CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

14-691/S-020

Administrative Documents

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 14-691 / SCS 020 FA

DATE OF SUBMISSION: June 5, 2001

DATE OF REVIEW: June 19, 2001

DRUG: ALKERAN (Melphalan) 2 mg Tablets

SPONSOR: Glaxo Smith Kline
PO Box 13398 / Five Moore Drive
Research Triangle Park, NC 27709-3398

Supplement SCS-020 was approved on May 24, 2001.This submission provides the final printed labeling for SCS-020 that related to manufacture of Alkeran in a Facility at Glaxo Smith Kline Operations in Dartford, UK and included the results of a biocomparability study.

I have reviewed the package insert, comparing it with the May 21,2001 draft labeling. The labeling is identical to the approved draft except that in the HOW SUPPLIED section, GSK has deleted the bottle of 25 tablets since it is not commercially available at this time.

The labeling is acceptable.

/S/

6/19/01
Maureen A. Pelosi
Project Manager

/S/

Concur:
Dotti Pease
Supervisor, Proj. Management Staff

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/s/

Maureen Pelosi
6/19/01 02:40:11 PM
CSO

Dotti Pease
6/19/01 03:31:24 PM
CSO

Electronic Mail Message

Date: 5/24/01 9:27:16 AM
From: Fitzgerald, Kevin C (kcf31517@GlaxoWellcome.com)
To: 'Pelosi, Maureen' (pelosim@A1)
Subject: FW: Alkeran again.....

Maureen,

Just a note to confirm our telecon/ voicemail today that we commit to incorporate the requested labeling change in the FPL that will be submitted following approval of Alkeran Tablets, S-020. The text will then read:

In a separate study in 18 patients given single oral doses of 0.2 to 0.25 mg/kg of ALKERAN, Cmax and AUC, when dose adjusted to a dose of 14 mg, were (mean * SD) 212 * 74 ng/mL, and 498 * 137 ng*h/mL, respectively. Elimination phase t1/2 in these patients was approximately 1 hour and the median tmax was 1 hour.

If you have any questions please let me know.

Kevin

> -----Original Message-----
> From: Maureen Pelosi 301-594-2473 FAX 301-594-0498
> [SMTP:PELOSIM@cder.fda.gov]
> Sent: Wednesday, May 23, 2001 3:10 PM
> To: Fitzgerald, Kevin C
> Subject: Alkeran again.....
> Sensitivity: Confidential
>
> Hi Kevin,
>
> The draft AP letter for ALkeran S-020 is being circulated. Chances are
> slim that it will go out tomorrw but you never know...
>
> Here's a new problem - Someone told the biopharm people that in the
> label change, last sentence, it would be betteer to use the word
> "elimination" rather than "terminal". Do you have any heartache with
> this new wording? Please let me know.
>
> thanks,
> Maureen
>

"WorldSecure Server <cder.fda.gov>" made the following
annotations on 05/24/01 09:21:42

[INFO] -- Access Manager:
This message was sent by Glaxo Wellcome across the Internet in encrypted format and was successfully decrypted, unless otherwise noted.

==========
RFC-822-headers:

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/s/

Maureen Pelosi
5/24/01 10:32:50 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Kevin Fitzgerald		Maureen Pelosi
Fax:	**919-483-0464**	Fax:	301-827-4590
Phone:	919-483-5727	Phone:	301-594-5778
Pages, including cover sheet:	2	Date:	21-MAY-01
Re:	**Biopharm review of NDA 14-691 SCS-020**		

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

●Dear Kevin:

After receiving your suggestion regarding rewording the labeling change in the Clinical Pharmacology section, I have been asked to forward another version to you.

Please respond as soon as possible. The application is due soon and I would like to issue the letter before my vacation begins on May 25, 2001.

Please phone me if I may be of further assistance,

Maureen Pelosi
Regulatory Project Manager

LABELING COMMENTS

The following statements in CLINICAL PHARMACOLOGY section:

In a separate study in 18 patients given single oral doses of 0.2 to 0.25 mg/kg of ALKERAN, the mean dose adjusted (± SD) plasma C_{max} was 212 ± 74 ng/mL, the AUC was 498 ± 137 ng•h/mL, the $t_{1/2}$ was 1.12 ± 0.15 hours, and the t_{max} was 1.0 ± 0.5 hours.

Should be changed to:

In a separate study in 18 patients given single oral doses of 0.2 to 0.25 mg/kg of ALKERAN, C_{max} and AUC, when dose adjusted to a dose of 14 mg, were (mean ± SD) 212 ± 74 ng/mL, and 498 ± 137 ng•h/mL, respectively. [redacted] phase $t_{½}$ in these patients was approximately 1 hour and the median t_{max} was 1 hour.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Maureen Pelosi
5/21/01 10:29:06 AM
CSO

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To:	Kevin Fitzgerald		Maureen Pelosi
Fax:	**919-483-0464**	Fax:	301-827-4590
Phone:	919-483-5727	Phone:	301-594-5778
Pages, including cover sheet:	2	Date:	15-MAY-01
Re:	**Biopharm review of NDA 14-691 SCS-020**		

☐ Urgent ☐ For Review ☐ Please Comment ☐ Please Reply ☐ Please Recycle

●Dear Kevin:

We have completed our review of NDA 14-691 SCS-020. Attached is a labeling change to the Clinical Pharmacology section. For Approval we are requesting that GSK make the labeling change and submit final labeling.

Please respond as soon as possible. The application is due soon and I would like to issue the letter before my vacation begins on May 25, 2001.

Please phone me if I may be of further assistance,

Maureen Pelosi
Regulatory Project Manager

GENERAL COMMENTS

1. The new worldwide formulation of ALKERAN ® is considered to be bioequivalent to the current US formulation in terms of AUC; however, the C_{max} of reformulated product is 13% higher in comparison to the current US formulation.

2. The dissolution specifications of the reformulated tablets are as follows.
Meets USP requirements where Q = 80% dissolved in 30 minutes at the following instrumental conditions. This is acceptable.

Apparatus: USP <711> Apparatus II
Media: 900 mL 0.1 N hydrochloric acid
Paddle Speed: 50 ± 2 rpm
Temperature: 37.0 ± 0.5°C

LABELING COMMENTS

The following statements in CLINICAL PHARMACOLOGY section:

In a separate study in 18 patients given single oral doses of 0.2 to 0.25 mg/kg of ALKERAN, the mean dose adjusted (± SD) plasma C_{max} was 212 ± 74 ng/mL, the AUC was 498 ± 137 ng•h/mL, the $t_{1/2}$ was 1.12 ± 0.15 hours, and the t_{max} was 1.0 ± 0.5 hours.

Should be changed to:

DRAFT

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/s/

Maureen Pelosi
5/15/01 01:56:22 PM
CSO

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 14-691 / SCS 020

DATE OF SUBMISSION: December 6, 2000

DATE OF REVIEW: April 2, 2001

DRUG: ALKERAN (Melphalan) 2 mg Tablets

SPONSOR: Glaxo Wellcome Inc.
PO Box 13398 / Five Moore Drive
Research Triangle Park, NC 27709-3398

This submission provides for manufacture of reformulated Alkeran in a Facility [redacted] at Glaxo Wellcome Operations in Dartford, UK and includes the results of a biocomparability study.

I have reviewed the proposed draft labeling, comparing it with the approved labeling from submission YY-040, August, 1999 (RL-746). I also went back through the file to identify when the last labeling change occurred (SLR-019/CBE in March 1994) and worked up to the current annual report. I did not find any changes other than minor acceptable changes. For this supplement, no changes have been made other than those indicated. The biopharmaceutics reviewer should review the CLINICAL PHARMACOLOGY section changes for appropriateness. The CMC reviewer should review the manufacturing changes as well as those in the label changes to the DESCRIPTION and HOW SUPPLIED sections for accuracy of content.

The excessive number of references has been revised according to the policy of the Office of Drug Evaluation I and the Division of Oncology Drug Products to include only those references which pertain to the handling of antineoplastic agents, listed below.

REFERENCES:

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing office, Washington, DC 20402.

2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. JAMA, 1985; 2.53(11):1590-1592.

3. National Study Commission on Cytotoxic Exposure - Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study

Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426-428.

5. Jones RB, et al: Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - A Cancer Journal for Clinicians, 1983; (Sept/Oct) 258-263.

6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. Am J. Hosp Pharm, 1990; 47:1033-1049.

7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), Am J Health-Syst Pharm, 1996; 53:1669-1685.

/S/

Maureen A. Pelosi
Project Manager

Concur: /S/

Dotti Pease
Supervisor, Proj. Management Staff

CC: Original NDA 10-669 SCS-020
HFD-150/Div File
/Duan, Rahman, Liang, Duffy
151/Pelosi

/s/

Maureen Pelosi
4/2/01 02:50:29 PM
CSO

Dotti Pease
4/4/01 09:31:58 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION SCS-020**			
TO *(Division/Office)*: HFD-860/150 A. Rahman : J. Duan, Ph.D.			FROM: HFD-150:S. Honig, M.D./ C. Liang, PhDF	
DATE: 12-12-00	IND NO.	NDA NO. **14-691**	TYPE OF DOCUMENT: CMC Supplment	DATE OF DOCUMENT 12-06-00
NAME OF DRUG Alkeran (melphalan) Tablets	PRIORITY CONSIDERATION: S		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: **End of March**
NAME OF FIRM: Glaxo Wellcome				

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ 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: This submission contains ccomparative dissolution profiles andbiocomparability information for review.

SIGNATURE OF REQUESTER: M. Pelosi for C. Liang, Ph.D.	METHOD OF DELIVERY : HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

CC: IND [redacted]008
HFD-150/Div File
/ **Pelosi,** Rahman, Duan, Duffy, Liang

/s/

Atiqur Rahman
12/12/00 06:14:48 PM