

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-954

PHARMACOLOGY REVIEW(S)

NDA 20-954

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



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 D₅W 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.

Busulfan total dose	Busulfan total dose	DMA Dose	DMA Dose	DMA total	PEG 400	PEG 400	PEG 400
mg/kg/dose	mg/m ²	mg/kg/dose	mg/kg/day	g	mg/kg/dose	mg/kg/day	g/70 kg man
0.8	473.6	41.6	166.6	46.6	101	402	113

This dose (0.8 mg/kg/dose) usually results in plasma AUC acceptably close to the targeted AUC (approximately 1600 to 2000 $\mu\text{mol}\cdot\text{min/l}$). 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.
WIL-258002. Submission 011, Vol. 1 to 4.
- c) Literature review.

Busulfan

- 1) Hassan *et al.* (1994, *Blood*, 84(7), 2144-2150)
- 2) H. Ehrsson *et al.* (1983, Busulfan Kinetics, *Clin. Pharmacol. Ther.*, 34(1):86-89.)
- 3) Nadkarni *et al.* (1959, *Cancer Res.* 19(Aug); 713-718)
- 4) R. H. Kitschner and J. R. Esterly (*Cancer*, 1971, 27(5):1074-1080)
- 5) R.E. Marcus and J. M. Goldman (*Lancet*, 1984, December 22/29: 1463)
- 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.)
- 2) Montaguti, P *et al.* (1994 *Arzneimittelforschung*, 44(4): 566-70).

DMA

- 1) Weiss *et al.* (1962, *Cancer Chemother. Reports*, 16;477-485).
- 2) Palmen *et al.* (1993. *Human Exp Toxicol* 12(2):127-133).
- 3) FR Johannsen *et al.* (1987 *Fund. Appl. Tox.*, 9(3):550-6).

Reviewed Studies:

PREVIOUS CLINICAL EXPERIENCE..... 2
 PREVIOUS REVIEWS:..... 3
 REVIEWED STUDIES:..... 4
 STUDIES SUBMITTED TO THE NDA BUT NOT REVIEWED:..... 6
REVIEW..... 8

CLINICAL STUDIES OF BUSULFAN:..... 8

1) E. Angelucci et al. Sudden cardiac tamponade after chemotherapy for marrow transplantation in thalassaemia. *The Lancet* 1992; 339(8788):287-289. Volume 7, page 93..... 8
 2) W. J. Filipek, 1979, Drug-induced pulmonary disease. *Postgraduate Medicine*. 65(2):131-140. Volume 7, Page 305..... 8
 3) D Israel-Biet et al. 1991; Drug-induced lung disease: 1990 review. *The European Respiratory Journal*. 4(4):465-478. Volume 8, page 31..... 8
 3) F T Fraunfelder and S M Meyer. 1983. Ocular toxicity of antineoplastic agents. *Ophthalmology*, 90(1):1-3..... 9

PRECLINICAL STUDIES OF BUSULFAN:..... 9

PHARMACOKINETICS AND TOXICOKINETICS:..... 9

1) H.P. Bhagwatwar, B.S. Andersson, and DS-L Chow. Undated and unpublished manuscript. Comparative pharmacokinetics of a single-dose intravenous busulfan with oral tablets in rats. Volume 7, page 140. 9
 2) S. P. Dix et al. 1995. Studies of the pharmacokinetics and toxicity of once daily bolus intravenous busulfan in non-human primates. *Blood*, 86(10 Supplement 1):225a. Volume 7, Page 252..... 11
 3) M. Hassan and H. Ehrsson, 1987b. Metabolism of ¹⁴C-busulfan in isolated perfused rat liver. *European J. of Drug Metabolism and Pharmacokinetics*, 12(1):71-76. Volume 7, page 380..... 12
 4) M. Hassan and H. Ehrsson, 1987a. Urinary metabolites of busulfan in the rat. *Drug Metabolism and Distribution*. 15(3):399-402. Volume 7, page 387..... 13
 5) M. Hassan et al. 1988. Pharmacokinetics and metabolic studies of busulfan in rat plasma and brain. *European Journal of Drug Metabolism and Pharmacokinetics* 13(4):301-305. Volume 7, page 392. 14
 6) M Hassan et al. 1992. In vivo distribution of ¹¹C-busulfan in cynomolgus monkey and in the brain of a human patient. *Cancer Chemotherapy and Pharmacology*, 30:81-85. Volume 7, page 398. 14
 7) W. E. Fitzsimmons, et al., 1990, Anti-convulsants and busulfan, *Annals of Internal Medicine*, 112(7):552-553. Volume 7, page 314..... 15
 8) 8) W. E. Fitzsimmons, et al., 1990. The effect of hepatic enzyme inducers on busulfan neurotoxicity and myelotoxicity, *Cancer Chemother Pharmacol*, 27:226-228. Volume 7, page 317..... 15
 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

PHARMACOLOGY:..... 18

1) M. Cherian and U.M. Rawal. 1989. Effect of busulfan on crystalline lens- glutathione, glutathione reductase and glucose-6-phosphate dehydrogenase. *Indian J. Experim. Biol.* 27(10): 915-916. Volume 7... 18
 2) P Grimes and L. Von Sallmann, 1966. Interference with cell proliferation and induction of polyploidy in rat lens epithelium during prolonged myleran treatment. *Experimental Cell Research*, 42(2):265-273. Volume 7, page 342. 19
 3) A. E. Light. 1967. Additional observations on the effects of busulfan on cataract formation, duration of anesthesia, and reproduction in rats. *Toxicology and Applied Pharmacology* 10(3):459-466. Volume 8, page 183..... 19

4) R. B. Epstein et al. 1992. A canine model for hepatic veno-occlusive disease. <i>Transplantation.</i> , 54:12-16. Volume 7, page 281.	20
5) H. P. Lohrmann and W. Schreml, 1982. Cytotoxic drugs and the granulopoietic system. <i>Recent Results in Cancer Research</i> 81:1-22. Volume 8, page 210.	20
MUTAGENICITY AND GENOTOXICITY:.....	20
1) International Agency for Research on Cancer (IARC), 1,4-butanediol dimethanesulphonate (Myleran). IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans: <i>Chemicals, Industrial Processes and Industries Associated with Cancer in Humans, 1982; Suppl 4:68-71.</i> Volume 8, page 27.....	20
REPRODUCTIVE TOXICITY:.....	22
1) G. F. Jansz and D. K. Pomerantz, 1984, The effects of prenatal treatment with busulfan on in vitro androgen production by testes from rats of various ages. <i>Can J Physiol Pharmacol</i> 1985; 63(9):1155-1158. Volume 8, page 46.	22
2) Z. Krawczyk and N. Szymik 1989, Effect of age and busulfan treatment on the hsp70 gene-related transcript level in rat testes. <i>International Journal of Andrology</i> 12:72:79. Volume 8, page 155.....	23
PEG:.....	24
1) I. Berenblum and N. Haran, 1955, The influence of croton oil and of polyethylene glycol-400 on carcinogenesis in the forstomach of the mouse. <i>Cancer Res.</i> , 15(7):510-516. Volume 7, page 132.....	24
2) W. Bartsch et al. 1976. Acute toxicity of various solvents in the mouse and rat. <i>Arzneim.-Forsch (Drug Res.)</i> 26(8):1581-1583. Volume 7, page 129.	24
3) R.L. Carter, 1969. Early development of injection-site sarcomas in rats: a study of tumors induced by a rubber additive. <i>The British Journal of Cancer</i> , 23(2): 408-416. Volume 7, Page 213.	25
4) F. J. C. Roe et al. 1966. Carcinogenicity of certain glycidyl derivatives. <i>Food and Cosmetics Toxicology</i> 4(3):365-368. Volume 124, page 124.	25
5) H. F. Smyth et al. 1947. The toxicity of high molecular weight polyethylene glycol; chronic oral and parenteral administration. <i>J Am Pharmaceut. Assoc.</i> 36:157-160. Volume 9, page 155. Volume 9, page 155.	25
6) H. F. Smyth et al. 1955. The chronic oral toxicology of the polyethylene glycols. <i>J. Am. Pharmaceut. Assoc.</i> 44(1):27-30. Volume 9, page 160.....	25
7) H. F. Smyth et al. 1950. The toxicology of the polyethylene glycols. <i>J. Am. Pharmaceut. Assoc.</i> 89:347-354. Volume 9, page 165.	25
DMA:	27
PHARMACOKINETICS AND TOXICOKINETICS:	27
1) S.G. Hundley et al., 1994, Dimethylacetamide pharmacokinetics following inhalation exposures to rats and mice. <i>Toxicology Letters</i> , 73(3):213-225. Volume 8, page 12.	27
TOXICOLOGY:.....	29
1) G.L. Kennedy 1986(a), Biological effects of acetamide, formamide, and their monomethyl and dimethyl derivatives. <i>CRC Critical Reviews in Toxicology</i> , 17(2):129-182. Volume 8, page 59.	29
2) G. L. Kennedy and H Sherman, 1986(b) Acute and subchronic toxicity of dimethylformamid and dimethylacetamide following various routes of administration. <i>Drug and Chemical Toxicology</i> 9(2):147-170. Volume 8, page 114.	29
3) L Malley, et al. 1995. Chronic toxicity/oncogenicity of dimethylacetamide in rats and mice following inhalation exposure. <i>Fundamental and Applied Toxicology</i> 28:80-93. Volume 9, page 2.....	30
REPRODUCTIVE TOXICITY:.....	30
1) F. R. Johannsen et al., 1987, Teratogenic response of dimethylacetamide (sic) in rats. <i>Fundamental and Applied Toxicology</i> 9:550-556. Volume 8, page 52.....	30
2) W. L. Miller et al. 1981. Anti-fertility activity of DMA in hamsters: protection with a luteotropic complex (41046). <i>Proc. Soc. Exper. Biol. Med.</i> 166:199-204. Volume 9, page 64.....	31

3) G. M. Wang et al. 1989. Male fertility study on N,N-dimethylacetamide administered by the inhalation route to Sprague-Dawley rats. *Journal of Toxicology and Environmental Health* 27(3):297-305. 32

RECOMMENDATIONS..... 36
 COMMENTS DISCUSSED WITH THE MEDICAL OFFICER: 36
 LABELING: 36

Studies submitted to the NDA but not reviewed:

- 1) Anonymous. Final report on the safety assessment of polyethylene glycols (PEGs) -6, -8, -32, -75, -150, -14M, -20M. *Journal of the American College of Toxicology* 1993; 12(5):429-457. Volume 7, page 97.
- 2) J.B. Bishop and J.S. Wassom, 1986 Toxicological review of busulfan (Myleran) *Mutation Res.* 168:15-45). Volume 7, page 156.
- 3) D.J. Black and R.B. Livingston. 1990. Antineoplastic drugs in 1990: a review. *Drugs*, 39(4):489-501. Volume 7, page 189.
- 4) I. Buggia et al. 1994. Busulfan. *The Annals of Pharmacotherapy*, 28:1055-1062. Vol. 7, page 203.
- 5) S.G. Chaney and A Sancar. 1996. DNA repair: enzymatic mechanisms and relevance to drug response. *J. Nat. Cancer Inst.* 88(19):1346-1360. Volume 7, page 229.
- 6) R.L. Comis, 1985. Pulmonary toxicity of anticancer agents. *Recent Adv. Chemotherapy; Anticancer Section*, 1:174-176. A review.
- 7) K.T. Douglas. Anticancer drugs: DNA as a target. *Chemistry & Industry (London)* 1984; 20:738-742, a Review. Volume 7, page 254.
- 8) C.D.R. Dunn, 1974, The chemical and biological properties of busulfan (Myleran). *Exp. Hemat.* 2:101-117. A good review. Volume 7, page 260.
- 9) R. I. Feremz and G. L. Kennedy, 1986, Reproduction study of dimethylacetamide following inhalation in the rat. *Fundamental and Applied Toxicology*, 7:132-137. Volume 7, page 286.
- 10) L. R. Ferguson and A. W Pearson, 1996, The clinical use of mutagenic anticancer drugs. *Mutation Research*, 355:1-12. A review. Volume 7, page 292.
- 11) M. Fox et al. 1991. Neucleoside salvage and resistance to antimetabolite anticancer agents. *British Journal of Cancer*, 64(3):428-436). A review. Volume 7, page 321.
- 12) D A G Galton, 1953. Myleran in chronic myeloid leukaemia; results of treatment. *The Lancet.* 1:208-213. One of the initial descriptions of busulfan efficacy. Volume 7, page 335.
- 13) U Gupta et al., 1996. Developmental toxicity testing of alternative vehicles: PEG 400, cremophor and carboxymethylcellulose: comparison with methylcellulose. *The Toxicologist*, 30:192. Volume 7, page 352.
- 14) A. Hadow. 1973. On the biological alkylating agents. *Perspectives in Biology and Medicine*, 16:503-524. A review. Volume 7, page 354.
- 15) A Hadow and G. M. Timmis. 1953 Myleran in chronic myeloid leukaemia, Chemical constitution and biological action. *The Lancet*, 1:207-208. Initial demonstration of efficacy. Vol. 7, p. 377.
- 16) G.E.R. Hook and R.P. DiAugustine. 1976. Secretory cells of the peripheral pulmonary epithelium as targets for toxic agents, *Environmental Health Perspectives*, 16:147-156. Volume 8, page 1.
- 17) S. N. Kim, 1988. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metabolism Reviews* 19(3&4):345-368. Volume 8, page 128. A review.
- 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.
- 19) J. Larsen et al. 1996. An analysis of dimethylsulfoxide induced action potential block: a comparative study of DMSO and other aliphatic water soluble solutes. *Toxicology and Applied Pharmacology* 140(2):296-314. Volume 8, page 163. (nonphysiological concentrations).

- 20) J. C. March, 1976, The effects of cancer chemotherapeutic agents on normal and hematopoietic precursor cells: a review. *Cancer Research* 36(6):1853-1882. Volume 9, page 25.
- 21) V. J. Merkle and H. Zeller. 1980. Untersuchungen von acetamiden und formamiden auf ebryotoxische und teratogene wirkung bei kaninchen. *Arzneimittel Forschung*, 30(9):1557-1562. Volume 9, page 56.
- 22) E. E. Moore et al. 1986. Differentiation of F9 Embryonal carcinoma cells. Differences in the effects of retinoic acid, 5-bromodeoxyuridine, and N'-N'-dimethylacetamide. *Differentiation* 31(3):183-190. Volume 9, page 70.
- 23) A. Morley and J Blake, 1974. An animal model of chronic aplastic marrow failure. I. Late marrow failure after busulfan. *Blood* 44(1):49-56. Volume 9, page 80.
- 24) N. G. M. Palmen et al. 1993. Toxicokinetics of dimethylacetamide in rat isolated perfused liver. *Human and Experimental Toxicology* 12(2):127-133. Volume 9, page 88.
- 25) S. Phadungpojna et al. 1996a. Preclinical pharmacokinetics and pharmacodynamics of parenteral busulfan in dogs. *Pharmaceutical Research* 13(suppl):S-480. Abstract. Volume 9, page 96.
- 26) S Phadungpojna 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.
- 27) G. G. Pietra. 1991. Pathologic mechanisms of drug-induced lung disorders. *J Thoracic Imaging* 6(1):1-7. Volume 9, page 100.
- 28) M. J. Ratain et al. Pharmacodynamics in cancer therapy. *J. Clin. Oncol.* 8(10):1739-1753. A review. Volume 9, page 108.
- 29) J. M. Seidenberg and R. A. Becker, 1987. A summary of the results of 55 chemicals screened for developmental toxicity in mice (*sic*). *Teratogenesis, Carcinogenesis, and Mutagenesis* 7:17-28. Volume 9, page 129.
- 30) H. M. Shulman et al. 1987. Induction of hepatic veno-occlusive disease in dogs. *Am J Pathol.* 126(1):114-125. Volume 9, page 142.
- 31) H. M. Solomon et al. 1991. Developmental toxicity of dimethylacetamide by inhalation in the rat. *Fundamental and Applied Toxicology* 16:414-422. Volume 9, 172.
- 32) R. Strobe et al. 1976. Studies of marrow transplantation in dogs. *Transplantation Proceedings* 8(4):545-549.
- 33) W. P. Tong and D. B. Ludlum. 1980. Crosslinking of DNA by busulfan. Formation of diguanyl derivatives. *Biochimica et Biophysica Acta* 608:174-181. Volume 9, page 188.
- 34) M. Tsuchitani et al. 1984. Subacute toxicity test of polyethylene glycol treated human immunoglobulin, lyophilized (GV-523) and polyethylene glycol in rats by IV administration for 5 weeks. *Pharmacometrics* 27(1):23-37. This article is in Japanese. Volume 9, page 197.
- 35) G. Vassal. 1994. Pharmacologically-guided dose adjustment of busulfan in high-dose chemotherapy regimens: rationale and pitfalls (review). *Anticancer Research* 14:2363-2370. Volume 9, page 213.
- 36) C. P. J. Vendrik, 1992. Resistance to cytostatic drugs at the cellular level. *Cancer Chemotherapy and Pharmacology* 29(6):413-429. A review. Volume 9, page 222.
- 37) M. Vizel and M. W. Oster. 1982. Ocular side effects of cancer chemotherapy. *Cancer* 49(10):1999-2002. A review. Volume 9, page 240.
- 38) A dose range-finding toxicity study with intravenous busulfan in dogs. Report #WIL-258001. Volume 9, page

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

Review

Clinical Studies of Busulfan:

- 1) E. Angelucci *et al.* Sudden cardiac tamponade after chemotherapy for marrow transplantation in thalassaemia. *The Lancet* 1992; 339(8788):287-289. Volume 7, page 93.

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.

- 2) W. J. Filipek, 1979, Drug-induced pulmonary disease. *Postgraduate Medicine*. 65(2):131-140. Volume 7, Page 305.

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."

- 3) D Israel-Biet *et al.* 1991; Drug-induced lung disease: 1990 review. *The European Respiratory Journal*. 4(4):465-478. Volume 8, page 31.

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.

- 3) F T Fraunfelder and S M Meyer. 1983. Ocular toxicity of antineoplastic agents. *Ophthalmology*, 90(1):1-3.

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:

- 1) H.P. Bhagwatwar, B.S. Andersson, and DS-L Chow. Undated and unpublished manuscript. Comparative pharmacokinetics of a single-dose intravenous busulfan with oral tablets in rats. Volume 7, page 140.

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 diethyldithiocarbamic acid sodium salt. This reaction forms the spectroscopically detectable 1,4-bis(diethyldithiocarbamoyl) 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 $4.1 \pm 1 \mu\text{g}^*\text{h}/\text{ml}$.

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

Parameter	Tablet				IV	
	Fed	sd	Fasting	sd		sd
n	7		4		12	
animal wt., kg	0.29	0.04	0.30	0.06	0.29	0.05
Dose mg/kg	1		1		1	
K_a, h^{-1}	2.6	1.7	12.1	11.7	NA	
$t_{1/2\alpha}, \text{h}$	0.21	0.07	0.11	0.06	NA	
$C_{\text{max}}, \mu\text{g}/\text{ml}$	0.36	0.16	0.28	0.06	NA	
T_{max}, h	0.8	0.18	0.47	0.25	NA	
K, h^{-1}	0.38	0.12	0.59	0.46	0.34	0.08
$t_{1/2\beta}$	2.05	0.69	1.8	0.9	2.2	0.79
V, ml	207	93	177	104	233	53
CL, ml/h	68	8.6	70	16	77.9	21.9
AUC, $\mu\text{g}^*\text{h}/\text{ml}$	1.52	0.45	0.9	0.55	4.14	1.03
F, %	35	10	21	13	100	

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.

