

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-954**

**MEDICAL REVIEW(S)**

# **NDA Medical Review**

**NDA 20-954**

**Busulfex<sup>™</sup>  
(busulfan)**

**Applicant:  
Orphan Medical**

**Date of Submission:  
August 3, 1998**

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# 1. INTRODUCTION

## 1.1 Basic Information and Timeline

**Table 1 Basic Application Information**

Drug Name	Busulfex <sup>TM</sup> (busulfan)
Sponsor	Orphan Medical
NDA #20-954	
Proposed Indication	For use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation. Diseases in which patient benefit from this mode of therapy have been demonstrated include acute lymphocytic leukemia, acute non-lymphocytic leukemia, acute myeloid leukemia, chronic myeloid leukemia, non—Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, myelodysplastic syndrome, breast cancer, ovarian cancer, and genetic diseases. The patient's disease status should either be refractory to other therapies or carry sufficiently high-risk for recurrence of disease that progenitor cell transplant is the treatment of choice in the opinion of a qualified physician.
Pre-NDA meeting	January 16, 1997
NDA Submission date	August 3, 1998
NDA Drug Classification	Priority
Pharmacological category	Bifunctional alkylating agent
45-day meeting	
60-day meeting	
ODAC meeting	January 1998

## 1.2 Drug Name and Chemical Characteristics

### 1.2.1 Generic Name:

Busulfan

### 1.2.2 Trade name

Busulfex

### 1.2.3 Chemical Name:

1,4-butanediol-dimethanesulfonate esters  
1,4-bis (methanesulfonyloxy)butane  
1,4-di(methanesulfonyloxy)butane  
1,4-di (methylsulfonyloxy)butane  
1,4-butanediolbis (methanesulfonate)  
methanesulfonic acid tetramethylene ester  
tetramethylene bis(methanesulfonate)

### 1.2.4 Molecular Formula

$C_6H_{14}O_6S_2$

### 1.2.5 Molecular Weight:

246.31 g

### 1.2.6 Chemistry/Manufacturing Controls:

See chemistry review for details.

## 1.3 Pharmacologic Category:

Antineoplastic Agent. Bifunctional alkylating agent.

### 1.3.1 Indications and Off-Label Use

None.

### 1.3.2 Preclinical Pharmacology/Toxicology

See pharmacology/toxicology review for details.

### 1.3.3 Clinical Pharmacology/Pharmacokinetics

See clinical pharmacology/PK report for details

## 1.4 Paper and Electronic Submission

The application consisted of a complete archival copy of 116 volumes. The clinical and statistical data section, Section 8, consisted of Volumes 31-116. The sponsor's review of the literature evidence for the efficacy and safety of oral busulfan as conditioning therapy for bone marrow transplantation was submitted in Volumes 51-53. Electronic data sets were submitted in

SAS and ACCESS. Annotated CRF's were submitted in section 10.6, Volume 65, of the application.

## **1.5 Brief Overview of the Application and Its Issues**

Busulfex™ is an intravenous formulation of busulfan. From a clinical standpoint, the safety and efficacy of this new method of administration of an old drug were addressed in this application through the submission of pharmacokinetic data, the results of two phase 2 studies employing the intravenous formulation, and an extensive literature review of oral busulfan's use in conditioning therapy for transplantation. The phase 2 studies were performed to provide evidence that the safety and efficacy of the intravenous formulation were comparable to that of oral busulfan in the setting of conditioning for hematopoietic stem cell transplantation (autologous and allogeneic). The efficacy endpoints examined in these two phase 2 trials were myeloablation and engraftment. The purpose of the literature review component of this application was to establish the diseases for which hematopoietic stem cell transplantation with a busulfan-containing conditioning regimen has been established as effective and safe. Thus, the clinical issues addressed in this application include:

- Is the pharmacokinetic profile of the intravenous formulation of busulfan similar to that of the oral formulation?
- Do the phase 2 studies establish comparable efficacy (in the setting of hematopoietic stem cell transplantation) of the intravenous formulation and oral busulfan in terms of the endpoints – myeloablation and engraftment?
- Do the phase 2 studies establish that the safety of the intravenous formulation is comparable to that of oral busulfan when given in high doses as part of a conditioning regimen for hematopoietic stem cell transplantation?
- Does the literature establish that high dose oral busulfan is safe and efficacious when given as part of a conditioning regimen for hematopoietic stem cell transplantation? If so, in which diseases and specific settings?

These issues will be addressed in this review by first reviewing the results of the pivotal phase 2 studies submitted in this application. A discussion of the literature review will follow in Section 6.0. The reader is referred to the Biopharmaceutics Review for a detailed discussion of the pharmacokinetic issues involved in this application.

## **2. Summary of Clinical Studies**

### **2.1 Pivotal Trials**

The sponsor has submitted the study reports from 3 clinical trials that employed Busulfex (busulfan) Injection in combination with cyclophosphamide as conditioning therapy for hematopoietic progenitor cell transplantation. The first study, OMC-BUS-2, was a phase 1 dose escalation study in which patients with a variety of hematological malignancies received a single dose of Busulfex, followed by 15 doses of oral busulfan, as part of conditioning therapy for either

autologous or allogeneic bone marrow and/or peripheral stem cell infusion. The remaining two studies, OMC-BUS-3 and OMC-BUS-4, were both phase 2 studies in which the entire course of busulfan in the conditioning regimen was administered as Busulfex (busulfan) Injection. In OMC-BUS-3 patients with hematological malignancies underwent autologous bone marrow and/or peripheral stem cell transplantation. In OMC-BUS-4 participants with hematological malignancies underwent allogeneic bone marrow and/or peripheral stem cell transplantation. A table summarizing these studies follows.

**Table 2 Study Summary Table**

Study No.	Design	No. Pts.	Population	Type of Transplant
OMC-BUS-2	Phase 1, dose escalation trial. Multi-center, open-label. Single dose	15		Autologous or Allogeneic
OMC-BUS-3	Phase 2, Multi-center, Open label.	42	Lymphoma=35 Acute Leukemia=7	Autologous Marrow or PBSC
OMC-BUS-4	Phase 2, Multi-center, Open label	62	Lymphoma=9 Acute Leukemia=26 CML = 17 MDS = 9	Allogeneic Marrow or PBSC

In addition, the pharmacokinetic and safety data from patients treated on an Amendment to OMC-BUS-3 (N=3) and OMC-BUS-4 (N=9) have been submitted. Patients treated under this amendment received a single dose of oral busulfan 1.0 mg/kg as the first of 16 doses of busulfan in the conditioning regimen. The remaining busulfan doses were all intravenous busulfan. This amendment became necessary because pharmacokinetic data from the phase 1 study was inadequate, due to numerous patients' data from that study having been incomplete or uninterpretable.

### 3. Pivotal Study – OMC-BUS-3: A Phase 2 Study of High-Dose Intravenous Busulfan and Cyclophosphamide with Autologous Marrow or Peripheral Blood Progenitor Cell Transplantation for Hematologic Malignancies

**Trial Accrual Dates: June 24, 1996 – January 7, 1998**

**Data Cutoff Date: January 9, 1998**

#### 3.1 Rationale

A commonly used conditioning regimen for hematopoietic stem cell transplantation is a non-TBI based regimen that combines the chemotherapeutic agents busulfan and cyclophosphamide. This regimen was originally developed at Johns Hopkins by Santos and Tutschka as busulfan 4mg/kg/d (q 6h) x 4d + cyclophosphamide 50mg/kg/d x 4d (BU/CY200 or BU/CY4). A modified regimen was subsequently developed, which reduces the dose intensity of the cyclophosphamide 60 mg/kg/d x 2d (BU/CY120 or BU/CY2). Oral busulfan is formulated in a 2 mg tablet. The high doses of busulfan required in the described conditioning regimens necessitate that patients swallow a large number of pills with each q 6h dose, which can be particularly difficult as the BU/CY regimen can be associated with significant nausea and vomiting. The sponsor has developed the intravenous formulation of busulfan as a means of easing the administration of busulfan in this situation – eliminating the necessity to swallow multiple pills and theoretically increasing busulfan's bioavailability by eliminating losses that potentially occur through emesis. This phase 2 trial was designed to demonstrate that the intravenous formulation of busulfan can also induce myeloablation and has an acceptable safety profile in the setting of autologous transplantation.

The intravenous busulfan dose selected for this study, 0.8 mg/kg, was suggested to achieve a similar AUC (plasma concentration) to that of an oral busulfan dose of 1.0 mg/kg in the phase 1 study conducted by the sponsor. A target AUC of  $<1500 \mu\text{M} \times \text{min/l}$  was selected on the basis of literature reports that indicate the risk of hepatic veno-occlusive disease (VOD) increases at higher AUC's.

### **3.2 Objectives of the Study**

- To administer multiple doses of intravenous busulfan at a dose previously shown to be pharmacokinetically equivalent to the oral formulation when it (the oral drug) is given at a dose of 1 mg/kg, and associated with an AUC less than  $1500 \mu\text{M} \times \text{min/l}$ , and to administer this dose intravenously over 2 hours every six hours for 16 doses in combination with cyclophosphamide as preparation for autologous hematopoietic stem cell transplantation. The latter could be marrow or peripheral blood derived progenitor cells. Patients with advanced malignancies would be treated in order to demonstrate that this dose and schedule is myeloablative and that engraftment will occur after such myeloablation.
- To determine the median time to engraftment of patients undergoing autologous transplantation after treatment with this regimen. Data regarding relapse rate, long-term disease-free outcome, and overall survival would be collected.
- To determine the toxicity profile of this regimen when utilized as preparation for autologous transplantation.
- To describe the plasma pharmacokinetics of busulfan when administered intravenously in this regimen.

### **3.3 Study Design**

This trial was an open-label, multicenter phase 2 study. Five centers accrued patients.