CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-954/S-004

Medical Review(s)

Clinical Review Cover Sheet

Application #	**20-954/SE2-004**
Drug Name	**Busulfex Injection**
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Documents reviewed	**SE2-004 BZ , BL Electronic/Hard copy**

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Clinical Review for NDA

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The Division of Oncology Drug Products (DODP), Center for Drug Evaluation and Research (CDER), FDA recommends the addition of limited dosing and safety information for children to the patient package insert for busulfan injection (busulfex) based on data submitted in this supplemental application. Busulfex is currently approved for use with cyclophosphamide as a component of the preparative regimen prior to hematopoietic stem cell transplantation for chronic myelogenous leukemia (CML). No new indication is being sought.

Although the sponsor has agreed with FDA's proposed label revisions regarding dosing recommendations based on body weight, they did not agree with FDA's recommendations for therapeutic drug monitoring to be included in the label. They have proposed formulae for dose adjustment based on a calculation of AUC, with a recommendation for 3 blood samples after Dose #1 in order to calculate dose modification. Since the sponsor has indicated that providing FDA's requested justification for this approach will require a time period that extends beyond the deadline for an action to be taken, the FDA will issue an approvable letter, with the following outlined in the letter as information required before an approval can be issued :

1. Justification of the choice of the 2, 4, and 6 hr times for sampling Busulfex concentrations.

2. Demonstration that the use of these three samples can be used to accurately determine AUC. This should include a comparison of the Busulfex AUC derived from the complete data for each patient in the OMC-BUS-5 trial with the AUC derived using the three samples at the proposed time points for each patient.

3. Busulfex labeling instructions that explain how to take the samples and how to calculate the AUC.

The data submitted in this labeling submission consisted of results from a single phase 2 pharmacokinetic trial (OMC-BUS-5) of busulfan injection, used in combination with cyclophosphamide, as a preparative regimen prior to allogeneic hematopoietic cell transplantation in 24 pediatric patients with a variety of hematologic malignant and non-malignant conditions. The study and its results are summarized in section II of this document. Efficacy could not be fully assessed in this study due to the heterogeneity of the patient population, the small number of patients on the study, and the lack of a control arm.

Myeloablation and engraftment should be regarded as providing information on safety, not efficacy in this setting.

With regard to risks associated with intravenous busulfan treatment in combination with cyclophosphamide as a component of the preparative regimen for hematopoietic stem cell transplantation, the FDA's previous review of busulfan injection for the treatment of adults with hematologic malignancies identified a number of concerns. The review of the database of children with a variety of hematologic and non-hematologic conditions has allowed identification of the following safety issues, common to those noted in the prior review :

Nausea and Vomiting : All patients experienced vomiting and a majority experienced nausea.

Stomatitis : The majority of patients experienced stomatitis, which is a common side effect of preparative regimens used for allogeneic hematopoietic cell transplantation.

Hepatic Veno-Occlusive Disease (HVOD) : HVOD occurred in 21% of children treated in the study. One child died on day +28 with pneumonia and HVOD.

Graft Versus Host Disease (GVHD) : GVHD was noted in 25% of the children treated, and mainly involved the skin. GVHD was not fatal in any patient, however one child who had developed acute GVHD died on BMT day +97 due to multi-organ failure and Klebsiella pneumonia. Furthermore, it must be noted that the collection of adverse event data (AE) up to day +100 post BMT limits the assessment to acute GVHD.

Cytopenias : As expected, cytopenias occurred in all patients.

Infection : Infections were reported in more than half the patients. Pneumonia was diagnosed in 21% of patients. Two children died of pneumonia and comorbid conditions during the first 100 days post-transplant.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No new phase 4 commitments are contemplated. As a component of the approval process for this supplemental application, prior phase 4 commitments made by the applicant will be reiterated in the approval letter.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Busulfan injection is an intravenously administered bifunctional alkylator given in conjunction with cyclophosphamide as a component of the preparative regimen used in hematopoietic stem cell transplantation.

The applicant has submitted a single, phase 2 , multi-center, uncontrolled pharmacokinetic study of busulfan intravenous injection used with cyclophosphamide as a preparative regimen for allogeneic hematopoietic stem cell transplantation in 24 pediatric patients with malignant hematologic and non-malignant conditions. Patients received busulfan for a total of 16 doses given over 4 days followed by cyclophophamide daily for 4 days. After a 1 day rest period, hematopoietic stem cells were infused. The study period was defined as BMT day –10 to +28, and the post-study surveillance period from day +29 to day +100. Initial busulfan dosing (mg/kg) was based on age, with dose adjustment allowed based on PK data collected. PK data were collected around doses 1 and 9, with more limited sampling around dose 13.

B. Efficacy

Efficacy could not be evaluated properly due to the small number of patients in the trial, the heterogeneity of diagnoses, and the lack of a controlled setting. Myeloablation was achieved in all 24 patients. Engraftment was documented in 23 patients (96%). Myeloablation and engraftment should be regarded as providing safety information, and do not constitute evidence of benefit.

C. Safety

1. Adequacy of safety testing

All 24 patients received all 16 doses of busulfan. All adverse events (AEs) that occurred during the study (BMT day –10 through day +28, inclusive) were recorded in the CRF. Only serious adverse events (SAEs) and toxicity grade 3 or 4 AE's were reported from BMT day +28 to day +100.

In addition to the 24 pediatric patients receiving busulfan injection on study OMC-BUS-5, FDA has previously reviewed safety data from a total of 119 adult patients in one phase 1 study (OMC-BUS-2) and two phase 2 studies (OMC-BUS-3, 4) receiving busulfan injection or a combination of busulfan injection and oral busulfan as a component of a preparative transplant regimen for hematologic malignancies. The prior review also evaluated the sponsor's literature review describing the use of oral busulfan in a number of disease settings.

2. Serious side effects

Preparative regimens for allogeneic hematopoietic stem cell transplantation, including those with busulfan as a component, are associated with a number of serious adverse events which are mostly related to the cytotoxic effect of alkylators and the vulnerability of proliferating cells of the marrow and gastrointestinal tract. Stomatitis, cytopenias, vomiting, and diarrhea are examples of such toxicity. GVHD and VOD are toxicities somewhat unique to the transplant setting, and these were observed in the children treated on OMC-BUS-5 as they have been observed in children and adults undergoing allogeneic hematopoietic cell transplantation in a number of settings.

a. Nausea and Vomiting

Nausea occurred in 83% of patients and vomiting occurred in all 24 patients. However, grade 3 nausea or vomiting occurred in 8% and 13% of patients, respectively.

b. Stomatitis

Nineteen patients (79%) experienced stomatitis. Grade 3 or 4 stomatitis was reported in 17% of patients.

c. HVOD

HVOD occurred in 21% of patients. One patient who died on BMT day +28 had diagnoses of HVOD and pneumonia at the time of death. Although the incidence of HVOD appears to be increased in OMC-BUS-5 over that observed in the adult phase 2 trial of busulfan injection (8% in OMC-BUS-4), the two populations differ in age, diagnosis, dosing of preparative regimen, and prior therapy.

d. Cytopenias

As expected, these occurred in all patients. These events included anemia, thrombocytopenia, leukopenia, and neutropenia.

e. Infection

Infections were reported in more than half the patients. Pneumonia was diagnosed in 21% of patients. One patient died with pneumonia on BMT day +28 and a concomitant diagnosis of VOD and another patient died of pneumonia/capillary leak syndrome on BMT day +16.

f. Nervous System

The most common nervous system adverse events reported were agitation (29%) and nervousness (25%). Serious nervous system AE's were uncommon (total 8%). Specifically, one patient had a convulsive episode on BMT day +3 associated with acidosis. Another patient had an episode of hypertensive encephalopathy on BMT day +70.

3. Drug-drug interactions

Cautions relevant to drug interactions already outlined in the label include the following:

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 and granisetron 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.

4. Warnings

Warnings pertaining to physiologic effects of busulfan injection in the setting of allogeneic transplantation are already present in the label and cover hematologic, neurologic, hepatic, cardiac, and pulmonary effects. No changes are contemplated.

D. Dosing

The currently recommended adult dose of busulfan injection 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). 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 16^{th} dose of BUSULFEX.

The applicant conducted a trial of busulfan injection in combination with cyclophosphamide as a preparative regimen for a variety of hematologic malignant and non-malignant diseases in 24 pediatric patients. This pharmacokinetic study based initial busulfan dose on body weight, with dose adjustment based on PK data. The sponsor performed a retrospective population pharmacokinetic (PPK) analysis to describe the PK

characteristics of busulfan injection in children. Based on this analysis, the sponsor has proposed a 4-step dosing regimen based on weight.

FDA medical and biopharmaceutics reviewers agree that this 4-level dosing regimen based on weight is cumbersome and prone to error. The sponsor's division of dosing recommendations into 4 different groups based on weight ranges is derived from a division of the exposure curve as calculated by the sponsor. There is an increase in the dosing recommendation with increased weight and subsequently a decrease with further weight increases, a pattern likely to be misinterpreted by physicians and pharmacists. The sponsor's silence on specific recommendations for modification of dosing beyond Dose #1 based on AUC also raises safety concerns given the known PK/PD relationship between busulfan exposure and clinical outcomes.

The FDA has conducted an independent analysis and developed two simpler dosing regimens. The first is a two-step dosing scheme that is based on actual body weight (1.1 mg/kg if $\leq$ 12 kg and 0.8 mg/kg if >12 kg). The second dosing regimen consists of a _____ The biopharmaceutics review team is recommending the first regimen due to the familiarity of the oncology community with body weight-based dosing of intravenous busulfan and the equivalence between the two regimens with respect to achieving target AUC. Because the FDA modeling and simulations indicated that 60% of patients will achieve a target AUC of 900 to 1350 μM-min with the first dose of busulfan, therapeutic drug monitoring is recommended. FDA has devised formulae for dose adjustment to achieve target exposure. FDA also recommends providing instructions on blood sampling for therapeutic drug monitoring in the label.

See section VIII of the clinical review document for further details.

E. Special Populations

1. Pediatrics

See above. OMC-BUS-5 was conducted in children up to 16 years of age. Limited dosing and safety information in children will be added to the current label.

2. Elderly

Five of sixty-one patients treated in the Busulfex adult clinical trial (OMC-BUS-4) were over the age of 55 (range 57-64). All achieved myeloablation and engraftment.

3. Renal or Hepatic Impairment

Busulfan injection has not been studied in patients with renal impairment or hepatic insufficiency.

4. Gender / Ethnicity

Adjusting busulfan dosage based on gender or race has not been adequately studied. In OMC-BUS-5, there were 12 males and 12 females. The small number of patients in the study precludes any definitive conclusions regarding gender or race as it relates to the safety profile of the drug.

5. Pregnancy

Busulfan injection should not be used in pregnant women. The drug is currently labeled as pregnancy class D, due to its teratogenic effects. Teratogenic changes observed in the offspring of mice, rats, and rabbits when given during gestation involved the musculoskeletal system, body weight, and size. In pregnant rats, busulfan produced sterility in both male and female offspring. The solvent, DMA, may also cause fetal harm when administered to a pregnant woman. In rats, DMA given during organogenesis caused significant developmental anomalies.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: **Busulfan Injection**
Proprietary Name: **Busulfex**
Applicant: **Orphan Medical, Inc.**
Drug Class: **Bifunctional alkylating agent**

Indication:

Current: Busulfex (busulfan) injection is currently indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

Proposed by Sponsor: No change

Dosage and Administration

Current : 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 AUC's, 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 one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, six hours following the 16th dose of BUSULFEX.

Proposed by Sponsor : When BUSULFEX is administered as a component of the BuCy conditioning regimen prior to bone marrow or peripheral blood progenitor cell replacement, the recommended doses are as follows :

Adults (BuCy2) : The usual adult dose 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 one-hour infusion at a dose of 60 mg/kg beginning on BMT day –3, no sooner than six hours following the 16th dose of BUSULFEX.

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Table 1 : Sponsor's Suggested Dosing Recommendations

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Cyclophosphamide is given on each of four days as a one-hour infusion at a dose of 50 mg/kg beginning on BMT day –5, no sooner than six hours following the 16th dose of BUSULFEX.

BUSULFEX diluted in normal saline or 5% dextrose, 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 AUC's, 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. Where available, pharmacokinetic monitoring may be considered to further optimize therapeutic targeting.

Special Populations- Pediatric

Current : 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.

Proposed by Sponsor: The — effectiveness of BUSULFEX

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Patients received BUSULFEX doses every six hours as a two-hour infusion over four days for a total of 16 doses, followed by cyclophosphamide 50 mg/kg once daily for — four days. After one rest day, hematopoietic progentior cells were infused. All patients received phenytoin as seizure prophylaxis.

— The target AUC (900-1350 ±5% μM•min) was achieved at Dose 1 in 71% (17/24) of patients.

— steady-state dose PK testing was performed (Dose 9 or 13).
range.

B. State of Armamentarium

The combination of high dose oral busulfan and intravenous cyclophosphamide is a widely used conditioning regimen in preparation for stem cell transplantation. One drawback to the use of busulfan in an oral form is its erratic and unpredictable absorption from the gastrointestinal tract which can result in wide variation in the concentrations achieved after oral dosing. Marked interpatient and intrapatient variability in busulfan disposition has been observed in both adult and pediatric populations. (1, 2, 3)

In the pediatric population, studies have demonstrated that the apparent clearance of oral high dose busulfan is larger relative to body size in children under the age of 4 years as compared

with older children or adults. (3, 4, 5) The reasons for these differences have not been identified, but may include increased hepatic clearance and a relatively higher intestinal first-pass elimination of busulfan.

Variations in bioavailability may be of concern given the association of busulfan's PK profile with clinical outcomes. The literature suggests that there is increased risk of developing serious complications such as hepatic veno-occlusive disease (HVOD) and seizures with high busulfan concentrations and greater AUC values. Conversely, patients with poor absorption, lower plasma concentrations, and hence lower AUC's may have difficulties with engraftment or inadequate disease treatment. (6, 7)

Given the existence of a pharmacokinetic/pharmacodynamic relationship between busulfan exposure and clinical outcomes, pharmacokinetically guided dose adjustment has been advocated to reduce inter-patient variability in systemic busulfan exposure in an effort to control toxicity and retain or increase therapeutic efficacy. This strategy has met with variable success. Recently, Bolinger et al have reported an improvement in engraftment rate from 74% to 94% in 32 pediatric patients undergoing allogeneic bone marrow transplantation by targeting busulfan steady state concentrations of 600-900 ng/ml. (8,9)

Given the variations in bioavailabilty of oral busulfan and the difficulty of administering oral medications to children, especially those undergoing therapies associated with mucositis and nausea/vomiting, intravenous preparations may offer potential advantages for use in the pediatric population.

Currently, busulfex (busulfan injection) is indicated for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation (HPCT) for chronic myelogenous leukemia (CML). Although a specific pediatric indication does not exist, busulfan injection is being administered to pediatric patients as a component of preparative regimens for hematopoietic stem cell transplantation.

CML occurs infrequently in children, representing less than 5% of all childhood leukemias. Although diagnosed in children as young as 3 months of age, 80% of pediatric CML cases are diagnosed after the age of 4 years. (10) The clinical and laboratory characteristics of childhood CML are similar to those of CML as it occurs in adults. In both children and adults, the disease is characterized by the presence of a specific translocation t(9;22) (q34;q11) known as the Philadelphia chromosome. (11, 12)

Although allogeneic hematopoietic progenitor cell transplanation (HPCT) has been associated with 17-41 months of event free survival after HPSCT in individual pediatric patients with CML (13), this strategy has not been evaluated in children using a uniform preparative regimen containing busulfan and cyclophosphamide in the setting of a controlled trial.

The labeling supplement submitted by Orphan Medical on 12/21/01 includes data from a single open label uncontrolled clinical pharmacokinetic trial performed in 24 pediatric patients treated with busulfex as part of a preparative regimen prior to HPCT for a variety of malignant and non-malignant diseases (OMC-BUS-5). Orphan Medical is requesting changes to the package insert

to incorporate pediatric information on dosing, pharmacokinetics, and safety. Orphan Medical also requested an additional 6 months of marketing exclusivity regardless of whether the labeling supplement is approved or not. This exclusivity extension was granted on 3/12/02.

See section IV D for literature listing.

C. Important Milestones in Product Development

7/28/94 Busulfan received orphan drug status.

11/16/97 OMC-BUS-5 initiated in children with malignant and non-malignant disorders.

08/04/98 Original NDA 20954 for busulfan intravenous injection submitted to FDA.

02/04/99 Busulfan intravenous injection was approved by the United States Food and Drug Administration for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia.

01/20/00 Pre-sNDA meeting. ⊏

⊐ It was stated that submission of data from OMC-BUS-5 may justify addition to the pediatric section of the package insert of some information on safety, dosing and pharmacokinetics.

3/27/00 Pediatric Written Request issued by FDA.

12/20/01 NDA 20954/SE2-004 submitted to FDA.

3/12/02 Pediatric exclusivity granted.

Three amendments to OMC-BUS-5 were submitted as follows :

1/05/98 Amendment #1 included changes associated with PK collection/processing/shipping, clarification of donor eligibility ('siblings' not just 'related') , target range of dose adjustment, clarification of GVHD grading and modification of chart to reflect pediatric values, clarification of treatment evaluations and statistical methodology

9/22/98 Amendment #2 updated the definition of SAE/AE events per FDA input. It also expanded eligibility to allow one-antigen mismatched sibling donors. Based on the published literature of busulfan pharmacokinetics in children and interim analysis of the PK data for the first 7 patients enrolled, the initial dose of busulfan for children $\leq$ 4 years of age was increased to 1.0 mg/kg/dose. The dose for children > 4 remained 0.8 mg/kg.

4/05/99 Amendment #3 added the collection of chimerism data, eliminated the requirement that at least 4 patients in the age group of 2 weeks - < 2 years be treated, and added evidence of acute hepatitis and prior BMT to the exclusion criteria.

D. Other Relevant Information

In addition to its approval in the United States for use in combination with cyclophosphamide as a conditioning regimen prior to allogeneic hematopoietic progenitor cell transplantation for chronic myelogenous leukemia, busulfan injection has been approved in Canada, Israel, and South Korea. A drug application was submitted to the EMEA in November, 2001. The approvals in other countries are listed in Table 2 below :

Table 2 : List of Approvals in Other Countries

Country	Approval Date	Indication
Canada	7/22/99	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, myelodysplastic syndrome, breast cancer, ovarian cancer, and several genetic diseases
Israel	1/20/00	For use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation
South Korea	11/14/01	For use in combination with cyclophosphamide as a conditioning regimen prior to hematopoietic progenitor cell transplantation, including : acute leukemia, chronic myeloid leukemia, lymphoma, myelodysplastic syndrome

E. Important Issues with Pharmacologically Related Agents

None.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Clinical Pharmacology and Biopharmaceutics

The applicant conducted a trial of busulfan injection in combination with cyclophosphamide as a preparative regimen for a variety of hematologic malignant and non-malignant diseases in 24 pediatric patients. This pharmacokinetic study based initial busulfan dose on body weight, with dose adjustment based on PK data. The sponsor performed a retrospective population pharmacokinetic (PPK) analysis to describe the PK characteristics of busulfan injection in children. Based on this analysis, the sponsor has proposed a 4-step dosing regimen based on weight.

FDA medical and biopharmaceutics reviewers agree that this 4-level dosing regimen based on weight is cumbersome and prone to error. The sponsor'sdivision of dosing recommendations into 4 different groups based on weight ranges is derived from a division of the exposure curve as calculated by the sponsor. There is an increase in the dosing recommendation with increased weight and subsequently a decrease with further weight increases, a pattern likely to be misinterpreted by physicians and pharmacists. The sponsor's silence on specific recommendations for modification of dosing beyond dose 1 based on AUC also raises safety concerns given the known PK/PD relationship between busulfan exposure and clinical outcomes.

The FDA has conducted an independent analysis and developed two simpler dosing regimens. The first is a two-step dosing scheme that is based on actual body weight (1.1 mg/kg if $\leq$ 12 kg and 0.8 mg/kg if >12 kg). The second [redacted] The biopharmaceutics review team is recommending the first regimen due to the familiarity of the oncology community with body weight-based dosing of intravenous busulfan and the equivalence between the two regimens with respect to achieving target AUC. Because the FDA modeling and simulations indicated that 60% of patients will achieve a target AUC of 900 to 1350 μM-min with the first dose of busulfan, therapeutic drug monitoring is recommended. FDA has devised formulae for dose adjustment to achieve target exposure. FDA also recommends providing instructions on blood sampling for therapeutic drug monitoring in the label.

See section VIII (Dosing, Regimen, and Administration Issues) for further details.

B. Statistics

A separate statistical review was not conducted.

C. Chemistry

The chemistry, manufacturing, and controls information has been cross-referenced to the original NDA. No changes have been made to the manufacture of the drug substance and the drug product. The supplement was recommended for approval from the standpoint of chemistry, manufacturing, and controls.

D. Animal Pharmacology and Toxicology

No animal pharmacology and toxicology review was conducted for this supplemental NDA as there was no new data submitted.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

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, which is thought to be responsible for the cytotoxic activity of busulfan.

In 59 adult patients participating in a prospective trial of busulfan injection/cyclophosphamide preparatory regimen prior to allogeneic HPSCT, patients received 0.8 mg/kg of busulfan injection every 6 hours for a total of 16 doses. Fifty-five of fifty-nine patients maintained AUC values below the target value of 1500 μM•min. Mean clearance, normalized to actual body weight, was 2.52 ml/min/kg.

In a pharmacokinetic study of busulfan injection in 24 pediatric patients (OMC-BUS-5), the population estimate of clearance was 4.04 L/hr/20 kg (3.37/ml/min/kg), and the volume of distribution was 12.8 L/20 kg (0.64 L/kg).

B. Drug Interactions

Itraconazole decreases busulfan clearance by up to 25%, and may produce AUC > 1500 μM•min in some patients.

Phenytoin increases the clearance of busulfan by 15% or more, possibly due to the induction of glutathione-S-transferase. Since the pharmacokinetics of busulfan injection were studied in patients treated with phenytoin, the clearance 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 busulfan injection may result in reduced busulfan clearance based upon the known property of acetaminophen to decrease glutathione levels in the blood and tissues.

C. Pharmacodynamics

See (State of Armamentarium, Efficacy Review, and Safety Review) sections of the review for further information on the PK/PD relationship between busulfan exposure and clinical outcome.

IV. Description of Clinical Data and Sources

A. Overall Data

OMC-BUS-5, an open label uncontrolled pharmacokinetic trial of busulfan injection used as a component of a busulfan/cyclophosphamide preparative regimen for allogeneic hematopoietic stem cell transplantation in children with hematologic malignant and non-malignant diseases was submitted.

B. Table Listing the Clinical Trials

A single trial was submitted, as listed in Table 3. It is entitled :

" A Phase II Trial of Intravenous Busulfan and Cyclophosphamide with Allogeneic Hematopoietic Stem Cell (Marrow or Peripheral Blood Progenitor Cell) Transplantation for Malignant or Non-Malignant Disease in Pediatric Patients. "

Table 3 : Clinical Trial Submitted to sNDA

Trial	Country	Enrollment Dates	N	Primary Endpoint
OMC-BUS-5	USA	11/17/97 to 1/5/02	24	Time to engraftment

C. Postmarketing Experience

Since approval of the NDA in February 1999, the sponsor has received five safety reports for seven adverse drug experiences (ADEs) including myocardiopathy, veno-occlusive disease, hepatomegaly, aspergilloma, sepsis, pulmonary hemorrhage, and acute pulmonary toxicity. All but myocardiopathy are known adverse events already described in the patient package insert. Although myocardiopathy is not specifically described in the label, a reference to the occurrence of cardiac tamponade in pediatric thalassemia patients who have received high doses of oral

busulfan and cyclophosphamide as the preparatory regimen for hematopoietic progenitor cell transplantation is present in the WARNINGS section. The myocardiopathy post-marketing adverse event was described as follows:

A 17 year old with CML who underwent stem cell transplantation after a preparative regimen of buuslfan/melphalan developed streptococcus mitis sepsis on BMT Day +8 and was intubated. On Day +11, an echocardiogram revealed an ejection fraction of 15-20%. After treatment with antibiotics and other supportive care, her condition improved, with stabilization of her hemodynamic status. Due to the multiple potential contributors to the change in ejection fraction from baseline, the FDA medical reviewer recommends no modification to the cardiovascular component of the WARNINGS section of the label at this time. However, any future reports of reduced myocardial function should be carefully evaluated.

D. Literature Review

The sponsor's literature review was extensive, and included many of the manuscripts listed here in support of the section describing the state of the armamentarium. References 11-13 listed below by the medical reviewer provide background information regarding CML in childhood. (See section 1.B State of Armamentarium)

1. Grochow LB. Busulfan Disposition : The Role of Therapeutic Monitoring in Bone Marrow Transplantation Induction Regimens. Seminars in Oncology 20 (4 Suppl 4):18-25, 1993.
2. Hassan M, Ehrsson H, and Ljungman P. Aspects concerning busulfan phamracokinetics and bioavailability. Leukemia Lymphoma 22: 395-407, 1996.
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V. Clinical Review Methods

A. How the Review was Conducted

The efficacy review is based primarily on data from the uncontrolled, open label phase 2 trial OMC-BUS-5 in children with malignant hematologic and non-malignant diagnoses undergoing allogeneic hematopoietic cell transplantation.

B. Overview of Materials Consulted in Review

The following materials were reviewed by the medical and statistical officers:

- The regulatory history of the application
- The 1998 review of busulfan injection as a component of the conditioning regimen for hematopoietic progenitor cell transplantation.
- Electronic submission of the sNDA
- Relevant published literature

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Data quality and integrity were evaluated by analysis of datasets provided as SAS transport files and imported into JUMP by the medical reviewer. Case report forms were provided electronically for all 4 patients who died during the study or post-study surveillance period.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

OMC-BUS-5 was a multicenter trial. The sponsor has provided documentation of IRB approval of the protocol and consent form at all participating institutions.

E. Evaluation of Financial Disclosure

The sponsor has submitted certification that Orphan Medical has not entered into any financial arrangement with any of its clinical investigators who participated in OMC-BUS-5. This certification was signed on 12/20/01 by Carol Curme, J.D., Senior Manager for Regulatory Affairs.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Although the sponsor is not seeking a new indication, the proposed label includes information on dosing, myeloablation, engraftment, survival, and adverse events of OMC-BUS-5, which would be added to the section on special populations – pediatrics. The reviewer considers the survival data uninterpretable given the small number of patients, the uncontrolled setting, and the diversity of the patient population with respect to diagnosis and recommends that such data not be incorporated into the label.

The sponsor has provided information on myeloablation and engraftment; however this should be regarded as providing safety information and does not constitute evidence of benefit. The reviewer agrees with the sponsor's assessment that myeloablation occurred in all 24 patients (100%) and that engraftment (as defined by absolute neutrophil count) was achieved in 23 patients (96%). The reviewer considers the chimerism data provided in support of engraftment to be limited by variability in the testing performed and the absence of chimerism data for some patients. Therefore, chimerism data for OMC-BUS-5 should not be incorporated into the label.

B. Detailed Review of Trials by Indication

The review was based on data from a single, uncontrolled, open-label pharmacokinetic trial of busulfan injection with cyclophosphamide as a preparative regimen for hematopoietic stem cell transplantation in 24 pediatric patients with a variety of malignant and non-malignant diagnoses (OMC-BUS-5).

1. Protocol Review

Table 4 lists the principal investigators and their corresponding participating institutions.

Table 4 : Principal Investigators and Address

Investigator Name	Address
Dr. Donna Wall	Cardinal Glennon Children's Hospital Pediatric Stem Cell Transplant 1465 South Grand Boulevard St. Louis, MO 63104
Dr. Robert Hayashi	St. Louis Children's Hospital 1 Children's Place Box 8116 St. Louis, MO 63110
Dr. Martin Klemperer	All Children's Hospital 801 Sixth Street, South St. Petersburg, FL 33701
Dr. Jay Feingold	University of Connecticut Health Center MC 1315, RM L-3092 263 Farmington Avenue Farmington, CT 06030-1315
Dr. Richard Kadota	Children's Hospital and Health Center Hematology/Oncology Division MC 5035 3020 Children's Way San Diego, CA 92123-4282
Dr. Morris Kletzel	Children's Memorial Hospital Division of Hematology/Oncology (Box #30) 2300 Children's Plaza Chicago, IL 60614
Dr. Ka Wah Chan	UT M.D. Anderson Cancer Center Department of Pediatrics Box 87 1515 Holcombe Blvd. Houston, TX 77030
Dr. Michael Nieder	Pediatric Hematology/Oncology Rm 310 Rainbow Babies and Children's Hospital 1100 Euclid Avenue Cleveland, OH 44106
Dr. Andrew M. Yeager	Emory University School of Medicine Department of Pediatrics Division of Hematology/Oncology and Bone Marrow Transplantation 2040 Ridgewood Drive, N.E.

	Atlanta, GA 30322
Dr. Donna Przepiorka	Baylor College of Medicine Center for Cell and Gene Therapy 6565 Fannin Street, M-964 Houston, TX 77030

Table 5 : Protocol Milestones

Milestone	Date	Comments
Protocol open	7/17/97	
Amendment #1	1/05/98	Changes associated with PK, donor, donor cells, target range of dose adjustment, GVHD grading, busulfex administration, treatment evaluations and statistical methodology
Amendment #2	9/22/98	1) changed dosing regimen: 2) eligibility expanded to allow one antigen mismatch 3) Update SAE/AE per FDA definitions
Amendment #3	4/05/99	1) evidence of acute hepatitis and prior BMT added to exclusion criteria 2) eliminated requirement that at least 4 patients be treated in age group of 2 weeks - < 2 yrs 3) added collection of chimerism data
Last patient completed	1/05/00	
Data cut-off date	3/16/00	

Objectives:

Primary : To determine the safety profile of a new formulation of intravenous busulfan when used in combination with cyclophosphamide as a preparative regimen for allogeneic hematopoietic progenitor cell (marrow or peripheral blood progenitor cell) transplantation in pediatric patients.

Secondary :

1) To describe the plasma pharmacokinetics of busulfan in pediatric patients when the drug is administered intravenously in this regimen
2) To determine the mean time to engraftment when using this regimen

Selection Criteria

Inclusion Criteria

1) Acute leukemia, chronic myelogenous leukemia, myelodysplastic syndrome, genetic diseases including combined immunodeficiency syndrome, storage disease, and disorders of red cell production, bone marrow dysfunction that would otherwise be treated with oral busulfan, or other condition after approval by study chairperson and Orphan Medical.
2) Age $\geq$ 2 weeks to < 18 years
3) Allogeneic donor : $\geq 1 \times 10^8$ nucleated cells/kg from normal, HLA-matched related sibling donors. The marrow should not be T-cell depleted. The marrow from normal donors may be processed per routine procedure for major or minor ABO-incompatibilities. As an alternative, filgrastim-mobilized peripheral blood stem cells (PBSCs) may be collected from HLA-matched related sibling donors in 1-4 aphereses and cryopreserved according to existing protocols. The apheresis collections must contain at least $\geq 1.0 \times 10^8$ nucleated cells/kg.
4) Lansky performance status > 70 for children less than 16 yrs old and a Zubrod performance score $\leq$ 2 for children 16 years of age or older
5) Life expectancy > 12 weeks
6) LVEF $\geq$ 50% or SF > 27%
7) No symptomatic pulmonary disease : $FEV_1/FVC \geq 60\%$ of expected or 0_2 saturation > 95% if pulmonary function tests are not feasible.
8) Serum creatinine < 2X ULN for age or creatinine clearance > 75% of normal for age
9) Transaminases (ALT, AST, and GGT) each $\leq$ 4 X upper limit of normal for age and serum total bilirubin < 1.5 X upper limit of normal for age
10) HIV-negative
11) Negative serum pregnancy test, no lactating women, and appropriate contraception for women of childbearing potential.
12) Parent or legal guardian able to sign informed consent
13) Central venous access through an indwelling catheter
14) Ability to obtain the required volume of blood samples for busulfan pharmacokinetics testing based on clinical assessment of the patient's condition at the time of enrollment

Reviewer Comment : In amendment #1 dated 12/22/97, the ability to obtain the required volume of blood was added as an inclusion criterion and the lower limit of 2 weeks for age was specified. The availability of a matched sibling donor was also specified. In amendment # 2

dated 09/14/98, eligibility was modified to include the availability of a partially matched (one antigen mismatch) related sibling donor.

Exclusion Criteria

1) cord blood transplants
2) uncontrolled arrhythmias or symptomatic cardiac disease
3) other investigational drug (s) administered within 30 days prior to trial enrollment (BMT Day –10)
4) active systemic infection at initiation of preparative regimen
5) evidence of chronic active hepatitis or cirrhosis
6) evidence of acute hepatititis
7) previous bone marrow transplant

Reviewer Comment : In amendment #3 dated 3/26/99, previous bone marrow transplantation and evidence of acute hepatitis were added to the exclusion criteria.

Patient Withdrawal or Discontinuation

1) withdrawal of consent
2) adverse experience or side effects
3) severe concurrent illness
4) request of the sponsor
5) noncompliance
6) disease progression warranting alternative treatments/protocols

Treatment Plan

The trial consisted of three stages :

1) a screening period
2) an inpatient period beginning on BMT day –10 and including the preparative regimen, stem cell infusion, inpatient evaluation through discharge and weekly followup to BMT day +28
3) a post-trial follow-up

Pretreatment evaluation included a complete history and physical examination, bone marrow aspirate or biopsy (with cytogenetics for patients with leukemia), CBC with differential and reticulocyte count, coagulation profile, baseline pulmonary function tests if available or 0_2 saturation, EKG, 2-D ECHO or MUGA to include measurement of left ventricular function, chemistry and electrolytes, urinalysis, ABO/Rh typing, serum titers for CMV, HSV, EBV, HIV, and a hepatitis screen.