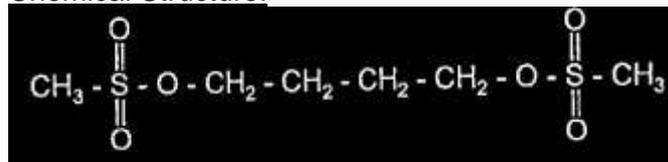
Note: Instructions for reconstitution and special precautions can be found under the section PHARMACEUTICAL INFORMATION, subsection RECONSTITUTED SOLUTIONS.

PHARMACEUTICAL INFORMATION: Drug Substance:

Common Name: Busulfan

Chemical Names: 1,4-butanediol-dimethanesulfonate

Chemical Structure:



Molecular Formula: C₆H₁₄O₆S₂

Molecular Weight: 246.31

Description: Busulfan is a white crystalline solid that is only very slightly soluble in water, sparingly soluble in acetone and slightly soluble in ethanol. The pH profile is not applicable since the drug product is only very slightly soluble in water.

Melting Range: 115-118° C

Composition:

Active Ingredient: Each 10 mL vial contains 60 mg busulfan, USP.

Non-medicinal Ingredients: Each 10 mL vial contains the ingredients dimethylacetamide and polyethylene glycol 400, NF, in quantities of 3.333 mL and 6.667 mL, respectively.

Stability and Storage Recommendations: Unopened vials of BUSULFEX injection must be stored under refrigerated conditions between 2°-8°C (36°-46°F). 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.

Reconstituted Solutions: Preparation for Intravenous Administration: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Discard unused portion. BUSULFEX must be diluted prior to use with either 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D5W). The diluent quantity should be 10 times the volume of BUSULFEX injection, so that the final concentration is approximately 0.5 mg/mL. 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).

All transfer procedures require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing.

Using a syringe fitted with a needle, remove the calculated volume of BUSULFEX Injection from the vial and dispense the contents of the syringe into an intravenous bag (or syringe) that already contains the calculated amount of either normal saline or D5W, making sure that the drug flows into and through the solution. DO NOT put the BUSULFEX into an intravenous bag, which does not contain normal saline or D5W. Always add the BUSULFEX to the diluent, not the diluent to the BUSULFEX. Mix thoroughly by inverting several times.

Infusion pumps should be used to administer the diluted BUSULFEX solution. Set the flow rate of the pump to deliver the entire prescribed BUSULFEX dose over two hours. Prior to and following each infusion, flush the indwelling catheter line with approximately 5 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. DO NOT infuse concomitantly with another intravenous solution of unknown compatibility. WARNING: BUSULFEX SHOULD NOT BE GIVEN BY RAPID INTRAVENOUS INJECTION OR BOLUS.

Parenteral Products: 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:

$(70 \text{ kg patient}) \times (0.8 \text{ mg/kg}) / (6 \text{ mg/mL}) = 9.3 \text{ mL BUSULFEX (56 mg total dose)}$.

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:

$(9.3 \text{ mL BUSULFEX}) \times (10) = 93 \text{ mL of either diluent plus the 9.3 mL of BUSULFEX to yield a final concentration of busulfan of } 0.54 \text{ mg/mL } (9.3 \text{ mL} \times 6 \text{ mg/mL} / 102.3 \text{ mL} = 0.54 \text{ mg/mL})$.

Special Instructions: Preparation and Administration Precautions: As with other cytotoxic compounds, caution should be exercised in handling and preparing the solution of BUSULFEX. Skin reactions may occur with accidental exposure. The use of gloves is recommended. If BUSULFEX or diluted BUSULFEX solution contacts the skin or mucosa, wash the skin or mucosa thoroughly with water.

DO NOT USE POLYCARBONATE SYRINGES OR POLYCARBONATE FILTER NEEDLES WITH BUSULFEX.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no

general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

AVAILABILITY OF DOSAGE FORMS

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 vials. Formulation and use in bone marrow transplant and other conditions covered by United States Patent numbers 5,430,057 and 5,559,148 and Canadian Patent number CA2171738 and European Union Patent number EP0725637B1.

Manufacturer:

Otsuka Pharmaceutical Development & Commercialization, Inc.

Marketing Authorization Holder:

Tzamal Bio-Pharma, Petah-Tikva.

Registration number: 117 29 29837 00