

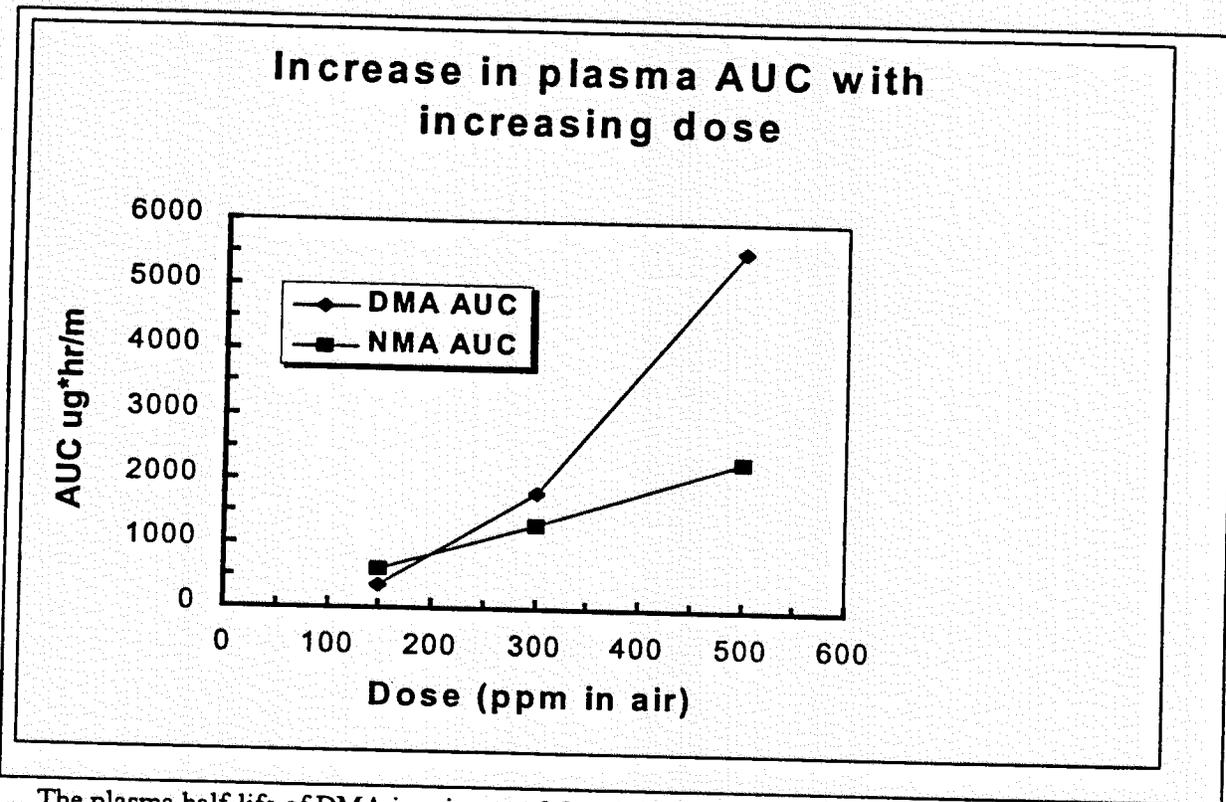
DMA:

Pharmacokinetics and Toxicokinetics:

- 1) S.G. Hundley *et al.*, 1994, Dimethylacetamide pharmacokinetics following inhalation exposures to rats and mice. *Toxicology Letters*, 73(3):213-225. Volume 8, page 12.

In this work, Hundley *et al.* exposed 150 male rats and 340 male mice to different concentrations of DMA in the air for 1, 3 or 6 hours. They also exposed groups to different concentrations for two weeks (6 hours per day, 10 exposure days). At various times after the exposures they took blood samples and analyzed for DMA and its major metabolite, N-methyl acetamide (NMA), by gas chromatography. The following table shows that, in rats, the AUC of DMA increased proportionately more between 300 and 500 ppm than it did between 150 and 300 ppm. The AUC of NMA increases linearly with dose ($r^2 = 1.00$), suggesting that metabolism is not saturated at these doses. The increase in DMA AUC may be due to the saturation of some process that impedes the crossing of DMA from the air to the blood. This could be a physical process associated with solvation at high concentrations. More likely these results imply that metabolism is saturated. Exposure for two weeks does not change the pharmacokinetics of DMA or increase the formation of NMA in rats or mice.

| Exposure Concentration | AUC Values $\mu\text{g}\cdot\text{hr}/\text{ml}$ | | | | | | | |
|------------------------|--|-----------------|------|-------------------|------|-----|------|-----|
| | DMA | Single exposure | | Two-week exposure | | | | |
| | | sd | NMA | sd | DMA | sd | NMA | sd |
| Rats | | | | | | | | |
| 150 ppm | 350 | 160 | 600 | 70 | 400 | 340 | 700 | 310 |
| 300 ppm | 1800 | 370 | 1300 | 110 | 1700 | 180 | 1400 | 150 |
| 500 ppm | 5550 | 1040 | 2300 | 50 | 5060 | 180 | 2800 | 220 |
| Mice | | | | | | | | |
| 300 ppm | 129 | | 822 | | 297 | | 830 | |
| 500 ppm | 1115 | | 1523 | | 1105 | | 1600 | |



The plasma half-life of DMA in mice was 0.3 to 0.5 hours. This is an underestimate because of a 30-minute lag time between the end of exposure and the time the mice were exsanguinated. The plasma half-life of DMA in rats was 0.6 to 1.6 hours. In rats, NMA persisted in the plasma for greater than 24 hours. NMA was undetectable in mouse plasma after 12 hours. As the graph below shows, in several cases the sample times were not long enough to accurately determine these parameters. The authors assert that these results support an upper limit of 350 ppm for a chronic inhalation study in rodents.

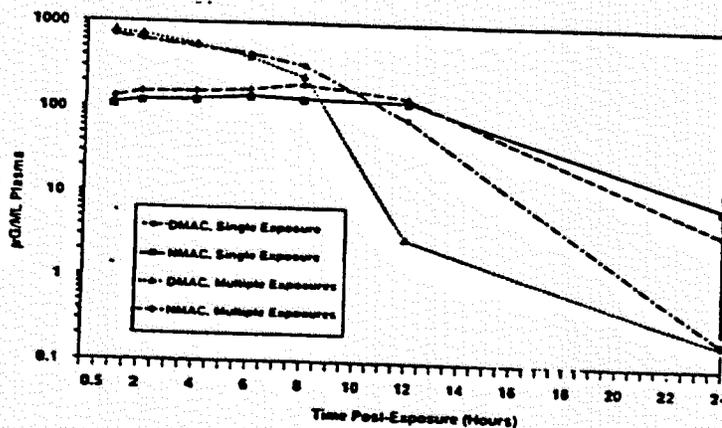


Fig. 3. DMAC and NMAC plasma concentrations from rats exposed to 500 ppm DMAC (single or multiple 6-h exposures).

Toxicology:

- 1) G.L. Kennedy 1986(a), Biological effects of acetamide, formamide, and their monomethyl and dimethyl derivatives. *CRC Critical Reviews in Toxicology*, 17(2):129-182. Volume 8, page 59.

This is a large and fact filled review that contains little information germane to the NDA. Nevertheless, the section on acute toxicity shows that relatively large doses of DMA are necessary to cause acute toxicity. It shows that rats given 2.25 g DMA/kg suffer pulmonary edema and congestion, hepatic necrosis and congestion, and renal tubule swelling. The paper also identifies the dog and the cat as the most sensitive species tested (LD₅₀ approximately 0.24 g/kg IV). Rodents are considerably less sensitive (rat LD₅₀ 2.8 g/kg IV).

The sponsor uses a section in this review to state that repeat oral doses of DMA for 260 days cause no increase in tumors in rats. This finding cannot be used as a label claim. The study is too short and the doses are too low.

- 2) G. L. Kennedy and H Sherman, 1986(b) Acute and subchronic toxicity of dimethylformamid and dimethylacetamide following various routes of administration. *Drug and Chemical Toxicology* 9(2):147-170. Volume 8, page 114.

Kennedy and Sherman did a series of toxicology studies on a small number of animals to determine the toxicity of DMF and DMA by various routes. Because the number of animals is small and the number of experiments is large, I will give only a narrative review. Neither shall I review their inhalation studies.

DMA produced mild reversible conjunctival inflammation when placed in rabbit's eyes with or without washing. The treated rabbit's eyes showed no gross or microscopic damage seven days after treatment.

A single oral dose of DMA (7.5 g/kg) killed male rats. A dose of 5 g/kg or less was not lethal, but the rat that received 5 g/kg suffered fasciculations, prostration, and rapid respiration immediately following dosing. On day 2 after dosing, the rat suffered diarrhea, tremors and chromodacryorrhea. By day 3 this rat appeared recovered. Single oral doses between 0.670 g/kg and 3.4 g/kg caused slight transient weight loss.

Rats survived nine oral doses of 450 mg/kg DMA given over a two-week period (workdays). This dose caused restlessness, irritability and decreased weight gain (40% less than controls). This decrease in weight gain was reversible. Microscopically this dose stopped spermatogenesis in approximately half the tubules in two of the three rats tested. "One of 3 rats showed liver cells that were uniformly smaller than normal."

Five SC doses of DMA (2 grams) killed rabbits. Before death these animals suffered anorexia, discomfort, marked weight loss, cyanosis, and labored breathing. The authors observed acute hepatic necrosis grossly and presumed this the cause of death. They found free fluid in both the thoracic and peritoneal cavities. The kidneys of three of six rabbits were slightly congested.

In a 90-day feeding study, male and female rats eating food containing 1,000 ppm DMA developed slight anemia (>10% less than controls) and leucocytosis (>30% greater than controls) by the end of the study.

- 3) L Malley, *et al.* 1995. Chronic toxicity/oncogenicity of dimethylacetamide in rats and mice following inhalation exposure. *Fundamental and Applied Toxicology* 28:80-93. Volume 9, page 2.

This research team exposed male and female mice to 0, 25, 100 or 350 ppm DMA for 6 hr/d, 5 days/week, for 18 months. They exposed male and female rats to these doses for two years. They evaluated clinical pathology in rats only at 3, 6, 12, 18, and 24 months. These doses did not affect survival. The high dose caused a decrease in body weight and body weight gain in rats but not in mice. These doses did not cause hematological changes in either species. The high dose increased serum sorbital dehydrogenase activity in male and female rats and increased serum cholesterol and glucose in females. The high dose caused morphological changes in the liver. Both the mid and high-doses caused increased liver weights and focal hepatic cystic degeneration, hepatic peliosis, and lipofuscin/hemosiderin accumulation in Kupffer cells. The high dose caused biliary hyperplasia. In mice, the mid and high dose caused increased absolute liver weights, accumulation of lipofuscin/hemosiderin, in Kupffer cells, and centrilobular single cell necrosis. The high dose caused an increase in relative liver weights in females. High-dose male mice had higher absolute and relative kidney weights that correlated with gross and microscopic changes suggestive of chronic progressive nephropathy. High-dose female mice had an increase in the incidence of bilateral diffuse retinal atrophy. The investigators observed no increase in tumor incidence at these doses. They determined a NOAEL of 25 ppm for both species.

Reproductive Toxicity:

- 1) F. R. Johannsen *et al.*, 1987, Teratogenic response of dimethylacetamide (sic) in rats. *Fundamental and Applied Toxicology* 9:550-556. Volume 8, page 52.

Johannsen *et al.* gave daily gavage doses of DMA dissolved in water to groups of pregnant CD rats on days 6 through 19 of gestation (organogenesis). The dose groups received 0, 65, 160, or 400 mg/kg/day (0, 390, 960, 2400 mg/m²/d). The fetuses were removed for examination on day 20. This treatment caused no changes in survival, appearance or behavior in the dams.

Mean maternal body weight gain was significantly reduced only in the high dose group (adjusted weight gain 82% of controls). There was some increase in post-implantation loss at 400 mg/kg but no clear dose response. There was a small but significant decrease in mean fetal body weight in the mid and high-dose groups (< 10% in mid dose, value for high dose group obliterated in the copy provided). There were 49 total fetal malformation (~17% of the fetuses) in the high dose group and only one or two in the other groups (21 of 24 litters, the numbers in parenthesis in the following sentence represent the number of litters with an abnormality in the 24 examined in the high dose group). The most striking abnormalities included anasarca, 5(2) (accumulation of serous fluid in various tissues and body cavities); serious anomalies of the vessels of the heart, 33 (18); cleft palate, 3(3), vertebral anomalies, 3(3), rib anomalies, 3(2). The vascular anomalies included truncus arteriosus, missing ductus arteriosus, intraventricular septal defects, retroesophageal-descending aorta, and coarctation of the pulmonary trunk and arteries. The authors considered these vascular malformations "highly unusual." There were also numerous variations in development. The most common involved failure of

ossification. For example, the sternum was completely unossified in 29 pups (13), there was reduced ossification in 30 pups (13). In six pups (5) the renal papillae were not developed or the ureters were distended or both.

DMA is seriously teratogenic in rats at doses approximately 6 times higher than the daily dose recommended in this therapy. The most serious lesions are vascular malformations of the heart and lungs. The dose that caused this toxicity was only mildly toxic to the dams. The company does not seem to mention the vascular malformation in their integrated summary.

- 2) W. L. Miller *et al.* 1981. Anti-fertility activity of DMA in hamsters: protection with a luteotropic complex (41046). *Proc. Soc. Exper. Biol. Med.* 166:199-204. Volume 9, page 64.

These authors showed that the termination of pregnancy in hamsters was dependent on the dose of DMA. The following table shows that the dose response curve for this toxicity is rather steep (0 to 100% in about a factor of two). The authors say that the single high dose (2.2 g/kg SC) is about one third the lethal dose in this species.

| Dose of DMA in g/kg | Number of trials, 6/trial | Route | Treatment day of pregnancy | % inhibition of pregnancy |
|---------------------|---------------------------|-------|----------------------------|---------------------------|
| 2.2 | 5 | SC | 4 | 100 |
| 1.8 | 2 | SC | 4 | 67 |
| 1.4 | 2 | SC | 4 | 50 |
| 1.1 | 2 | SC | 4 | 17 |
| 0.9 | 2 | SC | 4 | 0 |
| 2.2 | 2 | SC | 3 | 67 |
| 2.2 | 2 | SC | 2 | 33 |
| 2.2 | 2 | SC | 1 | 17 |
| 2.2 | 4 | PO | 4 | 67 |

The investigators also combined the treatment with DMA with SC injections of progesterone, pregnant mare's serum (PMS) or prolactin or a combination of these treatments. The following table shows the effect of these treatments.

| Group | DMA treatment on day 4 | SC hormonal treatment on days 4, 5, 6, and 7 of pregnancy | Percent inhibition of pregnancy |
|-------|------------------------|---|---------------------------------|
| I | 0 | Control, daily vehicle injections | 0 |
| II | 2.2 g/kg | Daily vehicle injections | 100 |
| III | 2.2 g/kg | Progesterone | 17 |
| IV | 2.2 g/kg | PMS | 67 |
| V | 2.2 g/kg | Prolactin | 67 |
| VI | 2.2 g/kg | Prolactin + PMS | 0 |

DMA alone caused changes in ovarian tissue. "The ovaries of hamsters given DMA showed normal follicular development and maturation." But, the corpora lutea showed "congestion, frank hemorrhage, and pyknotic nuclei before attaining mature size." The authors suggest that the process was atrophic. The addition of the hormone therapy decreased this degeneration. The authors do not suggest a mechanism for the reversal of DMA toxicity by hormonal treatment.

NDA 20-954

- 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.

These investigators exposed male rats to 0, 40, 120 or 400 ppm DMA 6 hr/day for five days per week by inhalation. The rats began inhaling DMA for 49 days before mating and continued the exposure for a total of 69 days. These males were mated to unexposed virgin females. The mid and high-dose caused an increase in absolute liver weight and liver to body weight ratio in the exposed males. These doses did not cause a decrease in reproductive capacity, fetal toxicity or fetal malformation.

APPEARS THIS WAY
ON ORIGINAL

Summary

Busulfan is an extremely toxic bi-functional alkylating drug. This drug has long been used as palliative treatment for chronic granulocytic leukemia and chronic myelogenous leukemia. The oral preparation is used extensively off-label for bone marrow ablation in adult and children. The doses used for bone marrow ablation are considerably higher than those used for the long-term treatment of CML.

The toxicity of alkylating drugs is not cell cycle dependent, but these compounds usually block poisoned cells in late G₁ or S phase. Nevertheless, busulfan reacts with many different nucleophilic biochemicals, undoubtedly many in the cytoplasm. Bifunctional alkylation of DNA initiates cell death, possibly through a p53 mediated mechanism, but the mechanism by which busulfan kills cells is poorly understood.

Pharmacokinetic studies in the rat, monkeys and human have established that these species require hours to clear busulfan from the plasma. The following table compares some of the pharmacokinetic parameters in these three species.

| Parameter | Units | Rat IV | Monkey IV | Human Children | Human Adults |
|-------------------|--------------------------|--------|-----------|----------------|--------------|
| weight | kg | 0.29 | | ~25 | ~75 |
| dose | mg/kg | 1 | | 0.08 | 0.03 |
| dose | mg/m ² | 6 | 100 | 1.6 | 1.11 |
| t _{1/2β} | hour | 2.22 | 1.5 | 2.46 | 2.61 |
| Vd _{ss} | l/kg | 0.8 | 1.17 | 0.74 | 0.56 |
| CL | ml/min/kg | 4.48 | 9.4 | 3.62 | 2.49 |
| AUC | μM*min | 998.8 | 2345.0 | 171.5 | 46.5 |
| AUC/dose | μM*min*m ² /g | 166.5 | 22.8 | 107.2 | 41.9 |

In humans and rats, the elimination half-life of busulfan is greater than two hours. Busulfan pharmacokinetics also shows variability, not just across species but across patients. The clearance, volume of distribution and AUC values in the table above show some differences. This variability may be associated with the capacity of the species sulfur pool in the form of reduced glutathione to conjugate busulfan. It may also be associated with the individual's cytochrome-P450 induction state. Induction of P450s that can accomplish sulfoxidation diminish busulfan's toxicity. In rodents, primates and humans AUC increases linearly with dose to doses that are severely toxic. Inducers such as phenytoin and phenobarbital may diminish Busulfex efficacy.

Glutathione-S-transferase conjugates busulfan to a sulfonium conjugate in the liver of rats. This conjugate is secreted in the bile. Little of this sulfonium conjugate is found in the plasma or urine of intact animals. It recirculates and is further metabolized to 3-hydroxysulfolane, tetrahydrothiophene and sulfolane. Less than 6% of a total radioactive dose of busulfan is excreted in the urine as the parent compound. Less than two percent of a total radioactive dose is found in the feces. The recovery of ¹⁴-C radioactivity is never quantitative because busulfan reacts non-specifically with nucleophiles throughout the body. The urine metabolites show little cytotoxicity *in vitro*. Busulfan appears to cross the blood brain barrier.

Busulfan is profoundly toxic. Pancytopenia is limiting for single doses. Using the dose and schedule proposed in this NDA, the cumulative dose over four days of busulfan IV is ~475 mg/m². This dose is less than the established cumulative MTD of low dose oral busulfan, 640 mg/m² (Goodman and Gilman, 9th ed., p1237). Like other alkylating drugs, busulfan causes myelosuppression. Nevertheless, busulfan is very toxic to stem cells, particularly in combination with cyclophosphamide. The associated myelosuppression can be prolonged and severe. This is precisely the reason the sponsor chose busulfan for myeloablative therapy. Busulfan also causes toxicity in the gastrointestinal tract and the liver. It causes oral mucosal ulceration and intestinal denudation. High doses predispose a patient to infection.

A toxicity study of IV Busulfex in the dog confirms this clinical experience. Dogs suffered an anticipatable rapid decrease in WBC (41% by day four) and platelets. White and red cell parameters rebounded by day 11 to values as much as 20% higher than normal, suggesting stem cell recovery. Increased bilirubin suggested liver damage. A dog given high IV doses (20 mg/m² four times a day for four days) of Busulfex suffered hypoactivity, ataxia, diarrhea and prostration before death. Dogs that survived this dose showed abnormal gait, hypoactivity, and vomiting. This total dose of busulfan in this dog study was 320 mg/m², significantly less than the ~475 mg/m² recommended in this NDA. Dogs appear to be somewhat more sensitive to busulfan than humans.

Busulfan can cause fatal bronchopulmonary dysplasia with pulmonary fibrosis. This severe lung disorder is seen after cumulative doses of 500 mg/m², close to the clinical dose in this NDA. Chronic administration of busulfan has been shown to cause cataracts in rats and in humans. Busulfan has been documented to cause neurological symptoms such as dizziness, loss of consciousness and convulsion in humans. It can cause cytologic abnormalities in many organs, particularly the reticuloendothelial tissues. It is hepatotoxic and has caused fatal hepatic veno-occlusive disease, especially in combination with cyclophosphamide. Hepatotoxicities seen in dog models included central congestion, zone 3 necrosis, focal venous destruction, hemorrhage, and venous fibrosis. Importantly, the dogs did not show changes in Liver Function Tests. The correlation between the incidence of veno-occlusive disease and high busulfan AUC values limited the dose escalation for Busulfex.

Busulfan is a well established genotoxin. It is a mutagen and a clastogen. In *in vitro* tests it caused mutations in *Salmonella typhimurium* and *Drosophila melanogaster*. Chromosomal aberrations have been reported in animals (rats, mice and hamsters *in vivo* and cells *in vitro*) and humans (*in vivo* and cells *in vitro*). The intravenous administration of busulfan (48 mg/kg given as biweekly doses of 12 mg/kg, or 30% of the total Busulfex dose on a mg/m² basis) has been shown to increase the incidence of thymic and ovarian tumors in mice. Busulfan is mutagenic in mice and is probably leukemogenic in man.

| | DNA Damage | Mutation | Chromosomal Anomalies | Other |
|-------------------------------------|------------|----------|-----------------------|---------------------------|
| Prokaryotes | + | + | | |
| Fungi/Green plants | | + | + | |
| Insects | | + | | |
| Mammalian cells (<i>in vitro</i>) | + | + | + | Cell transformation |
| Mammalian cells (<i>in vivo</i>) | | + | + | Dominant Lethal mutations |
| Humans (<i>in vivo</i>) | | | + | Secondary Leukemia |

Busulfan damages all stem cell populations, depletes sperm cells and causes testicular atrophy. Busulfan produced teratogenic changes in the offspring of mice, rats and rabbits when given during gestation. Malformations and anomalies included significant alterations in the musculoskeletal system, body weight gain, and size. In pregnant rats, busulfan produces sterility in both male and female offspring due to the absence of germinal cells in the testes and ovaries.

Besides the predictable busulfan toxicities the study of Busulfex in dogs suggests that the vehicle for this therapy is also toxic. High dose IV infusion of vehicle caused cytoplasmic multifocal vacuolation and fibrosis in liver. Dogs in the vehicle control group suffered these symptoms more frequently than dogs in the high dose busulfan group. This toxicity is consistent with the toxicity of DMA documented in the literature. The clinical dose probably saturates hepatic clearance. The solvent PEG-400 is toxic only at very high doses.

A single oral dose of DMA (7.5 g/kg, 45 g/m²) killed male rats. A dose of 5 g/kg or less was not lethal, but the rat that received 5 g/kg suffered fasciculations, prostration, and rapid respiration immediately following dosing. On day 2 after dosing, the rat suffered reversible diarrhea, tremors and chromodacryorrhea. Single oral doses between 0.670 g/kg and 3.4 g/kg caused transient weight loss.

Rats survived nine oral doses of 2.7 g/m² DMA given over a two-week period (workdays). This dose caused restlessness, irritability and decreased weight gain (40% less than controls). This decrease in weight gain was reversible.

Five SC doses of DMA (2 grams) killed rabbits. Before death these animals suffered anorexia, discomfort, marked weight loss, cyanosis, and labored breathing. The authors observed acute hepatic necrosis grossly and presumed this the cause of death.

In the rat, chronically inhaled doses of DMA (350 ppm 6 hr/day five days a week for 24 months) caused morphological changes in the liver. These dose dependant liver toxicities included increased liver weights, focal hepatic cystic degeneration, hepatic peliosis, and lipofuscin/hemosiderin accumulation in Kupffer cells and biliary hyperplasia. In mice this dose given for 18 months caused increased absolute liver weights, accumulation of lipofuscin/hemosiderin in Kupffer cells, and centrilobular single cell necrosis. This dose caused an increase in relative liver weights in females. Male mice had higher absolute and relative kidney weights that correlated with gross and microscopic changes suggestive of chronic progressive nephropathy. Female mice had an increase in the incidence of bilateral diffuse retinal atrophy. The investigators observed no increase in tumor incidence at these doses.

DMA was unusually toxic to the developing rodent fetus at doses that caused decreases in maternal body weight gain (400 mg/kg/d during gestation). Doses of 160 mg/kg and 400 mg/kg caused a small but significant decrease in mean fetal body weight. The high dose caused fetal malformations in approximately 17% of the fetuses. The most striking abnormalities included anasarca, (accumulation of serous fluid in various tissues and body cavities), serious anomalies of the vessels of the heart, cleft palate, vertebral anomalies and rib anomalies. The highly unusual vascular anomalies included truncus arteriosus, missing ductus arteriosus, intraventricular septal defects, retroesophageal-descending aorta, and coarctation of the pulmonary trunk and arteries. Thus, DMA is seriously teratogenic in rats at doses approximately 6 times higher than the daily dose recommended in this therapy. DMA also decreases fertility in male and female rodents.

DMA has been studied as an anti-cancer drug. In this clinical study, neurological symptoms and hepatotoxicity were dose limiting, both toxicities that busulfan can cause. The MTD of DMA was 400 mg/kg/d X 4. The proposed daily dose of Busulfex contains 42% of this daily MTD dose of DMA. The toxicity of DMA and that of busulfan in Busulfex are possibly additive.

Recommendations

This drug product can be approved for the proposed indication. The doses of DMA in this formulation are high enough to cause significant toxicities. The use of DMA in other drug products should be carefully evaluated.

Comments discussed with the Medical officer:

Angelucci *et al.* (above) 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 these children had moderate to severe iron overload with systemic hemochromatosis. The sponsor should monitor closely for this severe toxicity in phase IV.

Labeling:

I have proposed labeling changes for Busulfex in a separate document.

/S/

W. David McGuinn, Jr., Ph. D., D.A.B.T.
Completed January 25, 1999
Revised February 1, 1999
Reprinted February 4, 1999

cc. Original NDA
/IND 46,232
/Division File
/W D McGuinn
/P Andrews
/P Guinn
/D Grebel

/S/

2/4/99

Feb 4, 99

Division of Oncology Drug Products, HFD-150
Review and Evaluation of Pharmacology and Toxicology Data
Review # 2, Labeling Changes

NDA: 20-954 **Serial: 000** **Type NDA**
Original NDA Dated August 4, 1998
Completed January 21, 1999

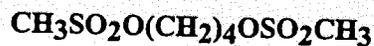
Title: Intravenous Busulfan (Myleran) for bone marrow ablation in adult and pediatric patients with leukemia or lymphoma.

Information to be conveyed to the sponsor: YES

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 sponsors dissolves Busulfan in N,N-dimethylacetamide (DMA), 18 mg/ml. They then dissolve this solution in polyethylene glycol 400 (PEG-400) to a final concentration of 6 mg/ml. This solution is dissolved in D₅W or normal saline to a total volume of 250 ml. In the final Phase I protocol, this solution was given as an i.v. 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 and using the density of DMA as 0.937 and a PEG density of 1.128 g/ml.

| Busulfan mg/kg/dose | Busulfan total dose mg/m ² | DMA Dose mg/kg/dose | DMA Dose mg/kg/day | DMA total g | PEG 400 mg/kg/dose | PEG 400 mg/kg/day | PEG 400 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 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.

The following are proposed labeling changes for Busulfex. Deletions are shown as strike-outs. Additions are shown underlined.

Redacted

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confidential

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information

NDA 20-954

Recommendation:

This drug product can be approved for the proposed indication. The doses of DMA in this formulation are high enough to cause significant toxicities. The use of DMA in other drug products should be carefully evaluated.

/S/

W. David McGuinn, Jr., Ph. D., D.A.B.T.
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- cc. Original NDA
- /IND 46,232
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- /D Grebel

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Feb 4, 99