CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

9-386/S-019

Administrative Documents

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 09-386 / S-019

SmithKlineBeecham d/b/a GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709-3398

Attention: Kevin A. Miller, R.Ph.
Associate Director, CMC Regulatory Affairs

Dear Mr. Miller:

We acknowledge receipt of your February 17, 2003 submission containing final printed labeling in response to our January 24, 2003 letter approving your supplemental new drug application for reformulated Myleran (busulfan) Tablets, 2 mg.

We have reviewed the labeling that you submitted in accordance with our January 24, 2003 approval letter and we find it acceptable.

If you have any questions, contact Maureen A. Pelosi, Project Manager, at 301-594-5778.

Sincerely yours,

/S/

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Dotti Pease
3/14/03 11:31:08 AM
Signing for Richard Pazdur, M.D.

CSO sNDA LABELING REVIEW OF PACKAGE INSERT

sNDA: 09-386 / FA

DATE OF SUBMISSION: February 17, 2003

DATE OF REVIEW: March 5, 2003

DRUG: Myleran (busulfan) Tablets

SPONSOR: SmithKlineBeecham d/b/a GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709-3398

The February 17, 2003 submission contains the final printed labeling for NDA 09-389 SCM-019 in response to our January 24, 2003 approval letter. This supplement provided for the manufacture of reformulated Myleran in a High Containment Facility (HCF) in Dartford, UK.

The January, 2003, FPL (Code RL1173) is identical to the labeling text accompanying the AP letter except for one change that I forgot to delete.

Under **OVERDOSAGE**, GSK removed the following sentence: "Dialysis may be considered in the management of overdose as there is 1 report of successful dialysis of busulfan (see CLINICAL PHARMACOLOGY)."

GSK's decision to delete this sentence was correct. The information referenced in the CLINICAL PHARMACOLOGY section was deleted during the review of the supplement.

The FPL is acceptable.

/S/

/03-11-03
Maureen A. Pelosi
Regulatory Project Manager

/S/

Dotti Pease
Supervisor, Project Management Staff

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/s/

Maureen Pelosi
3/12/03 05:13:21 PM
CSO

Dotti Pease
3/13/03 07:50:45 AM
CSO

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 09-386 / SCM-019
DATE OF SUBMISSION: AZ (7/16/02) and BL (1/16/03)
DATE OF REVIEW: January 21, 2003
DRUG: Myleran (busulfan) 2 mg Tablets

SPONSOR: SmithKlineBeecham Corporation dba GlaxoSmith Kline
Five Moore Drive
Research Triangle Park, NC 27709

In November 1996 it was agreed that two or more reformulation supplements would be filed for MYLERAN Tablets. The first (S-016) updated the drug substance synthesis, drug product specifications, and drug product analytical methods. Numerous comments were exchanged with the sponsor during 1997-1998. This supplement addresses all outstanding commitments.

The CMC reviewer (Chengyi Liang) reviewed the changes in the DESCRIPTION and HOW SUPPLIED sections and recommended approval on January 30, 2002.

A consult was sent to OCPB (John Duan) for review of comparative dissolution profiles, biocomparability, and revisions to the CLINICAL PHARMACOLOGY section which has been rewritten. A non-approval letter issued on 3/25/02. As a result GSK sent in the 7/16/02 AZ submission. Detailed labeling comments were exchanged and negotiated from September to December, 2002 between GSK and Dr. Rahman. In the 1/16/03 BL submission, GSK has addressed the remaining outstanding comments.

I have reviewed the proposed draft labeling and compared it with the approved labeling from insert RL-822 dated May 2000. Agreed upon changes to the DESCRIPTION, CLINICAL PHARMACOLOGY, and HOW SUPPPLIED sections have been accepted. The only revisions are those recommended for the CLINICAL PHARMACOLOGY and they are acceptable.

Approval is recommended.

/S/ /1-21-03
Maureen A. Pelosi
Project Manager

Concur: /S/ / 1-22-03
Dotti Pease
Supervisor, Proj. Management Staff

Concur: /S/ /1-22-03
Atik Rahman, PhD, OCPB Team Leader

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/s/

Maureen Pelosi
1/23/03 11:41:41 AM
CSO

Dotti Pease
1/23/03 12:30:09 PM
CSO

Atiqur Rahman
1/28/03 02:10:25 PM
BIOPHARMACEUTICS

Comments on Headaches w/ Myleran Reformulation to GSK

From: Pelosi, Maureen A
Sent: Tuesday, July 02, 2002 10:42 AM
To: 'kcf31517@glaxowellcome.com'
Subject: Myleran SCM-019 Not approvable

Contacts: Kevin Fitzgerald
Dear Kevin,

Reference is made to your 5/30/02 request for a meeting which was scheduled for 6/26/02. As a result of our internal meeting we asked to cancel and/or reschedule the 6/26/02 meting with you. Listed below are our concerns from our 6/19/02 internal meeting about the recent non approval of supplement 019 due to the incidence of headache with the new formulation:

We remain concerned that 3 out of 12 patients experienced headaches with the reformulated Myleran.

We have limited clinical information about the severity, time of onset, duration, previous history of headache, and possible interference with drug compliance.

In the 3 patients experiencing headache, there appears to be an increase in C_{max} of the new formulation compared to the marketed US formulation.

Please provide any additional information you may have regarding the 3 patients who experienced these headaches and a proposal to address this concern such as a Post Marketing commitment to more fully describe the clinical significance of this finding.

Regards,
Maureen

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

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/s/

Maureen Pelosi
7/3/02 11:39:41 AM
CSO

From: Pelosi, Maureen A
Sent: Tuesday, January 29, 2002 3:51 PM
To: 'kcf31517@glaxowellcome.com'
Subject: Myleran, SCM-019: Dissolution comments

Contacts: Kevin Fitzgerald

Hi Kevin,

The CMC reviewer sent a consult to clinical pharmacology/biopharmaceutics for NDA 09-386 SCM-019. The biopharm reviewer wishes to convey the following comments:

Inadequate data to support the dissolution methodology and specification were submitted in NDA 09-386/019. Please provide justifications for selecting the methodology and setting the specification.

1. The proposed dissolution procedure should be supported by adequate data. The dissolution profiles for the product should be studied in different media by using different methods as appropriate. For the water dissolution medium, pH should be determined before and after drug dissolution. The data for twelve dosage units per dosage form per dissolution medium should be provided.

2. For the to-be-marketed formulation, a minimum of three lots, with a minimum of 12 units randomly sampled from each lot, need be tested according to the specifications. Selection of each component (apparatus, media, speed, etc.) for the final dissolution specification should be properly justified.

3. All raw data should be included for all dissolution studies submitted. Raw data includes analytical method data, a description of the tablet studied (formulation, batch size, lot number, date of manufacture, expiration date, etc.) and % dissolved at each time point for each tablet studied.

Regards,
Maureen

Maureen A. Pelosi, RPh
Regulatory Project Manager
FDA, CDER, Oncology HFD-150
phone (301) 594-5778
fax (301) 827-4590
E-mail PELOSIM@CDER.FDA.GOV

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/s/

Maureen Pelosi
1/30/02 10:37:34 AM
CSO

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 09-386 / SCM-019

DATE OF SUBMISSION: October 4, 2001

DATE OF REVIEW: November 9, 2001

DRUG: Myleran (busulfan) 2 mg Tablets

SPONSOR: SmithKlineBeecham Corporation dba GlaxoSmith Kline
Five Moore Drive
Research Triangle Park, NC 27709

In November 1996 it was agreed that two or more reformulation supplements would be filed for MYLERAN Tablets. The first (S-016) updated the drug substance synthesis, drug product specifications, and drug product analytical methods. Numerous comments were exchanged with the sponsor during 1997-1998. This supplement addresses all outstanding commitments.

I have reviewed the proposed draft labeling and compared it with the approved labeling from insert RL-822 dated May 2000. No changes have been made other than those indicated in the DESCRIPTION, CLINICAL PHARMACOLOGY, HOW SUPPPLIED sections.

A consult has been sent to OCPB (John Duan) for review of comparative dissolution profiles, biocomparability, and revisions to the CLINICAL PHARMACOOGY section which has been rewritten.

The CMC reviewer (Chengyi Liang) should review the changes in the DESCRIPTION and HOW SUPPLIED sections.

/S/ /11-9-01
Maureen A. Pelosi
Project Manager

Concur: /S/ /
Dotti Pease
Supervisor, Proj. Management Staff

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/s/

Maureen Pelosi
11/13/01 10:22:16 AM
CSO

Dotti Pease
11/13/01 12:53:15 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION			**REQUEST FOR CONSULTATION**	
TO: (*Division/Office*) HFD-860/Biopharm **ATTN: John Duan, Ph.D.**			FROM: HFD-150/Division of Oncology Christy Wilson for Maureen Pelosi, CSO	
DATE October 10, 2001	IND NO. N/A	NDA NO. NDA 9-386	TYPE OF DOCUMENT SCM-019	DATE OF DOCUMENT October 4, 2001
NAME OF DRUG Myleran (busulfan) Tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 22, 2002
NAME OF FIRM GlaxoSmithKline				

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER (fax)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER

III. BIOPHARMACEUTICS

- ☒ HUMAN PK AND BIOAVAILABILITY INFO
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS*(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This CMC supplement contains human pharmacokinetics and bioavailability data. This is a prior approval supplement.

Due date: February 5, 2002 (4-month goal date)

Chemist is Dr. Chengyi Liang. PM is Maureen Pelosi.

Package hand delivered to Dr. Atik Rahman on 10-10-01

SIGNATURE OF REQUESTER Christy Wilson for Maureen Pelosi	METHOD OF DELIVERY *(Check One)* ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Christy Wilson
10/10/01 10:18:34 AM
DDR: Please process this outgoing Biopharm consult. The package was hand delivered to Dr. Atik Rahman on 10-10-01. Signing for Maureen Pelosi.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (*Division/Office*) HFD-150/ Greg Frykman, MD			FROM: HFD-860/150 John Duan, PhD	
DATE 2-4-02	IND NO.	NDA NO. 09-386	TYPE OF DOCUMENT SCM-019	DATE OF DOCUMENT 10-4-01
NAME OF DRUG Myleran (busulfan) tablets		PRIORITY CONSIDERATION P	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE ASAP

NAME OF FIRM Glaxo Smith Kline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER (fax)
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS*(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: While reviewing the dissolution data, John Duan noticed that the AUC was different for the cuurent US product versus the proposed world-wide product. Additionally, there have been episodes of headache. Please review the information in vol 6 and make a recommendation as to how important you believe these issues to be and what action should be taken, if any.

SIGNATURE OF REQUESTER M.Pelosi, CSO for John Duan, PhD	METHOD OF DELIVERY *(Check one)* ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Greg Frykman
2/6/02 08:25:48 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 09-386/S-019

SmithKline Beecham Corporation d/b/a GlaxoSmithKline
Five Moore Drive
Research Triangle Park, NC 27709

Attention: Kevin A. Miller, R.Ph., RAC
Assistant Director, CMC Post-Approval Regulatory Affairs

Dear Mr. Miller:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Myleran ® (busulfan) Tablets

NDA Number: 09-386

Supplement number: S-019

Date of supplement: October 4, 2001

Date of receipt: October 5, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act sixty days from date of receipt of application in accordance with 21CFR314.101(a).

All communications concerning this supplement should be addressed as follows:

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

Via U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Via Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Maureen Pelosi, Project Manager, at (301) 594-5778.

Sincerely,

/S/

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Maureen Pelosi
10/30/01 04:19:19 PM
M. Pelosi signing for Dotti Pease