# PRODUCT MONOGRAPH

# [Pr]BUSULFEX®
# (Busulfan)

**6 mg/mL Injection**

**Antineoplastic**

Otsuka Pharmaceutical Co., Ltd.
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Otsuka
Otsuka Canada Pharmaceutical Inc.

# PRODUCT MONOGRAPH

## NAME OF DRUG

$^{Pr}$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 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.

## 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 μMol•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 IV BUSULFEX (busulfan) (See PHARMACOLOGY).

| **Parameter** | **Oral Busulfan** | **BUSULFEX IV** |
|---|---|---|
| $C_{max}$ (ng/mL) (range) (CV%) | 870 (30%) | 1,167 (12%) |
| AUC (μMol•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 predominately metabolized through conjugation with glutathione, both spontaneously and through glutathione S-transferase (GST).

## INDICATIONS AND CLINICAL USE

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, including: acute lymphocytic leukemia, acute non-lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non-Hodgkin's lymphoma, Hodgkin's disease, multiple myeloma, and myelodysplastic syndrome. In any regimen utilizing BUSULFEX, the patient's disease status should either be refractory to other therapies or carry sufficiently high risk for recurrence of disease, so that progenitor cell transplant is the treatment of choice, in the opinion of a qualified physician.

## 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 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.

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 x $10^9$/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/$mm^3$ 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. Secondary malignancy has been reported in patients treated with BUSULFEX. Several cases of leukemia have occurred 5-8 years following oral busulfan treatment. Busulfan may also cause cellular dysplasia.

BUSULFEX may cause temporary or permanent infertility in females and males. 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 after 4 years of 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. BUSULFEX should not be administered to pregnant women or women who may possibly be pregnant. 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. Women of childbearing potential should be advised to use effective contraception during and up to 6 months after treatment. BUSULFEX may damage spermatozoa and testicular tissue, resulting in possible genetic fetal abnormalities. Men treated with BUSULFEX are advised not to father a child during and up to 6 months after treatment.

**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, breast-feeding should be discontinued during treatment

with BUSULFEX. The safety of BUSULFEX in nursing women has not been established.

**Hepatic Insufficiency:** BUSULFEX has not been administered to patients with hepatic insufficiency. However, patients who have received prior radiation therapy, greater than or equal to 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 (see ADVERSE REACTIONS).

## PRECAUTIONS

**General:** At the recommended dosage of BUSULFEX (busulfan), profound myelosuppression is universal, and can be manifested 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 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 be administered prophylactically to such patients (see Drug Interactions). Seizures have been reported with high dose oral busulfan treatment.

**Information for Patients:** The risks associated with the use of BUSULFEX, such as the risk of a second malignancy or the risk of veno-occlusive liver disease, as well as the plan for regular monitoring during therapy should be explained to the patient. Patients of reproductive potential should be advised of the potential risk to a fetus and the need to use effective contraception during and after treatment with BUSULFEX, and to inform their healthcare professional of a known or suspected pregnancy. Patients should be informed of the possibility of developing low blood cell counts and the need for hematopoietic progenitor cell infusion. They should also be instructed to immediately report to their healthcare professional if fever develops.

**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. Cardiac function should be monitored regularly in patients receiving BUSULFEX.

**Drug Interactions:** There are no known or manifest interactions with the antifungal agent fluconazole; however, administration of itraconazole to patients receiving busulfan may result in reduced busulfan clearance. It may increase plasma concentration of busulfan, resulting in the enhancement of BUSULFEX activity. 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.

**Special Populations**

**Pediatric:** A 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 six hours for 16 doses over four days. Ninety percent (90%) of patients receiving this dose of BUSULFEX maintained AUCs less than 1,500 μMol•min which has generally been considered efficacious in terms of myelosuppression, engraftment, and relapse prevention, and safe with respect to minimizing the risk of VOD, 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 (HVOD) 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[30] | CML, acute leukemia, MDS, NHL, MM | BuCy2 | 61 | 30 | 8 | 33 | Clinical |
| | | | | | 5 | 20 | Baltimore |
| Lee[31] | 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 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 that 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 that can be lethal, the most clinically relevant adverse events are for the liver, lung and brain.

**Table 2: Summary of the Incidence (≥ 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<br>Grade 3 (65 – 79 g/L)<br>Grade 4 (<65 g/L ) | <br>62 (64)<br>6 ( 6) |
| Leukopenia<br>Grade 3 (1.0 x $10^9$ – 1.9 x $10^9$ cells/L)<br>Grade 4 (<1.0 x $10^9$ cells/L) | <br>0 (0)<br>96 (99) |
| Thrombocytopenia<br>Grade 3 (25 x $10^9$ – 49 x $10^9$ cells/L)<br>Grade 4 (<25 x $10^9$ cells/L) | <br>2 (2)<br>91 (94) |
| Median number of Platelet transfusions per patient<br>Autologous (n=41)<br>Allogeneic (n=60) | <br>3<br>6 |
| Median number of Red Blood Cell transfusions per patient<br>Autologous (n=37)<br>Allogeneic (n=53) | <br>3<br>4 |

**Table 3: Summary of the Incidence (≥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-HEMATOLOGICAL 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 |
| Hypophosphatemia | 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 event 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 that 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 (52/172) |
| 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 $\geq$500 cells/mm$^3$ 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 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 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 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 in 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 graft versus host disease that was considered serious.

**Edema:** Seventy-one percent (71%) of patients exhibited some form of edema, hypervolemia, or weight increase; all events were 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 or 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%. 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 ≤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 HVOD 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 HVOD. 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 mild/moderately elevated in 17% of patients. BUN was increased in 2% of patients and to a severe degree in 1%. 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%; 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%) or 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; sepsis; and tooth hypoplasia. 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.

## 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 overdosage, 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 (busulfan) 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 an overdose. Busulfan is metabolized through conjugation with glutathione, thus

administration of glutathione may be considered.

## DOSAGE AND ADMINISTRATION

BUSULFEX (busulfan) 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 anticonvulsants, such as phenytoin, to prevent seizures, as busulfan is known to cross the blood brain barrier. Antiemetics of the 5-$HT_3$ 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 x (height -152); IBW (kg, women) = 45 + 0.91 x (height -152). Adjusted ideal body weight (AIBW) should be calculated as follows: AIBW = IBW + 0.25 x (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, no sooner than six hours following the $16^{th}$ dose of BUSULFEX. Based on the literature evidence, there appears to be safety benefits in patients with hematologic malignancies receiving cyclophosphamide 6 hours or more following BUSULFEX.

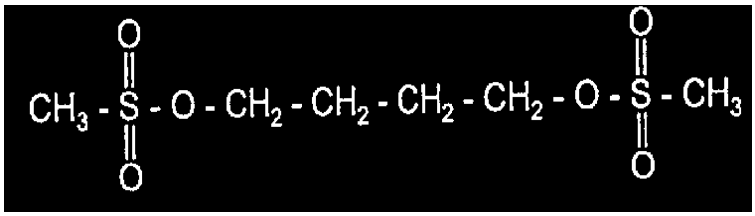
## PHARMACEUTICAL INFORMATION

**Drug Substance:**

Common Name: Busulfan

Chemical Names: 1,4-butanediol-dimethanesulfonate

Chemical Structure:



Molecular Formula: $C_6H_{14}O_6S_2$

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 ºC

**Composition:**

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

Non-medicinal Ingredients: Each 10 mL vial also 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 ºC (36 - 46 ºF).

BUSULFEX diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP is stable at room temperature (25 ºC) 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) x (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) x (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 x 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 Injection into an intravenous bag that 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 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 kg patient) x (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) x (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 x 6 mg/mL / 102.3 mL = 0.54 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 eight vials.

## PHARMACOLOGY

Busulfan is an alkylating agent producing DNA cross-linking and chromosomal damage that can be lethal to rapidly dividing cells. At the low end of the active dose range, busulfan causes a selective depression of granulocytopoiesis. Increasing doses lead to progressive general myelotoxicity culminating in marrow ablation due to cell death.

In several animal species and man, oral doses of busulfan result in a prolonged depression in hemopoietic progenitor cells. The drug reduces the ability of the cell to differentiate progeny and produces a delayed, but prolonged, hematological depression. High doses cause significant DNA and genetic damage and are myeloablative, killing the marrow cells.

The selectivity of busulfan for marrow cells has several explanations. One theory is based on the susceptibility of relatively undifferentiated stem cells during the G-phase of the cell mitotic cycle to alkylation by busulfan. Busulfan treatment during the G-phase prevents further differentiation and progression of the cell through other stages. Microscopic examination of various stem cell populations indicates arrested cell division with polyploidy and cell death. The more differentiated types of progenitor cells show relatively less genetic damage from busulfan exposure, which has been attributed to increased exposure in the S-phase of the cell cycle. In this phase, active DNA repair reduces the damage produced by busulfan. There were few general acute pharmacological effects of busulfan reported in the literature. Higher doses of busulfan in the myelotoxic range produce emesis, and myoclonic seizures in animals and man, but treatment with anticonvulsant drugs can prevent the seizures, and Droperidol and other antiemetics have been useful in treating the emesis. Flushing has been reported in monkeys after IV administration.

Most of the side effects reported for busulfan occurred more than three to four days following high acute doses or chronic treatment. These effects have been attributed to the genetic damage caused by busulfan. The relative selectivity of the drug for the more undifferentiated progenitor, or stem, cells has been used to explain certain actions of busulfan on other organ systems, especially gonadal changes leading to sterility and lenticular distortion and cataracts in the eye. Genetic damage to alveolar cells may explain the pulmonary fibrosis that can occur in the lung following chronic treatment with busulfan. In addition, mechanical damage from busulfan crystals in the liver may be the basis of veno-occlusive disease. There is also a low incidence of sudden cardiac tamponade related to haemochromatosis that occurs in man; this has not been reported in animals. There were no reports found in the literature of acute cardiovascular pharmacology.

Pharmacokinetic studies have demonstrated that busulfan distributes from the blood to various organs within minutes, but is primarily found in the liver, lung and brain. Despite its rapid tissue distribution, low, but constant levels remain in the plasma for an extended period of time. Following intraperitoneal (IP) or IV administration, three main urinary metabolites have been identified: 3-hydroxysulfolane, tetrahydrothiophene 1-oxide and sulfolane. The sulfonium ion of glutathione, or γ-glutamyl-β-(S-tetrahydrothiophenium) alanyl-glycine, was also hypothesized as a urinary metabolite, but because of its instability, it has only been measured indirectly. Unreacted busulfan is excreted in small amounts. Finally, excretion occurs primarily through the urine followed by exhaled $CO_2$ and the feces.

The pharmacokinetics of BUSULFEX (busulfan) were studied in 27 patients participating in two prospective trials of a busulfan/cyclophosphamide preparatory regimen prior to hematopoietic progenitor cell transplantation. Patients received busulfan every six hours for a total of 16 doses over four days. In twelve patients the initial dose was administered orally at 1.0 mg/kg, followed six hours later by the first of 15 two-hour intravenous infusions of 0.8 mg/kg. Nine of twelve patients contributed fully analyzable pharmacokinetic data for both oral and intravenous modes of administration (Table 5). In comparing the action of BUSULFEX to oral busulfan in the same patient group, 92% of patients administered BUSULFEX maintained AUC values below the target value (<1500 μMol•min) while only 67% of evaluable patients administered oral busulfan had an AUC below this target level. Of the three patients who could not be analyzed, two were due to delayed absorption of the oral formulation and one was due to delayed plasma collection.

**Table 5: Selected Pharmacokinetic Parameters Following Oral Busulfan (1 mg/kg) and BUSULFEX (busulfan) Injection (0.8 mg/kg) Administration (n=9)**

| | Median | Mean | CV (%) | Range |
|---|---|---|---|---|
| Maximum concentration (ng/mL) | | | | |
| Oral | 728 | 870 | 30 | 608-1318 |
| IV | 1127 | 1167 | 12 | 997-1405 |
| AUC (μMol•min) | | | | |
| Oral | 1356 | 1396 | 24 | 1021-1951 |
| IV | 1178 | 1156 | 14 | 965-1404 |
| Elimination Half-life (hr) | | | | |
| Oral | 3.17 | 3.55 | 33 | 2.41-5.66 |
| IV | 3.17 | 3.11 | 10 | 2.64-3.59 |
| Volume of distribution (L/patient) | | | | |
| Oral | 54 | 58 | 27 | 36-78 |
| IV | 50 | 49 | 15 | 35-61 |
| Plasma clearance (mL/min/Patient) | | | | |
| Oral | 176 | 195 | 27 | 133-310 |
| IV | 181 | 182 | 16 | 148-245 |

When maximum concentration, AUC, elimination half-life, and plasma clearance are compared for intravenous and oral routes of administration, intravenous busulfan had a more consistent pharmacokinetic profile among patients. When the coefficients of variation for all pharmacokinetic parameters are compared, those for BUSULFEX ranged from 9.8%-17% and those for the oral busulfan from 17-46%. BUSULFEX demonstrated consistency between dose 1 and dose 9, and between dose 9 and dose 13 as demonstrated by predictability of $T_{max}$, reproducibility of steady state $C_{max}$ and AUC, and low coefficients of variation of these parameters. Because BUSULFEX allows predictable drug exposure, the pharmacokinetic profile of the first intravenous BUSULFEX dose predicts with high precision the steady state AUC values of subsequent doses. The predictability of BUSULFEX allows the physician to target the optimal systemic exposure to achieve the appropriate balance between therapeutic effectiveness and dose-limiting toxicity effects. If the patient's body size is normalized as body surface area ($m^2$) or adjusted ideal body weight, differences in clearance are not significant among body weight groups (underweight, normal, obese, and severely obese).

Overall, 90% of patients delivered BUSULFEX, maintained AUCs lower than the targeted level of 1500 μMol•min. When BUSULFEX is delivered, the resulting AUC can be predicted with high precision.

BUSULFEX systemic exposure is immediate and complete due to intravenous administration.

Studies of distribution, metabolism, and elimination of BUSULFEX have not been done; however, the literature on oral busulfan is relevant. Additionally, for modulating effects on pharmacodynamic parameters, see PRECAUTIONS - Drug Interactions.)

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 eliminated through conjugation with glutathione, both spontaneously and through glutathione S-transferase (GST).

In humans, approximately 30% of $^{14}C$-labelled busulfan was excreted into the urine over 48 hours; negligible amounts were recovered in feces. The lack of complete urine label recovery may be due to the production of long-lived metabolites or due to nonspecific alkylation of macromolecules.

## CLINICAL STUDIES

Documentation of the safety and efficacy of busulfan in combination with cyclophosphamide or other drugs as a conditioning regimen prior to hematopoietic progenitor cell reconstitution derives from two sources:

i) analysis of two prospective clinical trials of BUSULFEX (busulfan) in 103 patients diagnosed with various hematologic malignancies,

ii) a review of the world literature addressing the clinical use of high-dose oral busulfan in the transplant setting since 1964. Forty-two publications (2,065 patients) were selected for review based on availability of engraftment rate and days to engraftment as well as sufficient patients ($\geq 23$) to provide confidence in the engraftment rate reported. In addition, information on disease response, relapse, durations of disease-free and overall survival, adverse events, and acute mortality (death within the first month following transplant) was included.

### Clinical Trials:

Two prospective, single-arm, open-label, uncontrolled trials of 103 patients administered BUSULFEX differed only in that hematopoietic progenitor cells were of autologous origin in one trial and allogeneic origin in the other and that allogeneic transplant patients received graft

versus host disease prophylaxis. Diseases included were acute leukemia past first remission, in first or subsequent relapse, in first remission (high-risk), or induction failures; chronic myelogenous leukemia in chronic phase, accelerated phase or blast crisis; primary refractory or resistant relapsed Hodgkin's disease or non-Hodgkin's lymphoma; and myelodysplastic syndrome. Patients received BUSULFEX doses of 0.8 mg/kg every 6 hours as a two-hour infusion for 4 days, followed by 2 daily doses of cyclophosphamide at 60 mg/kg once per day for two days (BuCy2 regimen). After one rest day, hematopoietic progenitor cells were infused. The primary efficacy parameters in these studies were myeloablation (defined as one or more of the following: absolute neutrophil count [ANC] less than 0.5 x $10^9$/L, absolute lymphocyte count [ALC] less than 0.1 x $10^9$/L, thrombocytopenia defined as a platelet count less than 20,000/$mm^3$ or a platelet transfusion requirement), engraftment (ANC $\geq$ 0.5 x $10^9$/L), relapse, and survival. In both studies, all patients received and retained their prescribed 16/16 dose regimen of BUSULFEX. No patients were discontinued from treatment due to adverse events related to BUSULFEX. All patients experienced profound myelosuppression. The studies are described individually in Table 6 and Table 7.

**Table 6: Summary of Autologous Study and Allogenic Study with BUSULFEX**

| Parameter | Autologous Study | Allogeneic Study |
|---|---|---|
| Number of patients | 42 patients; 5 centers | 61 patients; 7 centers |
| % Heavily Pretreated* | 81% | 48% |
| % Active Disease | 83% | 75% |
| Median Time to Neutropenia (ANC<0.5 x $10^9$/L) | 4 days | 4 days |
| Median Duration of Neutropenia | 6 days (range: 2-13) | 9 days (range: 1-28) |
| Median Duration of Lymphopenia | 3 days (range: 1-7) | 4 days (range: 1-19) |
| Median Time to Engraftment | 10 days (range: 8-19) | 13 days (range: 9-29) |
| % of Patients Relapsed | 43% | 38% |
| Median Time to Relapse | 146 days (range: 13-463) | 178 days (range: 36-406) |
| % of Patients Free from Disease (median follow-up) | 57% (321days) | 62% (269days) |
| Survival | At Day +100, survival was 100% (42/42).<br>80% alive with median follow-up of 264 days. Eight deaths at median of 217 days. | At Day +100, survival was 87% (53/61).<br>70% alive with median follow-up of 288 days. Eighteen deaths at median of 139 days. |
| Freedom from Relapse at 100 days | 0.93 | 0.93 |

*Defined as having at least one of the following: prior radiation, $\geq$ 3 prior chemotherapeutic regimens, or prior hematopoietic progenitor cell transplant.

**Table 7: Summary of Efficacy Results for Patients Who Received BUSULFEX 0.8 mg/kg Prior to Autologous or Allogeneic Hematopoietic Progenitor Cell Transplantation.**

| | Autologous (n=42) | | Allogeneic (n=61) | |
|---|---|---|---|---|
| | % Pts | Median Day (range) | % Pts | Median Day (range) |
| Myeloablation<br>Neutrophil (<0.5x10$^9$/L) | 100 | +4 (-7 to +6) | 100 | +4 (-7 to +5) |
| Lymphocyte (<0.1x10$^9$/L) | 69 | +2 (-3 to +11) | 75 | +3 (-2 to +21) |
| Platelet (<20,000/mm$^3$) | 98 | +6 (-3 to +9) | 98 | +5 (-7 to +10) |
| Engraftment | 100 | +10 (+8 to +19) | 100 | +13 (+9 to +29) |
| Relapse-free @ +365 Days (Kaplan-Meier) | 0.58 | | 0.51 | |
| Survival @ +365 Days (Kaplan-Meier) | 0.71 | | 0.67 | |
| Disease Free Survival @ +365 Days (Kaplan-Meier) | 0.58 | | 0.42 | |

Days expressed as BMT = day 0

## Alternative Dosing Regimens

Ryu et al examined QD dosing (3.2 mg/kg/day over a three hour infusion) of BUSULFEX in a randomised study comparing it to QID dosing (0,8 mg/kg every six hours). It was determined that all pharmacokinetic parameters, i.e. daily AUC, clearance etc, were comparable between the two groups. No significant differences were observed in engraftment rates or time to engraftment. No safety issues were reported in the QD arm, moreover there were no significant differences in the incidences of early post transplantation toxicity between the two arms. The one year survival rates were similar between the two groups. Additional evidence and support for this dosing regimen was provided by de Lima et al 2004 and Russell et al, 2002.

**Discussion of Literature:**

There were 2,065 patients treated with high-dose oral busulfan in the 42 publications analyzed. The availability of endpoint information was highly variable among publications. These trials included high-dose oral busulfan combined with other chemotherapeutic agents, including cyclophosphamide in 87% of patients and a smaller percentage with irradiation. Adult and pediatric patients, as well as multiple disease types were included in many studies. Data obtained are as follows: 72% of the transplants were allogeneic and 28% were autologous. Acute leukemias were the conditions most frequently treated (52%), followed by chronic myeloid leukemia (26%), lymphoma (8%), multiple myeloma (8%), myelodysplastic syndrome (4%), and other conditions (3%). The range of median days of duration of neutropenia in patients treated with a high-dose oral busulfan conditioning regimen was 7-11 days for

autologous and allogeneic transplant patients combined from the literature.

In a single dose escalation study of busulfan with total doses from 8-16 mg/kg, white blood cell nadirs occurred 2-8 days after transplant and granulocyte (neutrophil) levels recovered to 0.5 x $10^9$/L in a mean of 21 days (range 14-26 days). Among 34 studies reporting white blood cell recovery to 0.5 x $10^9$/L, the average of the medians was 16.5 days (range of medians 8-42 days). Among the 32 studies, which reported engraftment, 95% (1632/1712) of patients engrafted.

Eighteen papers provided analyses of disease response in patients who had active disease at transplant. Complete and/or partial response rates for patients are shown in Table 8 according to disease.

**Table 8: Response Rate of Patients Receiving High Dose Oral Busulfan According to Disease Type**

| Disease | Complete Response | Partial Response |
|---|---|---|
| AML | 12/12 (100%) | -- |
| ALL | 4/4 (100%) | -- |
| CML | 25/26 (96%) | -- |
| Multiple myeloma | 53/114(46%) | 48/114 (42%) |
| Lymphoma | 43/73 (55%) | 18/78 (23%) |

The overall acute mortality for oral busulfan (through day 30) was 6.7%, for autologous transplant it was 2.6% and for allogeneic transplant it was 7.9%.

Multiple factors including stage of disease, prior therapy, graft versus host disease therapy, and patient's age were reported to influence both relapse and survival.

BUSULFEX has also been used as a conditioning regimen prior to stem cell transplantation for the treatment of various genetic disorders and immune disorders including red cell production disorders, storage disease disorders and severe immunodeficiency disorders.

## TOXICOLOGY

An acute toxicity and two multiple-dose toxicity studies were conducted on BUSULFEX. In this acute intravenous toxicity study, male rats received single doses of 1, 5, 10, 20, or 40 mg/kg of two lots of the busulfan formulation; one representing a standard batch and one lot which underwent forced degradation. The purpose of this study was to show that potential degradation products did not affect the acute toxicity profile of the busulfan formulation. A dose of 40 mg/kg of both formulations produced mortality in all treated animals and 20 mg/kg of reference

busulfan produced mortality in three of five treated animals. No other deaths occurred. Clinical signs were primarily limited to 20 mg/kg (both formulations) and included scabbing, abnormal excretion, hair loss, hypoactivity and the appearance of material on the nose, mouth, neck forelimbs and uro- and anogenital areas. Overall, the total incidence of and number of rats exhibiting clinical signs were greater in the 20 mg/kg reference busulfan group than in the 20 mg/kg degraded busulfan group. Only isolated reports of clinical effects were noted at doses of 10 mg/kg and below. In addition, body weight gain and food consumption were decreased during the first and third weeks in rats treated with 20 mg/kg reference busulfan. At necropsy, effects were noted in the lungs of animals dying during treatment and in one animal surviving treatment; isolated findings were reported in other organ systems. The $LD_{50}$ for the reference busulfan formulation was 19 mg/kg, but the $LD_{50}$ for the degraded formulation could not be calculated due to the mortality pattern; it was concluded to be greater than 20 and less than 40 mg/kg. Based on the clinical signs, body weight, food consumption and mortality data, the degraded busulfan formulation was less toxic than the reference formulation, possibly due to a slightly lower percentage of active drug.

Two multiple dose toxicity studies have been conducted on BUSULFEX. In both, the drug was administered intravenously to beagle dogs at doses ranging from 0.25 to 4 mg/kg q.i.d. for 4 days. The highest dose produced severe toxicity expressed as hypoactivity, prostration, significant body weight loss and decreased food consumption; these effects required the animals to be euthanized. Other less severe treatment-related effects observed at doses greater than 0.25 mg/kg included decreases in body weight gain and food consumption, liver toxicity (measured as elevations in alanine aminotransferase, alkaline phosphatase, and gamma glutamyltransferase), serum chemistry changes and hematopoietic toxicity (i.e., decreased white blood cell, platelet and reticulocyte counts). No treatment-related gross or microscopic lesions were noted at necropsy. The lowest no-observable-effect-level for busulfan was 0.25 mg/kg q.i.d.

Studies in mice and rats from the literature revealed that busulfan produces sterility. Spermatogonia were the primary target in males and oocytes were the target in females. In addition, exposure of pregnant rats after gestation day 11 produced virtually complete sterility in the offspring. Busulfan was teratogenic producing adverse effects on gonadal development, weight gain and the musculo-skeletal system.

Busulfan was mutagenic in both *in vitro* and *in vivo* screens. Nevertheless, only “limited” evidence exists for a carcinogenic effect of busulfan treatment. Mixed results were reported in various bioassays.

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