CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-954

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA 20,954 **Submission:** ~~10/18~~ 08/03/98
11/25/98

Drug name: BUSULFEX

Generic name: Busulfan

Formulation: for infusion

Sponsor: Orphan Medical Inc.
13911 Ridgedale Dr., Suite 475
Minnetonka, MN 55305

Reviewer: Brian Booth, Ph.D.

I. Foreword

This review critiques the clinical pharmacology studies conducted by Orphan Medical Inc. in support of its New Drug Application N020954, BUSULFEX, and is primarily intended to aid the Agency in determining the acceptability of this application. The synopsis provides a summary of the studies conducted by Orphan Medical Inc., and the findings of the FDA. Greater detail of the study design and conduct, as well as explanations for FDA findings are provided in this report. The proposed labeling and relevant literature reports are also appended. This review is neither a comprehensive treatise of bone marrow transplantation, nor busulfan kinetics, but instead provides sufficient detail to assess the pharmacokinetic behavior of BUSULFEX for the proposed indication.

II. Synopsis

Orphan Medical Inc.(OMI) developed an intravenous formulation of busulfan (BUSULFX) for myeloablative conditioning prior to bone marrow transplant procedures (BMT). BMT is frequently used to treat a variety of hematological malignancies.

The sponsor determined the pharmacokinetics of 2-hour long BUSULFEX infusions using a myeloablative, q.i.d., four-day busulfan and two-day cyclophosphamide regimen, which is widely used with oral busulfan as a preparation for BMT. The sponsor determined the intravenous BUSULFEX pharmacokinetics in patients who received autologous bone marrow transplants, (OMC-BUS-3) and allogeneic bone marrow transplants (OMC-BUS-4). In addition, the sponsor compared the intravenous BUSULFEX pharmacokinetic characteristics to those of oral busulfan, in patients recruited to an amended protocol of studies OMC-BUS-3 and OMC-BUS-4 (Amendment 4).

The sponsor reported average (mean) values for C_{max}, AUC (drug exposure), clearance, volume of distribution, and elimination half-life for BUSULFEX that are the same as those determined for orally administered busulfan. The sponsor also reported that the pharmacokinetics of BUSULFEX had lower variability, and better predictability of later doses than oral busulfan.

An important issue in evaluating the OMI studies is the FDA review of the validity of the methods of pharmacokinetic analysis chosen by the sponsor (OMI). The determination of the pharmacokinetic characteristics is dependent upon an accurate determination of area-under-the plasma concentration vs. time curve (AUC), and elimination rate (λ_z). In order to do this, the sponsor developed and validated

Furthermore, oral busulfan was administered only as dose 1 to nine patients in the amended protocol, and a comparison of the pharmacokinetics of oral busulfan vs intravenous BUSULFEX at steady-state can not be made for the reason explained above. However, the FDA conducted an alternative analysis, in which the AUC of observed data during dose 1 busulfan was compared between the oral and intravenous formulations. The FDA concluded from this analysis that no difference exists between oral busulfan and BUSULFEX in the mean pharmacokinetic parameters nor the variability in the data. These results necessitate changes to the labeling proposed by Orphan Medical Inc.

In addition to the limitations of the busulfan clinical pharmacology studies, several issues have been raised from oral busulfan literature reports. The first of these concerns is a potential for drug interactions that need to be considered. Phenytoin is of particular note, as this drug induces time-dependent decreases in busulfan AUC. This anticonvulsant was ubiquitously used in the OMI studies, which further confounds any comparisons made between busulfan doses 1 and 9. Another important consideration is the necessity for BUSULFEX dosage adjustment in special populations. The clearance and the volume of distribution of busulfan is much higher in children under 4 years of age, and may require a different dosing regimen to ensure safe and effective treatment in pediatric patients. Furthermore, the clearance of busulfan can differ between normal and obese patients. These differences may be eliminated by normalizing busulfan clearance with selected factors such as body surface area. However, not all choices for busulfan clearance normalization will eliminate the differences between groups. The FDA

recommends that the possible drug interaction and special population issues for BUSULFEX should be clearly defined in the labeling.

III. Recommendations

The sponsor demonstrated in this New Drug Application that BUSULFEX, an intravenous formulation of busulfan, possesses pharmacokinetic characteristics that are similar to those of oral busulfan. However, the design of the studies and the analysis undertaken by the sponsor are inadequate to support the claim that BUSULFEX provides more predictable and less variable pharmacokinetic behavior than oral busulfan.

The sponsor must alter the labeling according to the changes specified by the FDA in the labeling section of this report.

/S/ 1/13/99

Brian Booth, Ph.D.
Reviewer
Division of Pharmaceutical Evaluation I

/S/ 1/13/99

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

cc: HFD-150/Division File/Original NDA 20,954
HFD-150/ PGuinn, DGreibel, JBeitz
HFD-850/LLesko
HFD-860/MMehta, ARahman, BBooth
CDR BMurphy

IV. Table of Contents

V. Background

Busulfan is a bifunctional alkylating agent approved for the palliative treatment of chronic myelogenous leukemia in the 1950's. Busulfan is available as Myleran, a 2 mg tablet, which is indicated for remission induction at doses up to 8 mg/day. However, Myleran is also used as a preparative conditioning agent for BMT at a dosage rate of 1mg/kg. Pharmacokinetic and efficacy studies of busulfan as a bone marrow ablative agent revealed that the severe side effects of hepatic veno-occlusive disease (VOD) and seizures are generally associated with busulfan plasma exposures (AUC's) in excess of 1500 μMol•min. Conversely, failure of bone marrow transplants to engraft is associated with busulfan plasma concentrations that are too low. OMI developed BUSULFEX, a busulfan formulation for infusion, as a bone marrow ablative agent. The sponsor claims that this infusion formulation will avoid the loss of the busulfan dose (approximately 35, 2 mg tablets for a 70 kg patient) that frequently occurs with patient vomiting, and improve engaftment rates. Furthermore, the sponsor states that busulfan pharmacokinetics demonstrate large inter- and intra-patient variability as a function of highly variable absorption kinetics. The sponsor claims that the infusion formulation of busulfan (BUSULFEX) provides more predictive, less variable plasma pharmacokinetic characteristics than the oral formulation, which reduces the risk of seizure and VOD associated with plasma AUC's in excess of 1500 μMol•min. The purpose of these studies was to demonstrate that BUSULFEX had the same pharmacokinetic characteristics as oral busulfan, but were less variable and more predictive than the oral formulation in patients who required bone marrow transplantation.

VI. OMI Pharmacokinetic Study Design

Foreword

The studies conducted by OMI are described in this section of the report. This section contains a description of the analytical methodologies and their associated problems, an explanation of the study design, drug administration, sampling, pharmacokinetic analysis and comparison, and the conclusions made by the sponsor. This section does not contain an exhaustive list of OMI findings, but reports the most relevant details concerning the studies performed and the claims made by the sponsor.

a. OMI Analytical Methodology

However, the sponsor failed to completely validate the methodology. Originally, no data on recovery of busulfan from whole blood or plasma was reported for this method. In response to an Agency query for this data, the sponsor referred to Table 7 "Benchtop Stability of Extracted Samples" on page 275 of vol. 1.17.

Vol 1.17 "Table 7. Benchtop Stability of Extracted Samples"

Elapsed Time (hours)	Clock Time	Busulfan Low Concentration (ng/ml)	Busulfan High Concentration (ng/ml)
0			
0			
0			
0			

The sponsor indicated that the low and high concentrations were ng/ml, respectively. The sponsor concluded that recovery of the low concentration was ng/ml, and ng/ml at the high concentration of busulfan. These data are insufficient to adequately assess recovery of busulfan by the method reported.

The sponsor also reported the time-effect of freezing, and multiple freeze-thawing of 2 samples obtained from one patient treated with busulfan. This procedure is also noncompliant with GLPs. The sponsor has not completed these long-term stability assessments.

method as a backup to the method. This methodology was also linear over the busulfan concentration range ng/ml. However, the results of the cross-validation study indicated that these two methods were not equivalent. The difference between the methods is indicated by a correlation coefficient of less than 1 (Fig. 7, page 286, vol. 1.17). In response to a FDA query, Orphan Medical Inc. reported that no patient data in OMC-BUS-3, OMC-BUS-4, or Amendment 4 were analyzed with the method. Furthermore, the sponsor did not cross-validate the method with the method, and comparisons of the data from OMC-BUS-2 cannot be made to the data from the other studies.

b. Dosing Regimen

The sponsor chose an established myeloablative dosing regimen for oral busulfan and cyclophosphamide. Busulfan tablets or a 2-hour intravenous infusion of BUSULFEX was administered every six hours for a period of four days at a dosage of 1 mg/kg (16 total doses). Cessation of busulfan was followed by two days of single dose cyclophosphamide at a dosage of 60 mg/kg. Following one day of rest, BMT was performed. This dosing regimen was employed in the four (4) studies conducted by the sponsor.

The order of the busulfan route of administration differed among the studies. In a dose-escalation, phase I trial (OMC-BUS-2), BUSULFEX was infused as dose 1, whereas the remaining doses of busulfan were administered orally.

The sponsor then determined the pharmacokinetics of BUSULFEX in three phase II trials at a dosage (0.8 mg/kg) which was adjusted according to the bioavailability of oral busulfan in OMC-BUS-2. In the first trial, OMC-BUS-3, BUSULFEX infusions were administered to 42 patients with various hematological malignancies who later received autologous bone marrow transplantation (BMT). In a similar study, BUSULFEX was also administered to 62 patients with various hematological malignancies, who received allogeneic BMT (OMC-BUS-4). Finally, in an amendment to OMC-BUS-3 and OMC-BUS-4, 12 patients were recruited under these protocols in which dose 1 busulfan was administered orally, followed by 15 intravenous doses of BUSULFEX. Thirty-nine patients from OMC-BUS-3 and 59 patients from OMC-BUS-4 provided evaluable data. Only 9 patients could be evaluated under the Amendment 4 protocol.

c. Busulfan Pharmacokinetic Analysis

The sponsor obtained ten blood samples for pharmacokinetic analysis during dose 1 and compared the results to the steady-state values determined during studies. The "predictability"of BUSULFEX pharmacokinetics was assessed between in the phase II studies. The area-under–the-curve (AUC) for busulfan was determined noncomparmentally using the and clearance (Cl) was determined as dose/AUC. Volume of distribution was determined as Cl/λ_z (terminal elimination rate), which is dependent upon an accurate measurement of λ_z, and is based on the assumption of monoexponential drug disposition. The elimination half-life (T1/2) was determined as the $\ln 2/\lambda_z$.

d. Busulfan Pharmacokinetic Parameters

The sponsor determined the bioavailability, F, of oral busulfan a % in OMC-BUS-2. This result agreed well with the value reported in the literature (Hassan et al. 1994). Based on this result, the sponsor proposed that the indicated dosage of BUSULFEX infusions for BMT should be 0.8 mg/kg, in order to provide drug exposures (AUC's) equivalent to that of oral busulfan. The sponsor implemented this BUSULFEX dosage in all three, phase II studies.

In OMC-BUS-3, the sponsor determined the pharmacokinetic parameters of BUSULFEX. The mean value and the variability of each parameter are listed in Table 1

Table 1: Summary of the Pharmacokinetic Data from OMC-BUS-3 (n=39)

	MEAN		S.D.		% CV	
Parameter	**I.v. Dose 1**	**I.v. dose 9**	**I.v. dose 1**	**I.v. dose 9**	**I.v. dose 1**	**I.v. dose 9**
AUC µMol•min	1193.6 ($AUC_{0-\infty}$)	1224.8 (AUC_{0-t})	323.7	216.0	27.1	17.6
C_{max} ng/ml	889.8	1284.3	185.4	290.4	20.8	22.6
Cl/F/ABW ml/min/kg	2.369	2.253	0.608	0.460	25.7	20.4
V_d/F/ABW L/kg	0.620	0.679	0.110	0.339	17.7	49.9
$T_{1/2}$ –hrs	3.20	3.47	1.06	1.36	33.1	39.2

The sponsor did not conduct inferential statistical comparisons. Nevertheless, the sponsor concluded that the dose1 pharmacokinetics of BUSULFEX were consistent with, and predictive of steady-state pharmacokinetics, and that this infusion rate of BUSULFEX produced plasma AUCs below 1500 µMol•min.

In OMC-BUS-4, the sponsor again determined the pharmacokinetic parameters of BUSULFEX (Table 2). The sponsor made conclusions that were identical to those of OMC-BUS-3.

Table 2: Summary of the Pharmacokinetic Data from OMC-BUS-4 (n=59)

	MEAN		S.D.		% CV	
Parameter	**I.v. Dose 1**	**I.v. dose 9**	**I.v. dose 1**	**I.v. dose 9**	**I.v. dose 1**	**I.v. dose 9**
AUC µMol•min	1105.7 ($AUC_{0-\infty}$)	1166.6 (AUC_{0-t})	318.3	228.1	28.8	19.6
C_{max} ng/ml	946.8	1221.7	239.4	216.1	25.2	17.6
Cl/F/ABW ml/min/kg	2.74	2.25	0.818	0.617	29.9	27.4

V_d/F/ABW L/kg	0.635	0.645	0.103	0.197	16.2	30.5
$T_{1/2}$ –hrs	2.83	2.97	0.755	0.559	26.7	18.8

In amendment 4, the sponsor compared the pharmacokinetics of oral busulfan to those of BUSULFEX infusions. The results of this study are listed in Table 3.

Table 3: Summary of the Pharmacokinetic Data from Amendment 4 (OMC-BUS-3 & OMC-BUS-4 Amendment) (n=9)

	MEAN		S.D.		% CV	
Parameter	p.o. dose 1	I.v. dose 9	p.o. dose 1	I.v. dose 9	p.o. dose 1	I.v. dose 9
AUC µMol•min	1396.2 ($AUC_{0-\infty}$)	1156.0 (AUC_{0-t})	333.5	158.4	23.8	13.7
C_{max} (ng/ml)	870.4	1166.6	260.3	140.7	29.9	12.1
Cl/F/ABW (ml/min/kg)	2.503	2.363	0.455	0.305	18.2	12.9
V_d/F/ABW (L/kg)	0.732	0.634	0.124	0.108	16.9	17.0
$T_{1/2}$ –hrs	3.55	3.11	1.17	0.32	33.0	10.3

The sponsor concluded that BUSULFEX was superior to oral busulfan in achieving more reproducible, less variable pharmacokinetics, and that more patients receiving BUSULFEX than oral buslufan demonstrated AUC's at the targeted level of < 1500 µMol•min. The sponsor made these conclusions on the basis that the coefficients of variation were lower for the BUSULFEX pharmacokinetic parameters than for those of oral busulfan. The sponsor did not perform inferential statistical comparisons.

Generally, the dose 9 steady-state pharmacokinetic parameters of BUSULFEX determined in all three studies were well conserved. Furthermore, the mean BUSULFEX pharmacokinetics are also apparently the same as those of oral busulfan which were determined in this study, as well as previously reported. Based on the results presented above, the sponsor concluded that BUSULFEX has the same mean pharmacokinetic values as oral busulfan, but that dose 1 BUSULFEX provides greater predictability of the pharmacokinetic characteristics of later doses of BUSULFEX. The sponsor also concluded that BUSULFEX is superior to oral busulfan, because it provides less variable

pharmacokinetic characteristics. This conclusion implies that seizures, VOD and engraftment failure are less likely to occur with BUSULFEX.

VII. FDA Comments

Foreword

This section of the report explains in detail the response of the FDA to the studies and the conclusions presented by Orphan Medical Inc. in this NDA. The Agency contends that OMI has not substantiated its claims that BUSULFEX infusions provide "more predictable, less variable" pharmacokinetic parameters than oral busulfan. The comparison of busulfan AUC's is of critical importance to the OMI claim of a superior formulation, because AUC is singly the most important factor which describes patient exposure to the drug. An accurate determination of AUC is also necessary to calculate other pharmacokinetic descriptors, such as clearance and volume of distribution. The Agency believes that the OMI AUC determination from dose 1 busulfan therapy is inaccurate. Furthermore, interpretation of the AUC comparison is complicated by potential time-dependent changes in busulfan disposition induced by concomitant phenytoin administration. The FDA conducted an alternative comparison of AUC's which was not prone to these problems. The Agency concluded that no difference in the variability of the pharmacokinetics exists between oral busulfan and BUSULFEX, based on the data provided by OMI.

a. Pharmacokinetic Study Design

1. Invalid AUC Comparison. It is the Agency position that the comparison of the dose 1 pharmacokinetics of either BUSUFEX or busulfan, to the dose 9 steady-state pharmacokinetics of BUSULFEX is an invalid comparison. In order to compare the BUSULFEX pharmacokinetics of dose 1 to those obtained at steady-state (dose 9), the total AUC of dose 1 is compared to the AUC of the interval (steady-state) at dose 9. The AUC at dose 1 consists of the following

$$AUC_{total} = AUC_{0-t} \text{ (AUC of the observed data)} + AUC_{t-\infty}.$$

The latter calculation of $AUC_{t-\infty}$ is determined by

$$AUC_{t-\infty} = \text{last plasma busulfan concentration}/\lambda_z$$

$AUC_{t-\infty}$ must account for no more than % of the total AUC, which necessitates the observation of drug disposition for at least three half-lives. The sponsor observed busulfan disposition for 6 hours only, or approximately 1.7 elimination half-lives. As a consequence, the sponsor extrapolated total AUC's ranging from %, rendering these measurements inaccurate. Therefore, no comparison of BUSULFEX pharmacokinetics between dose 1 and 9 can be made. Furthermore, the FDA discounts the comparison between oral busulfan and BUSULFEX for the same reason.

2. Inaccurate determination of terminal elimination rate (λ_z). The determination of the terminal elimination rate of busulfan, λ_z, is also flawed. The disposition of busulfan has not been adequately assessed during a 6-hour sampling period, and the sponsor cannot accurately determine the elimination rate from the data. Furthermore, the sponsor compounded this problem by calculating λ_z from 2 observations in some patients (Amendment 4,vol. 1.21 pg 35). This error also contributes to the inaccuracy of this measurement.

3. Inaccurate determination of volume of distribution. The sponsor determined the volume of distribution as Cl/λ_z, which is also likely inaccurate, because of the unreliable estimate of λ_z. Furthermore, the sponsor assumed a one-compartment model of busulfan disposition (which $V_d = Cl/\lambda_z$ describes), but noted that buslufan kinetics declined biphasically in OMC-BUS-3 (vol. 1.17 pg. 38) and OMC-BUS-4 (vol 1.20 page 38). These observations indicate that the BUSULFEX pharmacokinetics may be described more accurately by a two-compartment model. Therefore, the FDA believes that Vd should have been determined noncompartmentally to minimize the error associated with the assumption of a particular compartmental model.

4. Unsupported dose 1 vs. dose 9 Buslufan C_{max} comparisons. The FDA conducted statistical comparisons of C_{max} and C_{min}, respectively, between dose 1 and 9, and dose 9 and dose 13. C_{max} was statistically different between dose 1 and dose 9 in all three studies (Table 4).

Table 4. Comparison of Busulfan C_{max} Between Dose 1 and Dose 9.

Study	C_{max} Dose 1 ng/ml	C_{max} Dose 9 ng/ml	Significance P
OMC-BUS-3	899 ± 19 %	1267 ± 22 %	< 0.0001
OMC-BUS-4	944 ± 25 %	1222 ± 18 %	<0.0001
Amend. 4	835 ± 36 %	1177 ± 19 %	0.0044

Therefore, the FDA discounts the claim that the dosel BUSULFEX pharmacokinetics are predictive of the pharmacokinetics of later doses of BUSULFEX.
The mean C_{max} was statistically different between dose 9 and 13 in OMC-BUS-4, but this outcome was not observed in OMC-BUS-3 or Amendment 4. Therefore, the Agency will allow the sponsor to claim that the BUSULFEX C_{max} of dose 9 equaled that of dose 13. Furthermore, no difference in the BUSULFEX C_{min} values between dose 9 and 13 was detected, and the sponsor may also claim reproducibility between dose 9 and dose 13 based on this parameter.

b. FDA Pharmacokinetic Analysis

5. FDA comparison of oral busulfan and BUSULFEX. The FDA conducted an independent assessment of oral busulfan and BUSULFEX pharmacokinetics. The FDA

compared the dose 1 characteristics of BUSULFEX from OMC-BUS-3 and OMC-BUS-4 to those of dose 1oral busulfan from Amendment 4. The FDA used the data that was observed only; the AUC's were not extrapolated. The raw data provided by the sponsor was fit noncompartmentally with WinNonlin Ver 1.1. The AUC's for the dosing interval (6 hr) were determined using the linear trapezoidal rule. Clearance was determined as dose/AUC, and volume of distribution was dose•(AUMC)/AUC^2. The results are presented in Table 5.

Table 5. Comparison of Dose 1 Oral vs. Intravenous Busulfan Pharmacokinetics

Study	Route of Admin.	Cmax (ng/ml)	AUC_{0-t} (µMol•min) FDA	AUC_{0-t} (µMol•min) OMI	Cl/F/kg (ml/min/kg)	Vd/F (L/kg)	$T_{1/2}$ (hrs)
Amend.4 (n=9)	P.O.	870.4 ± 29.9 %	1793.7 ± 17.3 %	1790 ± 17.3 %	4.48 ± 12.5 %	0.80 ± 18.8 %	3.56 ± 33.4 %
BUS-3 (n=38)	I.V.	901.0 ± 19.1 %	784.0 ± 17.0 %	757 ± 19.6 %*	3.48 ± 18.1 %	0.63 ± 23.8 %	3.33 ± 30.9 %
BUS-4 (n=59)	I.V.	946.8 ± 25.2 %	750.9 ± 19.9 %	751 ± 19.8 %	—	—	—

*OMI analyzed data from 39 patients. FDA excluded one patient for insufficient data.

A comparison of the AUC's calculated by the FDA and OMI are highlighted by the shading in Table 4. This comparison indicates that there were no significant differences in the data* used or the analysis methodology employed. The C_{max} and AUC of busulfan are highly conserved, regardless of the route of administration. This analysis clearly demonstrates the error that was incorporated in the OMI analysis by including such large extrapolated AUC's. The Cl and Vd were higher for oral busulfan than BUSULFEX in this analysis, but this may be due to F, which was unavoidably calculated from the total AUC ($AUC_{0-t} + AUC_{t-\infty}$) determined during dose 1. It should be noted that, regardless of the route of administration, the clearance and volume of distribution are likely inaccurate, because λ_z was not accurately determined. However, clearance and volume of distribution may be accurately assessed by noncompartmental methods using the steady-state data from all three studies.

A visual comparison of the coefficients of variation reveal that the pharmacokinetic characteristics of oral busulfan very closely resemble those of BUSULFEX. Therefore, the FDA concludes that there is no difference in the pharmacokinetic characteristics and the variability between the oral and intravenous formulations of busulfan.

c. Potential Drug Interactions

6. Time-dependent, Phenytoin-induced changes in busulfan AUC. Hassan et al. (1993) demonstrated that concurrent administration of phenytoin produces a significant

decrease in the AUC of orally-administerd busulfan. Using a dosing regimen identical to that of OMI, Hassan and his associates showed that the clearance of busulfan increased by an average of 19% by the last dose of busulfan, possibly as a result of hepatic enzyme induction. Therefore, the comparisons made by OMI between dose 1 to dose 9 busulfan pharmacokinetics may be confounded by this fact. Furthermore, the pharmacokinetic results obtained by the sponsor must be limited to the clinical setting in which phenytoin is administered concurrently with BUSULFEX.

7. Itraconazole-induced decrease in busulfan clearance. Buggia et al (1996) demonstrated that itraconazole decreases the clearance of oral busulfan. These authors also administered oral busulfan according to a schedule identical to that of the sponsor. The authors report that the clearance of busulfan was reduced by an average of 25 % when itraconazole was administered concurrently with busulfan. Therefore, concurrent treatment with itraconazole increases the risk that the patients may exceed the 1500 μMol•min AUC considered as the safe maximum for busulfan. For this reason, the sponsor must correct labeling instructions regarding concurrent admnistration of anti-fungal agents.

8. Potential 5-HT_3 antiemetic-BUSULFEX interaction. The FDA compared the effect of 7-day, concurrently administered 5-HT_3 antiemetic on the plasma AUC's of BUSULFEX. In a post hoc analysis (unpaired t-test) of patient BUSULFEX AUC's from OMC-BUS-3, patients treated with 5-HT_3 antiemetics Zofran or Kytril from the start of BUSULFEX therapy yielded a mean AUC of 1164 ± 179.1 μMol•min. This was significantly lower than the mean AUC (1361 ± 236.9 μMol•min) in patients who had not been treated with 5-HT_3 antiemetics during the same period ($p = 0.0069$). The power of the statistical analysis (0.75) was lower than the desired level of 0.8 at an α-level of 0.05. Nevertheless, the finding is noteworthy because a greater number of patients who relapsed (5 vs. 2) belonged to the group treated with the 5-HT_3 antiemtics and demonstrated lower AUC's (no statistical comparison). These data suggest that the 5-HT_3 antiemetics may alter the disposition of BUSULFEX, which may produce BUSULFEX exposures that are subtherapeutic. The FDA tempers this conclusion with the finding that these results were not observed in a similar analysis of the data from OMC-BUS-4.

d. Special Populations

9. Busulfan pharmacokinetics in children. Several studies have demonstrated that the pharmacokinetics of busulfan are significantly different in children under 4 years of age, than in adults (Grochow et al, 1990; Vassal et al 1990; Regazzi et al 1993: Appendix Xb). These studies have demonstrated that children in this age group have a larger volume of distribution and greater clearance of busulfan than adults. Furthermore, successful engraftment without VOD or seizures might be obtained more successfully by dosing busulfan to children on the basis of body surface area (Vasssal et al 1990: Appendix Xb) and thus may require different dosage rates of BUSULFEX than adults. This advisory must be specified in the labeling.