APPLICATION NUMBER: NDA 20-954

PHARMACOLOGY REVIEW(S)
Division of Oncology Drug Products, HFD-150
Review and Evaluation of Pharmacology and Toxicology Data
Review # 1

NDA: 20-954
Serial: 000 Type NDA
Original NDA Dated August 4, 1998
Completed January 25, 1999

Title: Intravenous busulfan (Myleran) for bone marrow ablation in adult and pediatric patients with leukemia or lymphoma.

Information to be conveyed to the sponsor: No

Reviewer: W. David McGuinn, Jr., Ph. D., D.A.B.T.

Sponsor: Orphan Medical, Inc.
13911 Ridgedale Drive
Minnetonka, MN 55305

Drug Name: Busulfex (busulfan IV)
Chemical Name: 1,4-bis-(methanesulfonyl)butane
FW = 246.3, CAS 55-98-1

\[
\text{CH}_3\text{SO}_2\text{O(CH}_2)_4\text{OSO}_2\text{CH}_3
\]

Concomitant drugs: Cyclophosphamide (60 mg/kg X2) and dilantin

Vehicle: Dimethylacetamide (DMA) 33% v/v
CAS 127-19-5
Polyethylene Glycol 400 (PEG) 66% v/v

Route: IV central line

Dose: 0.8 mg/kg/dose (current clinical dose after escalation study)
Starting dose for escalation was 0.15 mg/kg/dose (5.6 mg/m²)

Schedule: Four times a day for four days

Class: bi-functional alkylating agent
Indications: Bone marrow ablation in patients with leukemia or lymphoma
Related IND:
Related NDA:
Proposed Dosage Forms and Route of Administration

The sponsor dissolves busulfan in N,N-dimethylacetamide (DMA), 18 mg/ml. They then dissolve this solution in polyethylene glycol 400 (PEG-400) to a final busulfan concentration of 6-mg/ml. This solution is dissolved in D2W or normal saline to a total volume of 250 ml before administration to the patient.

In the Phase 1 dose escalation protocol, this solution was given as an IV infusion over two hours q 6 hr for four consecutive days. The starting dose was 0.25 mg/kg/dose or 70-mg/day, total dose 280 mg for 70 kg human. After escalation, the sponsor determined that the optimum dose is 0.8 mg/kg/dose at the same four-day schedule. The following table shows the total exposure for busulfan and the vehicles at this dose. I have calculated the values for a 70-kg patient. The density of DMA is 0.937 and that of PEG is 1.128 g/ml.

<table>
<thead>
<tr>
<th>Busulfan</th>
<th>Busulfan</th>
<th>DMA Dose</th>
<th>DMA Dose</th>
<th>DMA total</th>
<th>PEG 400</th>
<th>PEG 400</th>
<th>PEG 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg/dose</td>
<td>mg/m²</td>
<td>mg/kg/dose</td>
<td>mg/kg/day</td>
<td>g/mg/kg/dose</td>
<td>mg/kg/day</td>
<td>g/70 kg man</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>473.6</td>
<td>41.6</td>
<td>166.6</td>
<td>46.6</td>
<td>101</td>
<td>402</td>
<td>113</td>
</tr>
</tbody>
</table>

This dose (0.8 mg/kg/dose) usually results in plasma AUC acceptably close to the targeted AUC (approximately 1600 to 2000 µmol*min/l). The sponsor believes that this dose will be clinically effective while avoiding one of the most serious complications of busulfan BMT, veno-occlusive disease of the liver.

Previous Clinical Experience.

The FDA has approved busulfan (Myleran) for the treatment of Chronic Myelogenous Leukemia (CML). This previously approved 2-mg tablet formulation has long been used off-label for myeloablation therapy before bone marrow transplant (BMT). Children with leukemia or lymphoma also are treated with busulfan myeloablation. In adults, the usual oral dose of busulfan for bone marrow conditioning is 35 2-mg tablets every six hours for four days, or 4 mg/kg/day (148 mg/m²/day). G.W. Santos et al. (1983, N. Engl. J. Med, 309(22); 1347-1352) have documented the efficacy of this myeloablative technique. Obviously, such a treatment regime is very difficult for the patient. The oncology community appears to have reached a consensus on the need for an IV formulation of busulfan.

The recommended dose for induction of remission of CML is considerably lower than that used for BMT. The recommended dose for CML is 1.8 mg/m²/d until the leukocyte count declines to 15,000/µl, usually twelve to twenty weeks.

Busulfan is extremely toxic. Its primary toxicity is pancytopenia. It can cause fatal bronchopulmonary dysplasia with pulmonary fibrosis. It can cause cytologic abnormalities in many organs. Busulfan is mutagenic in mice and is probably leukemogenic in man. It is hepatotoxic and has caused fatal hepatic veno-occlusive disease, especially in combination with cyclophosphamide.

The doses of the vehicles, DMA and PEG-400, proposed for this study are unusually high. This review will also consider the potential toxicity of these compounds.
Previous Reviews:

I) Safety Summary, completed October 21, 1994 by W. David McGuinn, Jr., Ph. D.

II) A review of all preclinical studies submitted up to September 29, 1997, by W. David McGuinn, Jr., Ph. D., This review included the following studies:

Busulfan plus DMA/PEG solvent system

a) Comparative Pharmacokinetics of single-dose i.v. busulfan with oral tablets in rats. This is a non-GLP study prepared as a manuscript and submitted with the original IND. The remainder of supporting information in Submission #000 is two volumes of appended clinical and pre-clinical literature articles. I have reviewed the relevant clinical and preclinical articles below.

b) A definitive toxicity study with intravenous busulfan in dogs.

c) Literature review.

Busulfan

1) Hassan et al. (1994, Blood, 84(7), 2144-2150)
3) Nadkarni et al. (1959, Cancer Res. 19(Aug); 713-718)
6) J. Musilova et al. (Mutation Research, 1979, 67:289-294)
7) H. Stott et al. (British Med. J., 1977, 2:1513-1517)

PEG

1) J.S. Lockard et al. (Epilepsia, 1979, 20, 77-84.)

DMA

Reviewed Studies:

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PRECLINICAL STUDIES OF BUSULFAN:

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9) D. H. Marchand et al. 1987. Biliary excretion of a glutathione conjugate of busulfan and 1,4-diiodobutane in the rat. Volume 9, page 17. .................................................. 16

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MUTAGENICITY AND GENOTOXICITY:


REPRODUCTIVE TOXICITY:


PEG:


DMA:

PHARMACOKINETICS AND TOXICOKINETICS:


TOXICOLGY:


REPRODUCTIVE TOXICITY:


NDA 20-954


RECOMMENDATIONS

COMMENTS DISCUSSED WITH THE MEDICAL OFFICER:

LABELING:

Studies submitted to the NDA but not reviewed:

18) L.A. Kinney et al. 1993. Inhalation studies in rats exposed to dimethylacetamide from 3 to 12 hours per day. Drug and Chemical Toxicology 16(2):175-194. Volume 8, page 142.


26) S Phadungponja et al. 1996b. Biodistribution kinetics of busulfan in rats after single and multiple doses of IV busulfan as compared with oral busulfan. Abstract submitted to the 1996 meeting of AACR. No indication it was accepted. Volume 9, page 98.


I have excerpted portions of this review directly from the sponsor's submission.
Review

Clinical Studies of Busulfan:


Angelucci et al. observed that eight of 400 children treated with high dose busulfan (14 mg/kg single dose) for thalassemia by marrow transplantation suffered severe tamponade secondary to rapid pericardial effusion. Six of the eight children died, two were saved by rapid pericardiocentesis. All the children who died were autopsied. All these children had moderate to severe iron overload with systemic hemochromatosis.

The authors examined many parameters before and after the incidents, they ultimately could not account satisfactorily for this terrible toxicity. The authors did not observe tamponade in 300 leukemia patient treated with BMT, but a Seattle BMT group (Bearman et al., *Bone Marrow Transplant*, 1990; 5:173) observed three cases in patients treated for various malignancies. All of these cases were seen in adults, all cases were less severe, and all recovered. Angelucci et al. did not report the doses in these studies; I assume the doses were less than the relatively high 14 mg/kg used in this study.

In the end, the authors postulate that the tamponade was associated with thalassemia, but their evidence does not seem to convince even them and it certainly did not convince me. This toxicity warrants watching in phase IV.


Dr. Filipek provides a clear review of drug induced pulmonary disease, including those diseases caused by antineoplastic drugs. His description of the etiology of busulfan-lung is helpful and succinct, so I will just quote his work. Busulfan, “the therapy of choice for chronic myelogenous leukemia, can produce pulmonary disease marked clinically by fever, cough, and dyspnea of insidious onset in patients who have taken the drug for years. Radiographs of the chest usually show a diffuse interstitial and alveolar infiltrate. The histological pattern is that of intraalveolar accumulation of fibrin and red blood cells frequently organized by fibroblasts and later replaced by reticulin and collagen. Some investigators feel that the basic process involves chemical alveolitis and proliferation of granular pneumonocytes followed by fibrosis of the alveolar walls.”


This review also covers a variety of chemicals that induce lung disease. The comments on busulfan are again succinct and informative.
Busulfan, mainly used in chronic myeloid leukemia, was the first cytotoxic drug to be identified as the cause of pulmonary complications. The incidence of busulfan-induced pulmonary manifestations is about 4%, but more than half of the reported cases are sub-clinical. Severe disorders have been reported only when total doses exceed 500 mg/m². Epithelial cells are particularly sensitive to busulfan, but little is known about the mechanism of busulfan induced injury.

The total cumulative busulfan dose in this NDA is 473 mg/m². Thus, there is probably some potential for severe pulmonary damage in some patients.


These authors report finding eight cases of cataracts in human patients associated with long term busulfan exposure in an ophthalmology registry and in the literature. These cataracts tend to be posterior and subcapsular with a polychromatic sheen. They also mention the possibility that keratitis sicca may be associated with long term busulfan treatment. These toxicities have been studied in rodents (see below). Though these ocular toxicities are severe and persistent, they are unlikely to be associated with the short-term exposure to high doses of busulfan used in BMT.

Preclinical Studies of Busulfan:

*Pharmacokinetics and Toxicokinetics:*


These authors have done much of the toxicology and pharmacokinetic development of Busulfex for the sponsors. They have considerable experience with this compound. In these experiments, they used commercially available Myleran tablets for the oral tablet experiments. They dosed the rats IV via a cannula in the jugular vein. They had three dose groups of rats:

1) Oral tablet ground and suspended in 0.2 ml of normal saline given by gavage - fasted-rats.
2) Oral tablet ground and suspended in 0.2 ml of normal saline given by gavage - fed-rats.
3) IV, powder solvated in the same PEG-400:DMA formulation proposed by the sponsor in this NDA.

They sampled the rat’s blood via the cannula at 0, 5, 10, 20, 30, 60 minutes and 2, 5, 8, and 24 hours. They determined the busulfan content in plasma samples by derivatization with diethylidithiocarbamic acid sodium salt. This reaction forms the spectroscopically detectable 1,4-bis(diethylidithiocarbamoyl)butane (DDCB). The detection limit for this method was 150 ng/ml (0.61 µM).
In a separate set of experiments they determined the dose linearity of the IV dosing by giving groups of rats varying doses between 0.34 and 5 mg/kg. In these experiments, weight normalized AUC increased linearly with weight normalized dose with a correlation coefficient of 0.92. In the IV experiments, the dose normalized AUC was $4.1 \pm 1 \text{ mcg} \cdot \text{h/ml}$.

The following table presents the results of the pharmacokinetic experiments at a dose of 1.0 mg/kg.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fed</th>
<th>sd</th>
<th>Fasting</th>
<th>sd</th>
<th>IV</th>
<th>sd</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7</td>
<td></td>
<td>4</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>animal wt., kg</td>
<td>0.29</td>
<td>0.04</td>
<td>0.30</td>
<td>0.06</td>
<td>0.29</td>
<td>0.05</td>
</tr>
<tr>
<td>Dose mg/kg</td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>$K_e$, h⁻¹</td>
<td>2.6</td>
<td>1.7</td>
<td>12.1</td>
<td>11.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$t_{1/2e}$, h</td>
<td>0.21</td>
<td>0.07</td>
<td>0.11</td>
<td>0.06</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$C_{max}$, mcg/ml</td>
<td>0.36</td>
<td>0.16</td>
<td>0.28</td>
<td>0.06</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$T_{max}$, h</td>
<td>0.8</td>
<td>0.18</td>
<td>0.47</td>
<td>0.25</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>$K_t$, h⁻¹</td>
<td>0.38</td>
<td>0.12</td>
<td>0.59</td>
<td>0.46</td>
<td>0.34</td>
<td>0.08</td>
</tr>
<tr>
<td>$t_{1/2}$, h</td>
<td>2.05</td>
<td>0.69</td>
<td>1.6</td>
<td>0.9</td>
<td>2.2</td>
<td>0.79</td>
</tr>
<tr>
<td>$V$, ml</td>
<td>207</td>
<td>93</td>
<td>177</td>
<td>104</td>
<td>233</td>
<td>53</td>
</tr>
<tr>
<td>$CL$, ml/h</td>
<td>68</td>
<td>8.6</td>
<td>70</td>
<td>16</td>
<td>77.9</td>
<td>21.9</td>
</tr>
<tr>
<td>$AUC$, mcg x h/ml</td>
<td>1.52</td>
<td>0.45</td>
<td>0.9</td>
<td>0.55</td>
<td>4.14</td>
<td>1.03</td>
</tr>
<tr>
<td>$F$, %</td>
<td>35</td>
<td>10</td>
<td>21</td>
<td>13</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Elimination is approximately first order. Half-life, clearance and volume of distribution are the same by all routes. Fasting may have some effect on bioavailability, but it is small and statistically questionable with these sample sizes. The following graphs show these results.