CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-945/S-005

Approved Labeling

BUSULFEX®

(busulfan) Injection

Caution: Must be diluted prior to use.

R_x Only

WARNING

BUSULFEX® (busulfan) Injection is a potent cytotoxic drug that causes profound myelosuppression at the recommended dosage. It should be administered under the supervision of a qualified physician who is experienced in allogeneic hematopoietic stem cell transplantation, the use of cancer chemotherapeutic drugs 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. SEE "WARNINGS" SECTION FOR INFORMATION REGARDING BUSULFAN-INDUCED PANCYTOPENIA IN HUMANS.

DESCRIPTION

Busulfan is a bifunctional alkylating agent known chemically as 1,4-butanediol, dimethanesulfonate. BUSULFEX® (busulfan) Injection is intended for intravenous administration. It is supplied as a clear, colorless, sterile, solution in 10 mL single use ampoules. Each ampoule of BUSULFEX contains 60 mg (6 mg/mL) of busulfan, the active ingredient, a white crystalline powder with a molecular formula of $CH_3SO_2O(CH_2)_4OSO_2CH_3$ and a molecular weight of 246 g/mole. Busulfan is dissolved in N,N-dimethylacetamide (DMA) 33% vol/vol and Polyethylene Glycol 400, 67% vol/vol. The solubility of busulfan in water is 0.1 g/L and the pH of a >0.5% BUSULFEX solution in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP as recommended for infusion reflects the pH of the diluent used and ranges from 3.4 to 3.9.

BUSULFEX is intended for dilution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP prior to intravenous infusion.

CLINICAL PHARMACOLOGY

Mechanism of Action:

Busulfan is a bifunctional alkylating agent in which two labile methanesulfonate groups are attached to opposite ends of a four-carbon alkyl chain. In aqueous media, busulfan hydrolyzes to release the

methanesulfonate groups. This produces reactive carbonium ions that can alkylate DNA. DNA damage is thought to be responsible for much of the cytotoxicity of busulfan.

Pharmacokinetics:

The pharmacokinetics of BUSULFEX were studied in 59 patients participating in a prospective trial of a BUSULFEX-cyclophosphamide preparatory regimen prior to allogeneic hematopoietic progenitor stem cell transplantation. Patients received 0.8 mg/kg BUSULFEX every six hours, for a total of 16 doses over four days. Fifty-five of fifty-nine patients (93%) administered BUSULFEX maintained AUC values below the target value (<1500 μM•min).

TABLE 1: STEADY STATE PHARMACOKINETIC PARAMETERS FOLLOWING BUSULFEX® (BUSULFAN) INFUSION (0.8 MG/KG;N=59)

	Mean	CV(%)	Range
C_{max} (ng/mL)	1222	18	496-1684
AUC (μM•min)	1167	20	556-1673
CL (ml/min/kg)*	2.52	25	1.49-4.31

* Clearance normalized to actual body weight for all patients.

BUSULFEX pharmacokinetics showed consistency between dose 9 and dose 13 as demonstrated by reproducibility of steady state C_{max} and a low coefficient of variation for this parameter.

Distribution, Metabolism, Excretion:

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 **Drug Interactions**.

Distribution: 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 ± 2.2% which is consistent with the reactive electrophilic properties of busulfan.

Metabolism: Busulfan is predominantly metabolized by conjugation with glutathione, both spontaneously and by glutathione *S*-transferase (GST) catalysis. This conjugate undergoes further extensive oxidative metabolism in the liver.

Excretion: Following administration of ^{14}C- labeled busulfan to humans, approximately 30% of the radioactivity was excreted into the urine over 48 hours; negligible amounts were recovered in feces. The incomplete recovery of radioactivity may be due to the formation of long-lived metabolites or due to nonspecific alkylation of macromolecules.

CLINICAL STUDIES

Documentation of the safety and efficacy of busulfan as a component of a conditioning regimen prior to allogeneic hematopoietic progenitor cell reconstitution is derived from two sources: i) analysis of a prospective clinical trial of BUSULFEX that involved 61 patients diagnosed with various hematologic malignancies, and ii) the published reports of randomized, controlled trials that employed high-dose oral busulfan as a component of a conditioning regimen for transplantation, which were identified in a literature review of five established commercial databases.

The prospective trial was a single-arm, open-label study in 61 patients who received BUSULFEX as part of a conditioning regimen for allogeneic hematopoietic stem cell transplantation. The study included patients with acute leukemia past first remission (first or subsequent relapse), with high-risk first remission, or with induction failure; chronic myelogenous leukemia (CML) in chronic phase, accelerated phase, or blast crisis; primary refractory or resistant relapsed Hodgkin's disease or non-

Hodgkin's lymphoma; and myelodysplastic syndrome. Forty-eight percent of patients (29/61) were heavily pretreated, defined as having at least one of the following: prior radiation, ≥ 3 prior chemotherapeutic regimens, or prior hematopoietic stem cell transplant. Seventy-five percent of patients (46/61) were transplanted with active disease.

Patients received 16 BUSULFEX doses of 0.8 mg/kg every 6 hours as a two-hour infusion for 4 days, followed by cyclophosphamide 60 mg/kg once per day for two days (BuCy2 regimen). All patients received 100% of their scheduled BUSULFEX regimen. No dose adjustments were made. After one rest day, allogeneic hematopoietic progenitor cells were infused. The efficacy parameters in this study were myeloablation (defined as one or more of the following: absolute neutrophil count [ANC] less than $0.5x10^9$/L, absolute lymphocyte count [ALC] less than $0.1x10^9$/L, thrombocytopenia defined as a platelet count less than 20,000/mm^3 or a platelet transfusion requirement) and engraftment (ANC$\geq$ $0.5x10^9$/L).

All patients (61/61) experienced myeloablation. The median time to neutropenia was 4 days. All evaluable patients (60/60) engrafted at a median of 13 days post-transplant (range 9 to 29 days); one patient was considered non-evaluable because he died of a fungal pneumonia 20 days after BMT and before engraftment occurred. All but 13 of the patients were treated with prophylactic G-CSF. Evidence of donor cell engraftment and chimerism was documented in all patients who had a chromosomal sex marker or leukemic marker (43/43), and no patient with chimeric evidence of allogeneic engraftment suffered a later loss of the allogeneic graft. There were no reports of graft failure in the overall study population. The median number of platelet transfusions per patient was 6, and the median number of red blood cell transfusions per patient was 4.

Twenty-three patients (38%) relapsed at a median of 183 days post-transplant (range 36 to 406 days). Sixty-two percent of patients (38/61) were free from disease with a median follow-up of 269 days post-transplant (range 20 to 583 days). Forty-three patients (70%) were alive with a median follow up of 288 days post-transplant (range 51 to 583 days). There were two deaths before BMT Day +28 and six additional patients died by BMT Day +100. Ten patients (16%) died after BMT Day +100, at a median of 199 days post-transplant (range 113 to 275 days).

Oral Busulfan Literature Review. Four publications of randomized, controlled trials that evaluated a high-dose oral busulfan-containing conditioning regimen (busulfan 4 mg/kg/d x 4 days + cyclophosphamide 60 mg/kg/d x 2 days) for allogeneic transplantation in the setting of CML were identified. Two of the studies (Clift and Devergie) had populations confined to CML in chronic phase that were randomized between conditioning with busulfan/cyclophosphamide (BU/CY) and cyclophosphamide/total body irradiation (CY/TBI). A total of 138 patients were treated with BU/CY in these studies. The populations of the two remaining studies (Ringden and Blume) included patients with CML, acute lymphoblastic leukemia (ALL), and acute myelogenous leukemia (AML). In the Nordic BMT Group study published by Ringden, et al., 57 patients had CML, and of those, 30 were treated with BU/CY. Patients with CML in chronic phase, accelerated phase, and blast crisis were eligible for this study. The participants with CML (34/122 patients) in a SWOG study published by Blume, et al., had disease beyond first chronic phase. Twenty of those CML patients were treated with BU/CY, and the TBI comparator arm utilized etoposide instead of cyclophosphamide.

Table 2 below summarizes the efficacy analyses reported from these 4 studies.

Table 2: Summary of efficacy analyses from the randomized, controlled trials utilizing a high dose oral busulfan-containing conditioning regimen identified in a literature review.

Clift, 1994 CML Chronic Phase;							
3 year Overall Survival		3 year DFS (p=0.43)		Relapse		Time to Engraftment (ANC ≥ 500)	
BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI
80%	80%	71%	68%	13%	13%	22.6 days	22.3 days
Devergie, 1995 CML Chronic Phase;							

5 year Overall Survival (p=0.5)		5 year DFS (p=0.75)		Relapse (Relative Risk analysis BU/CY:CY/TBI) (p=0.04)		Time to Engraftment (ANC ≥ 500)	
Bu/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI
60.6% ±11.7%	65.8% ±12.5%	59.1% ±11.8%	51.0% ±14%	4.10 (95% CI = 1.00-20.28)		None Given	None Given
Ringden, 1994 CML, AML, ALL;							
3 year Overall Survival (p<0.03)		3 year Relapse Free Survival (p=0.065)		Relapse (p=0.9)		Time to Engraftment (ANC >500)	
BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI	BU/CY	CY/TBI
62%	76%	56%	67%	22%	26%	20 days	20 days
Blume, 1993* CML, AML, ALL; Relative Risk Analysis BU/CY: Etoposide/TBI							
RR of Mortality		DFS		RR of Relapse (Relative Risk analysis BU/CY:Eto/TBI)		Time to Engraftment	
BU/CY	Eto/TBI	BU/CY	Eto/TBI	BU/CY	Eto/TBI	BU/CY	Eto/TBI
0.97 (95% CI=0.64-1.48)		Not Given		1.02 (95% CI=0.56-1.86)		Not Given	

***Eto = etoposide. TBI was combined with etoposide in the comparator arm of this study.**

BU = Busulfan

CY = Cyclophosphamide

TBI = Total Body Irradiation

DFS = Disease Free Survival

ANC = Absolute Neutrophil Count

INDICATIONS AND USAGE

BUSULFEX® (busulfan) Injection is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

CONTRAINDICATIONS

BUSULFEX is contraindicated in patients with a history of hypersensitivity to any of its components.

WARNINGS

BUSULFEX should be administered under the supervision of a qualified physician experienced in hematopoietic stem cell transplantation. Appropriate management of complications arising from its administration is possible only when adequate diagnostic and treatment facilities are readily available.

The following warnings pertain to different physiologic effects of BUSULFEX in the setting of allogeneic transplantation.

Hematologic: 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 dropped below $0.5x10^9/L$ at a median of 4 days post-transplant in 100% of patients treated in the BUSULFEX clinical trial. The absolute neutrophil count recovered at a median of 13 days following allogeneic transplantation when prophylactic G-CSF was used in the majority of patients. Thrombocytopenia ($<25,000/mm^3$ or requiring platelet transfusion) occurred at a median of 5-6 days in 98% of patients. Anemia (hemoglobin <8.0 g/dL) occurred in 69% of patients. Antibiotic therapy and platelet and red blood cell support should be used when medically indicated.

Neurological: Seizures have been reported in patients receiving high-dose oral busulfan at doses producing plasma ~~drug~~ levels similar to those achieved following the recommended dosage of BUSULFEX. Despite prophylactic therapy with phenytoin, one seizure (1/42 patients) was reported during an autologous transplantation clinical trial of BUSULFEX. This episode occurred during the cyclophosphamide portion of the conditioning regimen, 36 hours after the last BUSULFEX dose. Anti-convulsant prophylactic therapy should be initiated prior to BUSULFEX treatment. Caution should be exercised when administering the recommended dose of BUSULFEX to patients with a history of a seizure disorder or head trauma or who are receiving other potentially epileptogenic drugs.

Hepatic: Current literature suggests that high busulfan area under the plasma concentration verses time curve (AUC) values (>1,500 μM•min) may be associated with an increased risk of developing hepatic veno-occlusive disease (HVOD). 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 HVOD with the recommended BUSULFEX dose and regimen. Hepatic veno-occlusive disease developed in 8.2% (5/61) of patients treated with BUSULFEX in the setting of allogeneic transplantation and was fatal in 2/5 cases (40%). Jones' criteria were used to diagnose HVOD (hyperbilirubinemia and two of the following three findings: painful hepatomegaly, weight gain ≥ 5% or ascites) in this clinical trial. The incidence of HVOD reported in the literature from the randomized, controlled trials (see CLINICAL STUDIES) was 7.7%-12%.

Cardiac: Cardiac tamponade has been reported in pediatric patients 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 (busulfan) Injection clinical trials experienced cardiac tamponade.

Pulmonary: Bronchopulmonary dysplasia with pulmonary fibrosis is a rare but serious complication following chronic busulfan therapy. The average onset of symptoms is 4 years after therapy (range 4 months to 10 years).

Carcinogenicity, Mutagenicity, Impairment of Fertility:

Busulfan is a mutagen and a clastogen. In *in vitro* tests it caused mutations in ***Salmonella typhimurium*** and ***Drosophila melanogaster***. Chromosomal aberrations induced by busulfan have been reported *in vivo* (rats, mice, hamsters, and humans) and *in vitro* (rodent and human cells). The intravenous administration of busulfan (48 mg/kg given as biweekly doses of 12 mg/kg, or 30% of the total BUSULFEX dose on a mg/m^2 basis) has been shown to increase the incidence of thymic and ovarian tumors in mice. Four cases of acute leukemia occurred among 19 patients who became pancytopenic in a 243 patient study incorporating busulfan as adjuvant therapy following surgical resection of bronchogenic carcinoma. Clinical appearance of leukemia was observed 5-8 years following oral busulfan treatment. Busulfan is a presumed human carcinogen.

Ovarian suppression and amenorrhea commonly occur in premenopausal women undergoing chronic, low-dose busulfan therapy for chronic myelogenous leukemia. Busulfan depleted oocytes of female rats. Busulfan induced sterility in male rats and hamsters. Sterility, azoospermia and testicular atrophy have been reported in male patients.

The solvent DMA may also impair fertility. A DMA daily dose of 0.45 g/kg/d given to rats for nine days (equivalent to 44% of the daily dose of DMA contained in the recommended dose of BUSULFEX on a mg/m^2 basis) significantly decreased spermatogenesis in rats. A single sc dose of 2.2 g/kg (27% of the total DMA dose contained in BUSULFEX on a mg/m^2 basis) four days after insemination terminated pregnancy in 100% of tested hamsters.

Pregnancy: Busulfan may cause fetal harm when administered to a pregnant woman. Busulfan produced teratogenic changes in the offspring of mice, rats and rabbits when given during gestation. Malformations and anomalies included significant alterations in the musculoskeletal system, body weight gain, and size. In pregnant rats, busulfan produced sterility in both male and female offspring due to the absence of germinal cells in the testes and ovaries. The solvent, DMA, may also cause fetal harm when administered to a pregnant woman. In rats, DMA doses of 400 mg/kg/d (about 40% of the daily dose of DMA in the BUSULFEX dose on a mg/m^2 basis) given during organogenesis caused significant developmental anomalies. The most striking abnormalities included anasarca, cleft palate, vertebral anomalies, rib anomalies, and serious anomalies of the vessels of the heart. There are no adequate and well-controlled studies of either busulfan or DMA in pregnant women. If BUSULFEX is used during pregnancy, or if the patient becomes pregnant while receiving BUSULFEX, the patient

should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Hematologic: At the recommended dosage of BUSULFEX, profound myelosuppression is universal, and can manifest as neutropenia, thrombocytopenia, anemia, or a combination thereof. Patients should be monitored for signs of local or systemic infection or bleeding. Their hematologic status should be evaluated frequently.

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

Laboratory Tests: 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 BMT Day +28.

Drug Interactions: Itraconazole decreases busulfan clearance by up to 25%, and may produce AUC > 1500 μM•min in some patients. Fluconazole, and the 5-HT_3 antiemetics odansetron (Zofran®) and granisetron (Kytril®) have all been used with BUSULFEX.

Phenytoin increases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione-S-transferase. Since the pharmacokinetics of BUSULFEX were studied in patients treated with phenytoin, the clearance of BUSULFEX at the recommended dose may be lower and exposure (AUC) higher in patients not treated with phenytoin. Because busulfan is eliminated from the body via conjugation with glutathione, use of acetaminophen prior to (<72 hours) or concurrent with BUSULFEX may result in reduced busulfan clearance based upon the known property of acetaminophen to decrease glutathione levels in the blood and tissues.

Pregnancy: Pregnancy Category D. See **WARNINGS**.

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.

SPECIAL POPULATIONS

Pediatric: The safety and efficacy of BUSULFEX in children have not been established. Busulfan clearance has been demonstrated to be higher in children than in adults. This has necessitated the development of alternative dosing regimens for oral busulfan in this population. Studies are underway to define the pharmacokinetics of BUSULFEX in children. Currently the recommended dose of BUSULFEX in children has not been defined.

Geriatric: Five of sixty-one patients treated in the Busulfex clinical trial were over the age of 55 (range 57-64). All achieved myeloablation and engraftment.

Gender, Race: Adjusting BUSULFEX dosage based on gender or race has not been adequately studied.

Renal Insufficiency: BUSULFEX has not been studied in patients with renal impairment.

Hepatic Insufficiency: BUSULFEX has not been administered to patients with hepatic insufficiency.

Other: Busulfan may cause cellular dysplasia in many organs. Cytologic abnormalities characterized by giant, hyperchromatic nuclei have been reported in lymph nodes, pancreas, thyroid, adrenal glands, liver, lungs and bone marrow. This cytologic dysplasia may be severe enough to cause difficulty in interpretation of exfoliative cytologic examinations of the lungs, bladder, breast and the uterine cervix.

ADVERSE REACTIONS

Dimethylacetamide (DMA), the solvent used in the BUSULFEX formulation, was studied in 1962 as a potential cancer chemotherapy drug. In a Phase 1 trial, the maximum tolerated dose (MTD) was 14.8 $g/m^2/d$ for four days. The daily recommended dose of BUSULFEX contains DMA equivalent to 42%

of the MTD on a mg/m^2 basis. The dose-limiting toxicities in the Phase 1 study were hepatotoxicity as evidenced by increased liver transaminase (SGOT) levels and neurological symptoms as evidenced by hallucinations. The hallucinations had a pattern of onset at one day post completion of DMA administration and were associated with EEG changes. The lowest dose at which hallucinations were recognized was equivalent to 1.9 times that delivered in a conditioning regimen utilizing BUSULFEX 0.8 mg/kg every 6 hours x 16 doses. Other neurological toxicities included somnolence, lethargy, and confusion. The relative contribution of DMA and/or other concomitant medications to neurologic and hepatic toxicities observed with BUSULFEX is difficult to ascertain.

Treatment with BUSULFEX 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.

Adverse reaction information is primarily derived from the clinical study (N=61) of BUSULFEX and the data obtained for high-dose oral busulfan conditioning in the setting of randomized, controlled trials identified through a literature review.

BUSULFEX Clinical Trials. In the BUSULFEX allogeneic stem cell transplantation clinical trial, all patients were treated with BUSULFEX 0.8 mg/kg as a two-hour infusion every six hours for 16 doses over four days, combined with cyclophosphamide 60 mg/kg x 2 days. Ninety three percent (93%) of evaluable patients receiving this dose of BUSULFEX maintained AUC less than 1,500 μM• min for dose 9, which has generally been considered the level that minimizes the risk of HVOD.

Table 3: Summary of the Incidence (≥20%) of Non-Hematologic Adverse Events through BMT Day +28 in Patients who Received BUSULFEX Prior to Allogeneic Hematopoietic Progenitor Cell Transplantation

Non-Hematological Adverse Events*	Percent Incidence
BODY AS A WHOLE	
Fever	80
Headache	69
Asthenia	51
Chills	46
Pain	44
Edema General	28
Allergic Reaction	26
Chest Pain	26
Inflammation at Inj Site	25
Pain Back	23

CARDIOVASCULAR SYSTEM	
Tachycardia	44
Hypertension	36
Thrombosis	33
Vasodilation	25
DIGESTIVE SYSTEM	
Nausea	98
Stomatitis (Mucositis)	97
Vomiting	95
Anorexia	85
Diarrhea	84
Abdominal Pain	72
Dyspepsia	44
Constipation	38
Dry Mouth	26
Rectal Disorder	25
Abdominal Enlargement	23
METABOLIC AND NUTRITIONAL SYSTEM	77
Hypomagnesemia	66
Hyperglycemia	64
Hypokalemia	49
Hypocalcemia	49
Hyperbilirubinemia	36
Edema	31
SGPT Elevation	21
Creatinine Increased	
NERVOUS SYSTEM	
Insomnia	84
Anxiety	72
Dizziness	30
Depression	23
RESPIRATORY SYSTEM	
Rhinitis	44
Lung Disorder	34
Cough	28
Epistaxis	25
Dyspnea	25
SKIN AND APPENDAGES	
Rash	57
Pruritus	28

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

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

Hematologic: At the indicated dose and schedule, BUSULFEX produced profound myelosuppression in 100% of patients. Following hematopoietic progenitor cell infusion, recovery of neutrophil counts to ≥500 cells/mm^3 occurred at median day 13 when prophylactic G-CSF was administered to the majority of participants on the study. The median number of platelet transfusions per patient on study was 6, and the median number of red blood cell transfusions on study was 4. Prolonged prothrombin time was reported in one patient (2%).

Gastrointestinal: Gastrointestinal toxicities were frequent and generally considered to be related to the drug. Few were categorized as serious. Mild or moderate nausea occurred in 92% of patients in the allogeneic clinical trial, and mild or moderate vomiting occurred in 95% through BMT day +28; nausea was severe in 7%. The incidence of vomiting during BUSULFEX administration (BMT Day –7 to –4) was 43% in the allogeneic clinical trial. Grade 3-4 stomatitis developed in 26% of the participants, and grade 3 esophagitis developed in 2%. Grade 3-4 diarrhea was reported in 5% of the allogeneic study participants, while mild or moderate diarrhea occurred in 75%. Mild or moderate constipation occurred in 38% of patients; ileus developed in 8% and was severe in 2%. Forty-four percent (44%) of patients reported mild or moderate dyspepsia. Two percent (2%) of patients experienced mild hematemesis. Pancreatitis developed in 2% of patients. Mild or moderate rectal discomfort occurred in 24% of patients. Severe anorexia occurred in 21% of patients and was mild/moderate in 64%.

Hepatic: Hyperbilirubinemia occurred in 49% of patients in the allogeneic BMT trial. Grade 3/4 hyperbilirubinemia occurred in 30% of patients within 28 days of transplantation and was considered life-threatening in 5% of these patients. Hyperbilirubinemia was associated with graft-versus-host disease in six patients and with hepatic veno-occlusive disease in 5 patients. Grade 3/4 SGPT elevations occurred in 7% of patients. Alkaline phosphatase increases were mild or moderate in 15% of patients. Mild or moderate jaundice developed in 12% of patients, and mild or moderate hepatomegaly developed in 6%.

Hepatic veno-occlusive disease: Hepatic veno-occlusive disease (HVOD) is a recognized potential complication of conditioning therapy prior to transplant. Five of 61 (8%) patients treated in the allogeneic study developed HVOD and it was fatal in 2/5.

Graft-versus-host disease: Graft-versus-host disease developed in 18% of patients (11/61) receiving allogeneic transplants; it was severe in 3%, and mild or moderate in 15%. There were 3 deaths (5%) attributed to GVHD.

Edema: Seventy-nine percent (79%) of patients exhibited some form of edema, hypervolemia, or weight increase; all events were reported as mild or moderate.

Infection/Fever: Fifty-one percent (51%) of patients experienced one or more episodes of infection. Pneumonia was fatal in one patient (2%) and life-threatening in 3% of patients. Fever was reported in 80% of patients; it was mild or moderate in 78% and severe in 3%. Forty-six percent (46%) of patients experienced chills.

Cardiovascular: Mild or moderate tachycardia was reported in 44% of patients. In 7 patients (11%) it was first reported during BUSULFEX administration. Other rhythm abnormalities, which were all mild or moderate, included arrhythmia (5%), atrial fibrillation (2%), and ventricular extrasystoles (2%). Mild or moderate thrombosis occurred in 33% of patients, and all episodes were associated with the central venous catheter. Hypertension was reported in 36% of patients and was Grade 3/4 in 7%. Hypotension occurred in 11% of patients and was Grade 3/4 in 3%. Mild vasodilation (flushing and hot flashes) was reported in 25% of patients. Other cardiovascular events included cardiomegaly (5%), mild ECG abnormality (2%), grade 3/4 left-sided heart failure in one patient (2%), and moderate pericardial effusion (2%). These events were reported primarily in the post-cyclophosphamide phase.

Pulmonary: Mild or moderate dyspnea occurred in 25% of patients and was severe in 2%. One patient (2%) experienced severe hyperventilation; and in 2 (3%) additional patients it was mild or moderate. Mild rhinitis and mild or moderate cough were reported in 44% and 28% of patients, respectively. Mild epistaxis events were reported in 25%. Three patients (5%) on the allogeneic study developed documented alveolar hemorrhage. All required mechanical ventilatory support and all died. Non-specific interstitial fibrosis was found on wedge biopsies performed with video assisted thoracoscopy in one patient on the allogeneic study who subsequently died from respiratory failure on BMT Day +98. Other pulmonary events, reported as mild or moderate, included pharyngitis (18%), hiccup (18%), asthma (8%), atelectasis (2%), pleural effusion (3%), hypoxia (2%), hemoptysis (3%), and sinusitis (3%).

Neurologic: The most commonly reported adverse events of the central nervous system were insomnia (84%), anxiety (75%), dizziness (30%), and depression (23%). Severity was mild or 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 (2%), agitation (2%), and encephalopathy (2%). The overall incidence of confusion was 11%, and 5% of patients were reported to have experienced hallucinations. The patient who developed delirium and hallucination on the allogeneic

study had onset of confusion at the completion of BUSULFEX (busulfan) Injection. The overall incidence of lethargy in the allogeneic BUSULFEX clincial trial was 7%, and somnolence was reported in 2%. One patient (2%) treated in an autologous transplantation study experienced a seizure while receiving cyclophosphamide, despite prophylactic treatment with phenytoin.

Renal: Creatinine was mildly or moderately elevated in 21% of patients. BUN was increased in 3% of patients and to a grade 3/4 level in 2%. Seven percent of patients experienced dysuria, 15% oliguria, and 8% hematuria. There were 4 (7%) Grade 3/4 cases of hemorrhagic cystitis in the allogeneic clinical trial.

Skin: Rash (57%) and pruritus (28%) were reported; both conditions were predominantly mild. Alopecia was mild in 15% of patients and moderate in 2%. Mild vesicular rash was reported in 10% of patients and mild or moderate maculopapular rash in 8%. Vesiculo-bullous rash was reported in 10%, and exfoliative dermatitis in 5%. Erythema nodosum was reported in 2%, acne in 7%, and skin discoloration in 8%.

Metabolic: Hyperglycemia was observed in 67% of patients and Grade 3/4 hyperglycemia was reported in 15%. Hypomagnesemia was mild or moderate in 77% of patients; hypokalemia was mild or moderate in 62% and severe in 2%; hypocalcemia was mild or moderate in 46% and severe in 3%; hypophosphatemia was mild or moderate in 17%; and hyponatremia was reported in 2%.

Other: Other reported events included headache (mild or moderate 64%, severe 5%), abdominal pain (mild or moderate 69%, severe 3%), asthenia (mild or moderate 49%, severe 2%), unspecified pain (mild or moderate 43%, severe 2%), allergic reaction (mild or moderate 24%, severe 2%), injection site inflammation (mild or moderate 25%), injection site pain (mild or moderate 15%), chest pain (mild or moderate 26%), back pain (mild or moderate 23%), myalgia (mild or moderate 16%), arthralgia (mild or moderate 13%), and ear disorder in 3%.

Deaths: There were two deaths through BMT day +28 in the allogeneic transplant setting. There were an additional six deaths BMT day +29 through BMT day +100 in the allogeneic transplant setting.

Oral Busulfan Literature Review. A literature review identified four randomized, controlled trials that evaluated a high-dose oral busulfan-containing conditioning regimen for allogeneic bone marrow transplantation in the setting of CML (see CLINICAL STUDIES). The safety outcomes reported in those trials are summarized in Table 4 below for a mixed population of hematological malignancies (AML, CML, and ALL).

Table 4: Summary of safety analyses from the randomized, controlled trials utilizing a high dose oral busulfan-containing conditioning regimen that were identified in a literature review.

Clift CML Chronic Phase					
TRM*	VOD**	GVHD***	Pulmonary	Hemorrhagic Cystitis	Seizure
Death ≤100d =4.1% (3/73)	No Report	Acute ≥ Grade 2 = 35% Chronic = 41% (30/73)	1 death from Idiopathic Interstitial Pneumonitis and 1 death from pulmonary fibrosis	No Report	No Report
Devergie CML Chronic Phase					
TRM	VOD	GVHD	Pulmonary	Hemorrhagic Cystitis	Seizure
38%	7.7% (5/65) ~~Deaths=4.6~~ % (3/65)	Acute ≥ Grade 2 = 41% (24/59 at risk)	Interstitial Pneumonitis = 16.9% (11/65)	10.8% (7/65)	No report
Ringden CML, AML, ALL					
TRM	VOD	GVHD	Pulmonary	Hemorrhagic Cystitis	Seizure

28%	12%	Acute ≥ Grade 2 GVHD = 26% Chronic GVHD = 45%	Interstitial pneumonitis = 14%	24%	6%
Blume CML, AML, ALL					
TRM	VOD	GVHD	Pulmonary	Hemorrhagic Cystitis	Seizure
No Report	Deaths = 4.9%	Acute ≥ Grade 2 GVHD = 22% (13/58 at risk) Chronic GVHD = 31% (14/45 at risk)	No Report	No Report	No Report

*TRM = Transplantation Related Mortality

**VOD = Veno-Occlusive Disease of the liver

***GVHD = Graft versus Host Disease

OVERDOSAGE

There is no known antidote to BUSULFEX other than hematopoietic progenitor cell transplantation. In the absence of hematopoietic progenitor cell transplantation, the recommended dosage for BUSULFEX would constitute an overdose of busulfan. 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. The hematologic status should be closely monitored and vigorous supportive measures instituted as medically indicated. 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 is 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 phenytoin as busulfan is known to cross the blood brain barrier and induce seizures. Phenytoin reduces busulfan plasma AUC by 15%. Use of other anticonvulsants may result in higher busulfan plasma AUCs, and an increased risk of VOD or seizures. In cases where other anticonvulsants must be used, plasma busulfan exposure should be monitored (See DRUG INTERACTIONS). Antiemetics should be administered prior to the first dose of BUSULFEX and continued on a fixed schedule through administration of BUSULFEX.

BUSULFEX clearance is best predicted when the BUSULFEX dose is administered based on adjusted ideal body weight. Dosing BUSULFEX based on actual body weight, ideal body weight or other factors can produce significant differences in BUSULFEX (busulfan) Injection clearance among lean, normal and obese patients. The usual adult dose of BUSULFEX as a component of a conditioning 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, administered every 6 hours for 4 days (a total of 16 doses). For obese, or severely obese patients, BUSULFEX should be administered based on adjusted ideal body weight. Ideal body weight (IBW) should be calculated as follows (height in cm, and weight in kg): IBW (kg; men)= 50 + 0.91x(height in cm -152); IBW(kg, women)= 45 + 0.91x(height in cm -152). Adjusted ideal body weight (AIBW) should be calculated as follows: AIBW = IBW +0.25x(actual weight - IBW). Cyclophosphamide is given on each of two days as a one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, six hours following the 16th dose of BUSULFEX.

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.

BUSULFEX is a clear, colorless solution. Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration whenever the solution and container permit. If particulate matter is seen in the BUSULFEX ampoule the drug should not be used.

Preparation for Intravenous Administration:

BUSULFEX must be diluted prior to use with either 0.9% Sodium Chloride Injection, USP (normal saline) or 5% Dextrose Injection, USP (D_5W). The diluent quantity should be 10 times the volume of BUSULFEX, so that the final concentration of busulfan is approximately 0.5 mg/mL.

Calculation of the dose for a 70 kg patient would be performed as follows:

(70kg 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 D_5W) 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. In accordance with pharmacy practices, filter BUSULFEX using the 5 micron syringe filter provided with each package, using one filter per ampoule. If using the enclosed syringe filter in the forward flow direction, the calculated volume of Busulfex should allow for approximately 0.16 ml of residual Busulfex that will remain in the filter.

DO NOT put the BUSULFEX into an intravenous bag or large-volume syringe that does not contain normal saline or D_5W. Always add the BUSULFEX to the diluent, not the diluent to the BUSULFEX. Mix thoroughly by inverting several times. USE OF SYRINGE FILTERS OTHER THAN THE

SPECIFIC TYPE INCLUDED IN THIS PACKAGE WITH EACH AMPOULE IS NOT RECOMMENDED. DO NOT USE POLYCARBONATE SYRINGES OR POLYCARBONATE FILTER NEEDLES WITH BUSULFEX.

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 5mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. DO NOT infuse concomitantly with another intravenous solution of unknown compatibility. WARNING: RAPID INFUSION OF BUSULFEX HAS NOT BEEN TESTED AND IS NOT RECOMMENDED.

STABILITY

Unopened ampoules of BUSULFEX are stable until the date indicated on the package when stored under refrigeration at 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.

HOW SUPPLIED

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

NDC 62161-005-38	10mL (6mg/mL) in packages of eight ampoules including eight compatible 5 micron syringe filters.

Unopened ampoules of BUSULFEX must be stored under refrigerated conditions between 2°-8°C (36°-46°F).

HANDLING AND DISPOSAL

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[i,ii,iii,iv,v,vi] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

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United States Patent numbers 5,430,057 and 5,559,148. Patents pending in Canada and European Union.

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For questions of a medical-nature call 1-888-867-7426 (1-888-8ORPHAN).

To order BUSULFEX call 1-800-359-4304.