CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

9-386/S-019

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 09-386/019		**Submission Date:**	October 4, 2001
Drug Name:	Myleran (busulfan)		
Formulation:	Tablet, 2 mg		
Applicant:	Glaxo Wellcome Inc. Five moore Drive PO Box 13398 Research Triangle Park, NC 27709		
Reviewer:	John Duan, Ph.D.		
Team Leader:	Atiqur Rahman, Ph.D		
Type of Submission:	NDA (Supplement)		

I. EXECUTIVE SUMMARY

Myleran tablet is indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic granulocytic) leukemia. The applicant intended to reformulate and update the product prior to transferring the products to a new facility. Based on the agreement between the Agency and the applicant, a bioequivalence study was conducted to compare the in vivo performance of the current US and proposed reformulated 2 mg MYLERAN (busulfan) Tablets.

The statistical analysis of pharmacokinetic parameters showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range for AUC of busulfan when the new formulation was compared to the current US formulation. However, for the C_{max} of busulfan, the upper-limit of the 90% confidence interval was 152%. Thus, the new formulation of busulfan does not meet the bioequivalence criteria compared to the present US formulation. While mild to moderate headaches were the only adverse events reported, three of them were observed with the new formulation whereas none occurred in patients treated with the approved US formulation. This toxicity could be related to the elevated C_{max}.

The discrepancy between AUC and C_{max} indicates that the pharmacokinetic behavior of the new formulation is different from the current approved formulation. This difference could result in different toxicity profiles. Therefore, the new formulation is not considered to be comparable to the approved formulation. A consult review from the Medical Reviewer establishes that a clinical study is needed to evaluate toxicity differences between the two formulations and the Medical Officer's recommendation regarding the study design should be followed (please see Appendix II).

Adequate data to support the dissolution methodology and specifications were submitted. The dissolution specifications are recommended based on the data.

COMMENTS TO THE REVIEW CHEMIST

1. The proposed dissolution conditions were supported by adequate data.

2. The following dissolution specifications for the product are recommended.

Apparatus: USP <711> Apparatus II
Paddle Speed: 50 ± 2 rpm
Media: 500 mL de-aerated purified water
Temperature: 37.0 ± 0.5°C
Specifications: Meets USP requirements where Q = [redacted]% dissolved in 15 minutes.

GENERAL COMMENTS

1. The bioequivalence between the new worldwide formulation of MELERAN® and the current US formulation has not been established, because 90% confidence interval of the C_{max} ratio is outside the 80-125% range.

2. The new formulation is considered not to be comparable to the current marketed formulation based on the following considerations

   - The C_{max} of reformulated formulation is 32% higher in comparison to the current US formulation. This elevated C_{max} could be related to higher incidence of certain toxicities.

   - Busulfan is usually given on a chronic basis. AUC is the important parameter for pharmacodynamic behavior. However, if the toxicities caused by higher C_{max} of the new formulation limit the dose, the required AUC may not be reached and efficacy compromised.

   - The discrepancy between AUC and C_{max} indicates that the pharmacokinetic behavior of the new formulation is different from the current approved formulation.

RECOMMENDATIONS

The Office of Clinical Pharmacology and Biopharmaceutics recommends non approval of the supplemental NDA. The new formulation of busulfan does not meet the bioequivalence criteria compared to the present US formulation. Peak plasma concentration of busulfan with the new formulation is 32% higher and is likely associated with higher toxicity (headache). Based on the Medical Officer's recommendation (please see Appendix II), the applicant should conduct a randomized, controlled trial to determine the difference in the incidence of headache between the new and the old formulations. Please submit your clinical trial protocol for Agency review.

/S/

John Duan, Ph.D. Date

Reviewer
Division of Pharmaceutical Evaluation I

/S/

Atiqur Rahman, Ph.D Date

Team Leader
Division of Pharmaceutical Evaluation I

CC:

NDA	original
HFD-150	Division File
HFD-150	MPelosi
HFD-150	Gfrykmen, JJohnson
HFD-150	CLiang, RLostritto
HFD-860	MMehta, ARahman, JDuan
CDR	

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III. SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Myleran tablets are indicated for the palliative treatment of chronic myelogenous (myeloid, myelocytic granulocytic) leukemia. Myleran tablets have been marketed in the United States since 1954 and currently manufactured at the facility in Greenville, North Carolina, by the applicant. The applicant decided to transfer the product from the current production facility, Greenville, North Carolina, to the proposed facility, Dartford, United Kingdom (UK). At the same time, since Myleran Tablets were developed more than 40 years ago, the applicant intended to reformulate and update the product prior to transferring the products to the new facility. Based on the agreements reached at the meeting dated November 20, 1996 and the teleconference dated March 14, 1997, the applicant submitted an IND dated May 16, 1997, to the Agency to provide a basis for the review of clinical trials that will be conducted to compare two existing formulations of busulfan 2.0 mg with a new worldwide formulation that will be manufactured at a new facility in Dartford, UK.

In the current submission, the applicant submitted the results of a single-dose, 3-way crossover bioequivalence study to compare the in vivo performance of the current US and proposed reformulated MYLERAN (busulfan) Tablets 2 mg. The bioavailability of the proposed reformulation was compared to the current US formulation. Median and individual concentration-time profiles were assessed in 12 patients.

The statistical analysis of pharmacokinetic parameters showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range for AUC of busulfan when the new formulation was compared to the current US formulation. However, for the C_{max} of busulfan, the upper-limit was 152%. Thus, the new formulation of busulfan does not meet the bioequivalence criteria compared to the present US formulation. While mild to moderate headaches were the only adverse events reported, three of them were observed in new formulation whereas none occurred in approved US formulation. This could be related to elevated C_{max}. The discrepancy between AUC and C_{max} indicates that the pharmacokinetic behavior of the new formulation is different from the current approved formulation. This difference could result in different toxicity profiles. Therefore, the new formulation is not considered to be comparable to the approved formulation. Further study is needed and the Medical Officer's recommendation regarding the study design should be followed.

Adequate data to support the dissolution methodology. The applicant suggested the following dissolution methodology and specification.

Media: 500 mL de-aerated purified water
Apparatus: USP Apparatus II (paddle) at 50 ± 2 rpm
Temperature: 37.0 ± 0.5°C
Specification: Meets USP requirements where Q = [redacted]% dissolved in 20 minutes.

Based on the data, however, the specification is not adequate. The following specifications

are recommended.

Apparatus: USP <711> Apparatus II
Paddle Speed: 50 ± 2 rpm
Media: 500 mL de-aerated purified water
Temperature: 37.0 ± 0.5°C
Specifications: Meets USP requirements where Q = ▬ % dissolved in 15 minutes.

IV. QUESTION BASED REVIEW

A. General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Busulfan is a small highely lipophilic molecule with the following structural formula:

$$CH_3SO_2O(CH_2)_4OSO_2CH_3$$

Myleran is available in tablet form for oral administration.

2. What is the proposed mechanism of action and the therapeutic indication? What is the proposed dosage and route of administration?

Busulfan is a bifunctional alkylating agent for chronic myelogenous leukemia and is available in tablet form for oral administration (1.8 mg/m^2).

B. General Biopharmaceutics

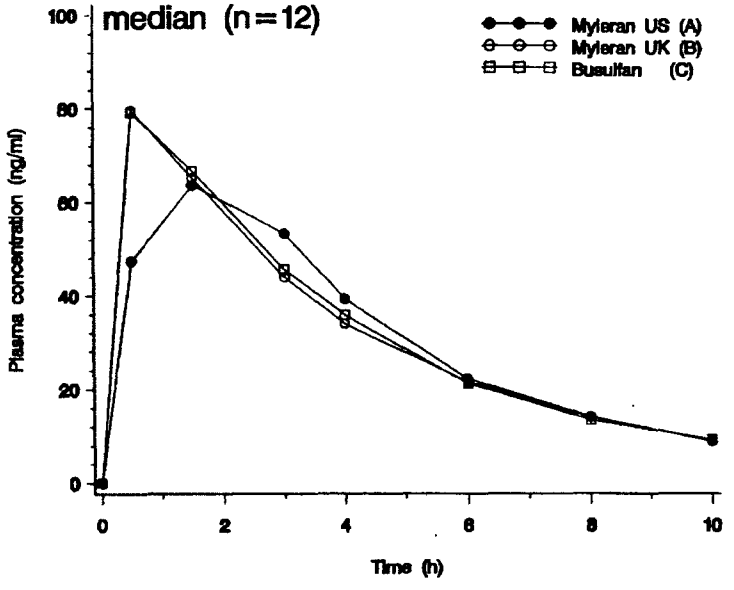
1. What is the in vivo relationship of the proposed reformulated product to the current US marketed formulation in terms of comparative exposure?

The applicant provided the current U.S. and the proposed formulations as shown below.

Current US Formulation		Proposed Reformulation	
Composition	Weight per Tablet	Composition	Weight per Tablet
Busulfan, USP	2.0 mg	Busulfan	2.00 mg
Magnesium Stearate, NF		Anhydrous Lactose, NF	
Sodium chloride		Pregelatinized Starch, NF	
USP		Magnesium Stearate, NF	
Total Core Weight		Total Core Weight	
Coating		Coating	
No coating			
Total Tablet Weight	150 mg	Total Tablet Weight	102.5 mg

From the bioequivalence study submitted in this sNDA, the plasma concentration profiles of patients treated with the proposed reformulation and the present US formulation are shown in the following figures. The analysis of the pharmacokinetic parameter of AUC indicated that the 90% confidence intervals were within the 80 to 125% bioequivalence range. However, the upper-limit of the C_{max} of the new formulation compared to the present US formulation was 152%. The results are summarized in the following table.

Median Busulfan Plasma Concentration Time Curves
Busulfan in the legend refers to MYLERAN World-wide Formulation



Dose Normalized:

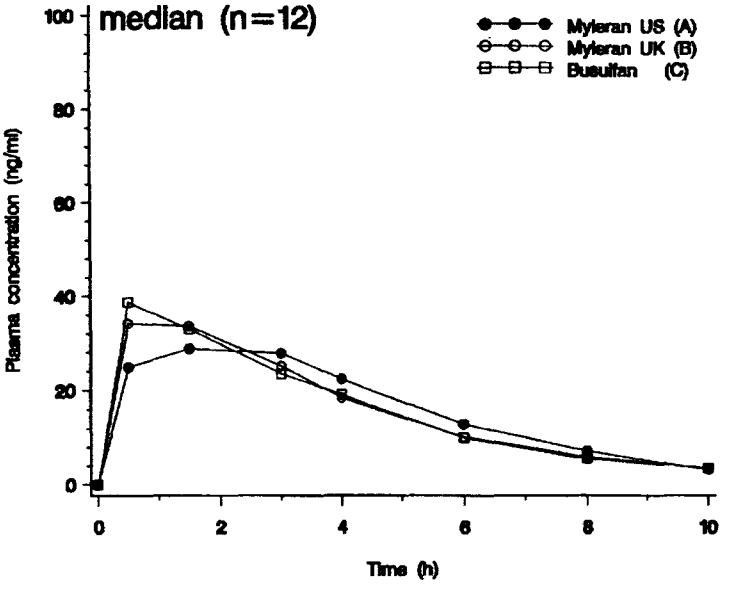


Table. Summary of Busulfan Plasma Concentration Data

	Busulfan Geometric LS Mean (95% CI)				
	MELERAN US	MELERAN World-Wide	Treatment Comparison	Estimate	90% CI
C_{max} (ng/mL)	49.0 (43.4, 55.3)	64.5 (57.2, 72.8)	C/A	1.32	(1.14 - 1.52)
AUC_{last} (ng•h/mL)	227 (219, 237)	237 (228, 246)	C/A	1.04	(0.99 - 1.09)
AUC_{∞} (ng•h/mL)	254 (245, 263)	262 (253, 272)	C/A	1.03	(0.99 - 1.08)

A = present US formulation, C = new worldwide formulation

The reviewer rechecked the calculations based on the raw data provided by the applicant. Thus, the new formulation of MELERAN® is not bioequivalent to the present US formulation because the C_{max} of reformulated product is 32% higher in comparison to the current US formulation. Although mild to moderate headaches were the only adverse events reported, three of them were observed in new formulation whereas none occurred in approved US formulation. This could be related to elevated C_{max}. The discrepancy between AUC and C_{max} indicates that the pharmacokinetic behavior of the new formulation is different from the current approved formulation. This difference could result in different toxicity profiles. Therefore, the new formulation is not considered to be comparable to the approved formulation. Further study is needed and the Medical Officer's recommendation regarding the study design should be followed.

2. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The applicant suggested the following dissolution specifications.

Typical Instrumental Conditions for Dissolution

Apparatus: USP <711> Apparatus II
Media: 500 mL de-aerated purified water
Paddle Speed: 50 ± 2 rpm
Temperature: 37.0 ± 0.5°C

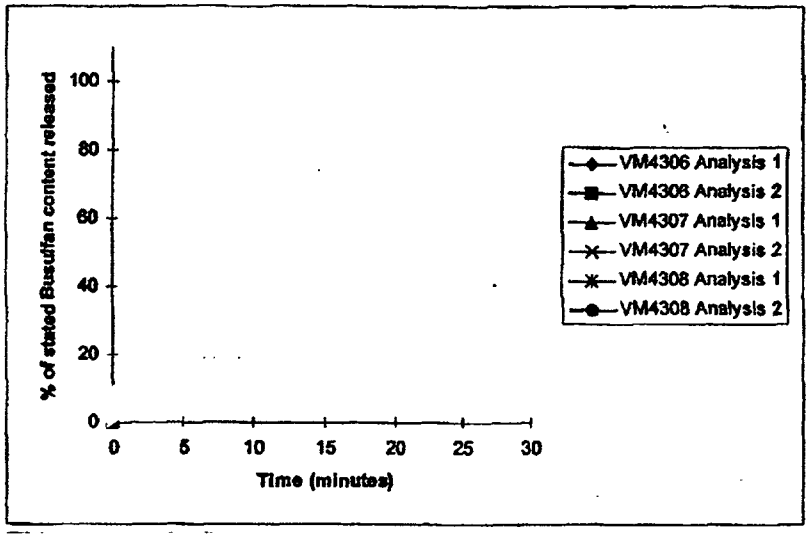
Specifications
Meets USP requirements where Q = [redacted] % dissolved in 20 minutes.

However, based on the data provided as shown in the following table and figure, the specification is not adequate.

Table 9 **Comparison of dissolution profiles of reformulated Myleran® (Busulfan) Tablets 2mg, in water, using a paddle speed of 50rpm**

Batch		VM4306		VM4307		VM4308	
Batch size		[illegible] tablets		[illegible] tablets		[illegible] tablets	
Date of manufacture		December 1997		December 1997		December 1997	
Date of expiry		December 1999		December 1999		December 1999	
Results		Busulfan released (as % of stated content)					
		Analysis 1	Analysis 2	Analysis 1	Analysis 2	Analysis 1	Analysis 2
5 minutes	Individual						
	Mean RSD (%)	38 14	39 11	34 15	36 12	37 11	32 12
10 minutes	Individual						
	Mean RSD (%)	76 3	81 5	74 6	71 9	76 5	71 6
15 minutes	Individual						
	Mean RSD (%)	89 3	90 2	87 1	88 1	88 1	85 1
20 minutes	Individual						
	Mean RSD (%)	88 2	90 2	90 2	90 1	90 1	87 2
30 minutes	Individual						
	Mean RSD (%)	94 2	92 1	91 2	93 2	92 1	88 3

Figure 4 **Comparison of dissolution profiles of reformulated Myleran® (Busulfan) Tablets 2mg, in water using a paddle speed of 50rpm**



Based on the data, the following specifications are recommended.

Apparatus: USP <711> Apparatus II
Paddle Speed: 50 ± 2 rpm
Media: 500 mL de-aerated purified water
Temperature: 37.0 ± 0.5°C
Specifications: Meets USP requirements where Q = —% dissolved in 15 minutes.

C. Analytical Section

1.

2. What bioanalytical methods are used to assess concentrations?

A summary of the pre-study assay validation data is presented in the following table.

Method	
Calibration model	Linear weighted 1/X
Quantifiable range	
precision (%CV)	< 10.2%
Accuracy (% bias)	< ±8.2%
Matrix stability	At least 38 days (at –20°C)
	At least 24 days (ambient temp)
Recovery	>90% at 50 and 500 ng/mL

The assay methods and validations are acceptable based on the current standards.

V. DETAILED LABELING RECOMMENDATIONS

18 pages redacted from this section of the approval package consisted of draft labeling

APPENDIX II. MEDICAL OFFICEER REVIEW

MEDICAL OFFICER REVIEW
DIVISION OF ONCOLOGY DRUG PRODUCTS (HFD-150)

CONSULTATION TO
OCPB/HFD-860 – John Z. Duan, Ph.D.

NDA#: 09-386

DRUG: Myleran® (busulfan) 2 mg scored tablets

SPONSOR: GlaxoSmithKline

DATE RECEIVED: 04 February 2002

DATE COMPLETED: 08 February 2002

MEDICAL OFFICER: Gregory K. Frykman, MD (x4-5757)

TEAM LEADER: John Johnson, MD

DOCUMENTS REVIEWED: sNDA Volume 6, OCPB Review

A review of the limited clinical data arising from the bioequivalence study of the old and new foumulations for Myleran® (busulfan) indicates that there was a relatively higher incidence of headache in the group assigned to the new formulation (volume 6, p. 61/95)

From the time-concentration profiles provided in the review (p. 8), it appears possible that headache is related to the higher Cmax observed with the new formulation. The scale used, the duration, quality of the headache and other associated factors are not provided in the clinical material provided.

The clinical concern is that if headache is found to be a true adverse effect of the new formulation, patients who are uncomfortable from their headache may be less motivated to continue their busulfan oral administration. The efficacy of busulfan in CML could be compromised if patient compliance diminishes.

To more carefully determine the clinical significance of this finding, I recommend a randomized controlled trial whose purpose is to determine a difference in the incidence of headache between the new and old formulations. The recommended difference to detect is approximately 20%, which is based on the following assumptions of a baseline incidence of headache of 5% and an observed incidence of headache of 25%. Because busulfan is administered chronically, I suggest 2-4 mg/m2 or 0.1 mg/kg p.o. daily until the WBC decreases by 50%. This should then be followed by a 50% dose reduction to maintain the WBC count between 20,000 and 50,000/mm3.

REFERENCE

DeVita VL, et al. eds. Principles and Practice of Oncology 6th ed, pp. 2347-2355; Lippincott, 2001

APPENDIX III. INDIVIDUAL STUDY SYNOPSIS

1. Bioequivalence study, MYLA1001

Study title: A biocomparability study of MYLERANT (Busulfan) Tablets 2mg in patients with chronic myeloid leukemia or other refractory malignancies.

Investigator & location: Investigator(s): [redacted]
Study center(s): [redacted]

Study period: 17 August 1998 - 22 March 1999

Study formulation:

- Test product: MYLERAN® Tablets (new worldwide formulation), 2 mg (batch # F97/033),
- Reference product: MYLERAN® Tablets (US formulation), 2 mg (batch # 6X1594), and MYLERAN® Tablets (UK formulation), 2 mg (batch # D3459A).

Objectives:

- To compare the pharmacokinetic profile of the new worldwide formulation of Busulfan to the present US and UK formulations of MYLERAN Tablets.
- To assess the biocomparability of the new worldwide formulations of Busulfan relative to the present US and present UK formulations of MYLERAN Tablets.
- To evaluate the acute toxicity profile of the new worldwide formulation of Busulfan relative to the present US and present UK formulations of MYLERAN Tablets.

Subjects: Twelve subjects were screened and evaluated.

Study Design:

This was an open-label, single dose, randomized, 3-way crossover bioequivalence study in patients with chronic myeloid leukemia or other refractory malignancies.

Plasma busulfan concentrations were monitored to evaluate pharmacokinetics. The criteria for evaluation for safety were physical examination, vital signs, ECG, laboratory test results and reported adverse events.

The pharmacokinetic analyses were descriptive statistics for log-transformed and untransformed C_{max}, AUC_{last}, $AUC_{0-\infty}$, and $t_{1/2}$ as well as untransformed t_{max} and %AUC extrapolated. ANOVA (analysis of variance) was used to assess the pharmacokinetic comparisons among formulations for dose adjusted C_{max}, $AUC_{0-\infty}$ and AUC_{last}. The effects due to sequence, subject within sequence, period and treatment were evaluated. Based upon the residual variation of ANOVA, 90% confidence intervals for the ratio of geometric least-squares means of test and reference were calculated. Bioequivalence was concluded if the 90% confidence intervals of C_{max} and AUC for the ratio of geometric means of test and reference intervals fell within the standard bioequivalence range of 80-125%. Non-

parametric methods were used to compare t_{max} across formulations.

Results:

Assay performance:

A summary of the pre-study assay validation data is presented in the following table.

Method	
Calibration model	Linear weighted 1/X
Quantifiable range	
precision (%CV)	< 10.2%
Accuracy (% bias)	< ±8.2%
Matrix stability	At least 38 days (at -20°C) At least 24 days (ambient temp)
Recovery	>90% at 50 and 500 ng/mL

The assay methods and validations are acceptable based on the current standards.

Pharmacokinetics:

The median busulfan plasma concentration time profile and the dose normalized profile are shown in the following figure. The statistical analysis of the pharmacokinetic parameter, AUC, showed that the 90% confidence intervals were within the 80 to 125% bioequivalence range. However, the upper-limit of the C_{max} of busulfan of the new formulation compared to the present US formulation was 132% (see Tables below).

Table. Summary of Busulfan Plasma Concentration Data

	Busulfan Geometric LS Mean (95% CI)				
	MELERAN US	**MELERAN World-Wide**	**Treatment Comparison**	**Estimate**	**90% CI**
C_{max} (ng/mL)	49.0 (43.4, 55.3)	64.5 (57.2, 72.8)	C/A	1.32	(1.14 - 1.52)
AUC_{last} (ng•h/mL)	227 (219, 237)	237 (228, 246)	C/A	1.04	(0.99 - 1.09)
AUC_{∞} (ng•h/mL)	254 (245, 263)	262 (253, 272)	C/A	1.03	(0.99 - 1.08)

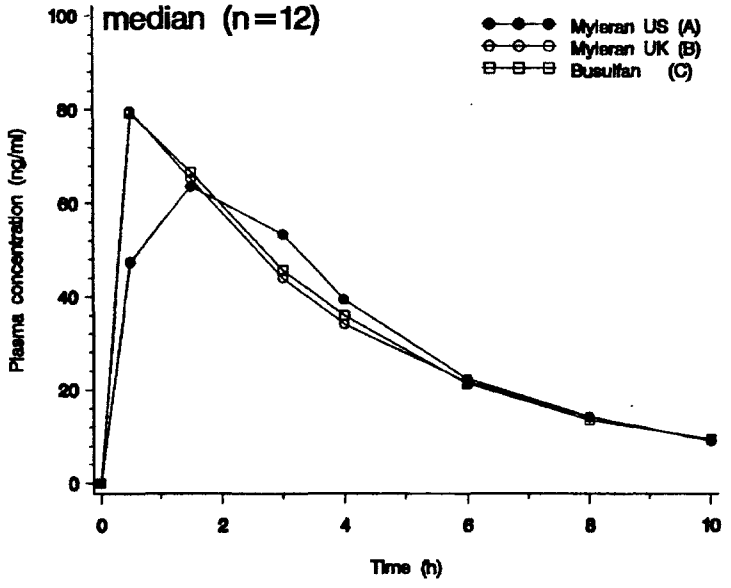
A = present US formulation, C = new worldwide formulation

The dissolution of the new formulation is faster at 15 and 30 minutes than that of the present US formulation. This appears to impact C_{max} of these two formulations.

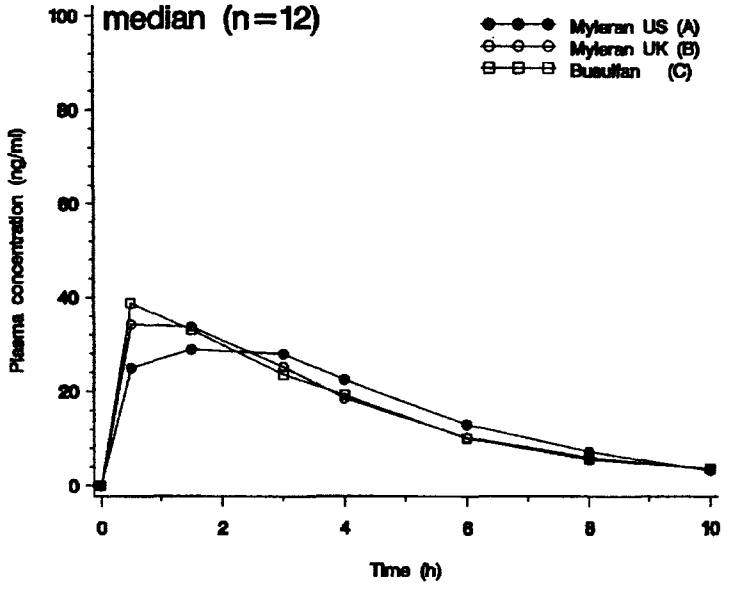
Safety

Mild to moderate headaches were the only adverse events reported. However, three adverse events were observed in new formulation whereas none occurred in current US formulation as summarized in the following table.

Median Busulfan Plasma Concentration Time Curves
Busulfan in the legend refers to MYLERAN World-wide Formulation



Dose Normalized:



Supporting Table 8
Summary of All Adverse Events

BODY SYSTEM event	MYLERAN US (n=12) Number of events	MYLERAN US (n=12) Number of Subj.	MYLERAN US (n=12) % of Subj.	MYLERAN UK (n=12) Number of events	MYLERAN UK (n=12) Number of Subj.	MYLERAN UK (n=12) % of Subj.	BUSULFAN (n=12) Number of events	BUSULFAN (n=12) Number of Subj.	BUSULFAN (n=12) % of Subj.
ANY ADVERSE EVENTS	0	0		2	2	(17%)	3	3	(25%)
NEUROLOGY									
Any event	0	0		2	2	(17%)	3	3	(25%)
headache	0	0		2	2	(17%)	3	3	(25%)

Comments:

1. The bioequivalence between the new worldwide formulation of MELERAN® and the current US formulation has not been established because the C_{max} of reformulated product is 32% higher in comparison to the current US formulation.

2. The new formulation is comparable to the current marketed formulation based on the following considerations

   - The 90% confidence interval of the AUC ratio of the reformulated product over the current US marketed formulation is within 80-125% range.

   - Busulfan is usually given on a chronic basis. AUC is the most important parameter for pharmacodynamic behavior.

   - Toxicity was relatively low.

2.Dissolution tests

Composition of the formulations:

The current U.S. and the proposed formulations are provided as shown below.

Current US Formulation		Proposed Reformulation	
Composition	Weight per Tablet	Composition	Weight per Tablet
Busulfan, USP	2.0 mg	Busulfan	2.00 mg
Magnesium Stearate, NF		Anhydrous Lactose, NF	
Sodium chloride		Pregelatinized Starch, NF	
USP		Magnesium Stearate, NF	
Total Core Weight		Total Core Weight	
Coating		Coating	
No coating			
Total Tablet Weight	150 mg	Total Tablet Weight	102.5 mg

Dissolution results:

Dissolution test for the proposed reformulated MYLERAN® Tablets, 2 mg and the current US commercial product were compared. The applicant provided the results in the Table and Figure below.

Table. Rate of Dissolution Comparison for MELKERAN® (busulfan) Tablets, 2 mg: Proposed Reformulated Product versus Current US Commercial Product

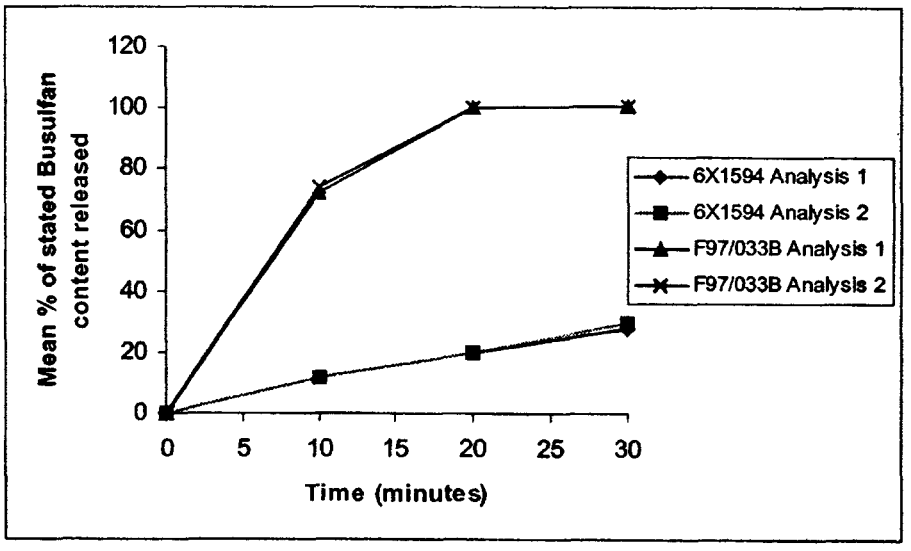
Batch Number		6X1594		F97/033B	
Formulation		Existing US Formulation		Proposed Formulation	
Results		% of Stated Busulfan Content Released			
		Analysis 1	Analysis 2	Analysis 1	Analysis 2
10 minutes	Individual				
	Mean	12	12	72	74
	RSD (%)	15	20	6	6
20 minutes	Individual				
	Mean	20	20	100	103
	RSD	11	4	1	2
30 minutes	Individual				
	Mean	28	30*	101	101
	RSD	7	9	1	2

* mean of 5 vessels only due to equipment malfunction

Figure. Comparative dissolution profiles of current US commercial product and proposed reformulated product of Meleran Tablets 2 mg in water using a paddle speed of 50 rpm.

Key: 6X1594 = Current US formulation

F97/033B = Proposed formulation



The applicant suggested the following dissolution specifications.

Instrumental Conditions for Dissolution

Apparatus: USP <711> Apparatus II

Media: 500 mL de-aerated purified water

Paddle Speed: 50 ± 2 rpm

Temperature: 37.0 ± 0.5°C

Specifications

Meets USP requirements where Q = ~ % dissolved in 20 minutes.

The selection of dissolution conditions is shown in the following table and figure.

Figure 1 **Comparison of dissolution profiles for one batch of reformulated Myleran® (Busulfan) Tablets 2mg, in different dissolution media using a paddle speed of 50rpm**

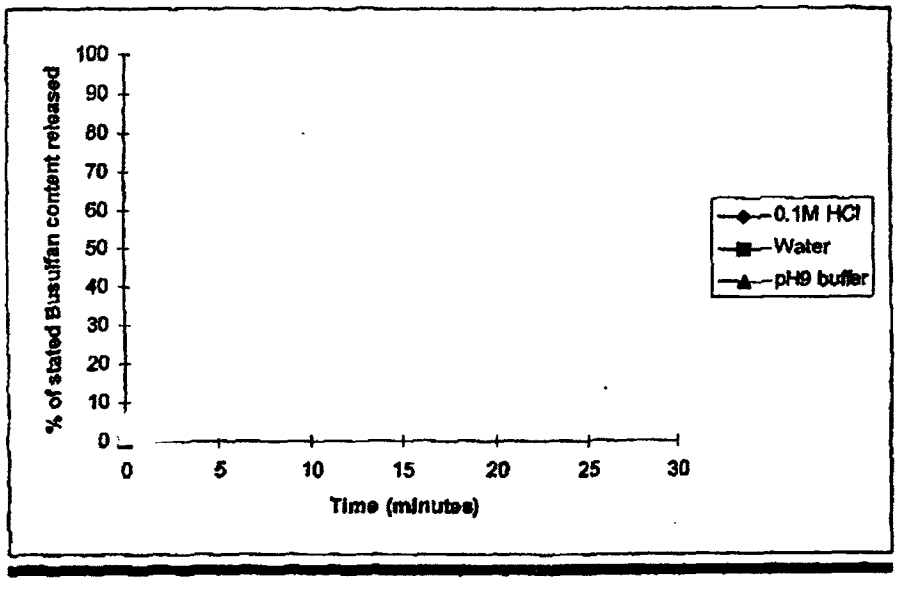


Table 6 **Dissolution profiles for one batch of reformulated Myleran® (Busulfan) Tablets 2mg, in different dissolution media using a paddle speed of 50rpm**

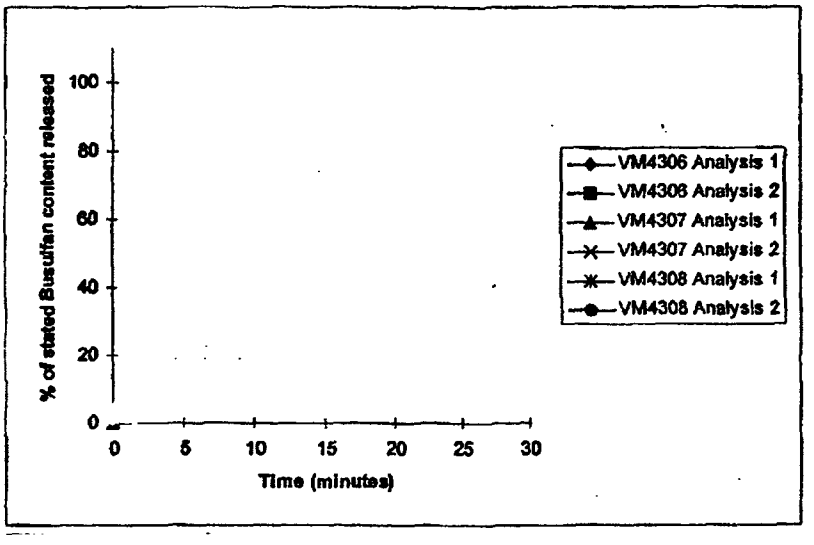
Batch number		VM4307		
Batch size		——— tablets		
Date of manufacture		December 1997		
Date of expiry		December 1999		
Dissolution media		0.1M HCl	Water	pH 9 phosphate buffer
Results		Busulfan released (as % of stated content)		
10 minutes	Individual			
	Mean	53	78	14
20 minutes	Individual			
	Mean	54	92	73
30 minutes	Individual			
	Mean	57	94	83

Using the selected condition, three batches were tested as shown in the following table and figure.

Table 9 **Comparison of dissolution profiles of reformulated Myleran® (Busulfan) Tablets 2mg, in water, using a paddle speed of 50rpm**

Batch		VM4306		VM4307		VM4308	
Batch size		[redacted] tablets		[redacted] tablets		[redacted] tablets	
Date of manufacture		December 1997		December 1997		December 1997	
Date of expiry		December 1999		December 1999		December 1999	
Results		Busulfan released (as % of stated content)					
		Analysis 1	Analysis 2	Analysis 1	Analysis 2	Analysis 1	Analysis 2
5 minutes	Individual						
	Mean RSD (%)	38 14	39 11	34 15	36 12	37 11	32 12
10 minutes	Individual						
	Mean RSD (%)	76 3	81 5	74 6	71 9	76 8	71 8
15 minutes	Individual						
	Mean RSD (%)	89 3	90 2	87 1	88 1	88 1	85 1
20 minutes	Individual						
	Mean RSD (%)	88 2	90 2	90 2	90 1	90 1	87 2
30 minutes	Individual						
	Mean RSD (%)	94 2	92 1	91 2	93 2	92 1	88 3

Figure 4 **Comparison of dissolution profiles of reformulated Myleran® (Busulfan) Tablets 2mg, in water using a paddle speed of 50rpm**



Comments:

1. The proposed dissolution conditions are supported by adequate data.

2. The dissolution specifications for the product should be set as follows.

Apparatus: USP <711> Apparatus II
Paddle Speed: 50 ± 2 rpm
Media: 500 mL de-aerated purified water
Temperature: 37.0 ± 0.5°C
Specifications: Meets USP requirements where Q = [redacted]% dissolved in 15 minutes.

APPEARS THIS WAY
ON ORIGINAL

APPENDIX III

Office of Clinical Pharmacology and Biopharmaceutics

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	**09-386**	**Brand Name**	**Myleran**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Busulfan**
Medical Division	**Oncology Drug Products**	**Drug Class**	**Alkylating agent**
OCPB Reviewer	**John Duan**	**Indication(s)**	**Chronic myeloenoous leukemia**
OCPB Team Leader	**Atique Rahman**	**Dosage Form**	**Tablet**
		Dosing Regimen	**1.8 mg/m^2**
Date of Submission	**10/4/01**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**1/24//02**	**Sponsor**	**GlaxoSmithkiline**
PDUFA Due Date	**4/4/02**	**Priority Classification**	**6P**
Division Due Date	**2/7/02**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
acute dose:				
chronic dose:				
Patients-				
acute dose:				
chronic dose:				
Dose proportionality -				
Fasting / non-fasting acute dose:				
Fasting / non-fasting chronic dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; acute / multi dose:	X	1	1	
replicate design; acute / multi dose:				
Food-drug interaction studies:				
Dissolution:	x	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	

Filability and QBR comments		
	"X" if yes	***Comments***
Application filable ?	**X**	Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?	**N/A**	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**1. Is the bioequivalence between reformulated and current tablet established? 2. is the dissolution specification adequate?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**John Duan 1/24/02**	
Secondary reviewer Signature and Date	**Atique Rahman 1/24/02**	

CC: NDA 09-386, HFD-850 (Electronic Entry or Lee), HFD-150 (CSO), HFD-860 (Rahmana, Mehta), CDR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Duan
3/21/02 04:15:52 PM
BIOPHARMACEUTICS

Atiqur Rahman
3/22/02 10:08:44 AM
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