CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 50-671/S-002

Trade Name: VANCOCIN HCL

Generic Name:(vancomycin Injection, USP)

Sponsor: Baxter Healthcare Corporation

Approval Date: January 8, 1998

INDICATION: Provides for specific dosing of premature neonates.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: NDA 50-671/S-002

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				
Approvable Letter	X			
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				
Administrative Document(s)	X			
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 50-671/S-002

APPROVAL LETTER

NDA 50-671/S-002

JAN 8 1998

Baxter Healthcare Corporation
Attention: Marcia Marconi
Vice President, Regulatory Affairs
Route 120 & Wilson Road
Round Lake, IL 60073-0490

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated December 16, 1996, received December 17, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vancocin® HCl (Vancomycin Injection, USP) in Galaxy® Plastic Container, PL 2040. We note that this product is subject to the exception provisions of Section 125(d)(2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your submission dated November 17, 1997. The User Fee goal date for this application is May 18, 1998.

This supplemental application provides for specific dosing of premature neonates.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 50-671/S-002. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 50-671
HFD-520/Div. files
HFD-520/CSO/B. Duvall-Miller
HFD-520/MO/J. Alexander JA 12/23/97
HFD-002/ORM (with labeling)
HFD-104/Office Director
HFD-101/L.Carter
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFI-20/Press Office (with labeling)

Concurrence only:
HFD-520/SCSO/J. Bona 12/24/97
HFD-520/MO/J. Alexander
HFD-520/SMO/J. Soreth 1/7/98
HFD-520/~~Act~~DivDir/G. Chikami
1/7/98

Drafted by: bdm/November 26, 1997/M:\SUPPAP\50671.002
Initialed by:
final: 12/24/97

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-671/S-002

APPROVABLE LETTER

NDA 50-671/S-002

Baxter Healthcare Corporation
Attention: Marcia Marconi
Vice President, Regulatory Affairs
Route 120 and Wilson Road
Round Lake, IL 60073

JUN 17 1997

Dear Ms. Marconi:

Please refer to your supplemental new drug application dated December 16, 1996, received December 17, 1996, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Vancocin® HCl (Vancomycin Injection, USP) in Galaxy® Plastic Container, PL 2040.

We acknowledge receipt of your submissions dated December 4, 1996 and January 30, 1997. The User Fee goal date for this application is June 17, 1997.

The supplemental application provides for specific dosing of premature neonates due to their altered pharmacokinetics.

We have completed the review of this supplemental application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

This change may not be implemented until you have been notified in writing that this supplemental application is approved.

If you have any questions, please contact Beth Duvall-Miller, Project Manager, at (301) 827-2125.

Sincerely yours,

/S/

Gary K. Chikami, M.D.
Acting Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc:

Original NDA 50-671
HFD-520/Div. Files
HFD-002/ORM
HFD-104/D. Feigal
HFD-101/L.Carter
HFD-92/DDM-DIAB
HFD-40/DDMAC (with draft labeling)
DISTRICT OFFICE
HFD-520/CSO/B. Duvall-Miller
HFD-520/MO/J. Alexander
HFD-520/SMO/J. Soreth 6/17/97
HFD-520/BioPharm/H. Sun
HFD-520/TLBioPharm/F. Pelsor

Concurrence:

HFD-520/SCSO/J. Bona 6/16/97
HFD-520/ActDivDir/G. Chikami
6/16/97

Drafted by: bdm/June 16, 1997/M:\SUPPAE\50671.002
Initialed by:
Final: BDM 6/16/97

APPROVABLE (AE)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 50-671/S-002

MEDICAL REVIEW(S)

CLINICAL REVIEW OF EFFICACY SUPPLEMENT

Date of Submission: Dec. 16, 1996

Date Review Begun: Apr. 24, 1997

Date Review Completed: June 5, 1997

Applicant: Eli Lilly and Co.

Drug Name: Generic- Vancomycin HCl
Trade- Vancocin® HCl

Dosage Form and Route of Administration: Injection for IV use

Category: Glycopeptide Antibiotic

Materials Submitted: Two Volumes

PURPOSE

This supplement was submitted by the sponsor as a labeling change pursuant to the final rule revising the "Pediatric Use" subsection of the label. The additions to the label are in larger font in brackets. The following paragraph shows the proposed changes to the **PRECAUTIONS** section of the label.

The following shows the proposed changes to the **DOSAGE AND ADMINISTRATION** section of the label.

DISCUSSION

The following is a reference list for the studies included by the sponsor in this submission:

1) Amaker RD, DiPiro JT, and Bhatia J "Pharmacokinetics of vancomycin in critically ill infants undergoing extracorporeal membrane oxygenation" Antimicrobial Agents and Chemotherapy 40(5):1139-1142; May 1996

2) McDougal A, Ling EW, and Levine M "Vancomycin Pharmacokinetics and dosing in premature neonates" Therapeutic Drug Monitoring 17(4):319-326; 1995

3) James A, Koren G, Milliken J, Soldin S, and Prober C "Vancomycin pharmacokinetics and dose recommendations for preterm infants" Antimicrobial Agents and Chemotherapy 31(1):52-54; Jan 1987

4) Naqvi SH, Reichley RM, Keenan WJ, and Fortune KP "Re-evaluation of vancomycin pharmacokinetics in premature infants using high-pressure liquid chromatography" Clinical Research 32(4):804A; 1984

5) Wandstrat TL, and Phelps SJ "Vancomycin dosing in neonatal patients: The controversy continues" Neonatal Network 13(3):33-39; April 1994

6) Saunders NJ "Why monitor peak vancomycin concentrations?" The Lancet 344:1748-1750; Dec 24-31, 1994

7) Catchpole C, and Hastings JGM "Routine measurement of serum vancomycin concentrations" Journal of Antimicrobial Chemotherapy 36:447-448; 1995

8) Catchpole C, and Hastings JGM "Measuring pre- and post-dose vancomycin levels--time for a change?" Journal of Medical Microbiology 45:309-311; 1995

9) Saunders NJ "Vancomycin administration and monitoring reappraisal" Journal of Antimicrobial Chemotherapy 36:279-282; 1995

The purpose of this supplement is twofold. First, it alters the labels references to 'children' in order to comply with the age categories set forth in the final rule for the pediatric use subsection. The changes in wording made by the sponsor are appropriate. The second purpose of this supplement is to make dosage recommendations for premature neonates. However, not all of the articles listed above discuss premature infants. The first study discusses neonates treated by extracorporeal membrane oxygenation(ECMO). All of the infants in this study are full term neonates. In addition, infants who receive ECMO are at risk for renal compromise, and the mechanics of ECMO effectively increase the blood volume by 75%. The pharmacokinetic data in this article are not applicable to premature infants, and will not be considered further. The last four articles (6-9) discuss

the utility of routine monitoring of serum peak and trough concentrations of vancomycin. These articles concentrate on adult pharmacokinetic data, and therefore do not apply to this supplement. Part of the discussion in these articles includes the controversy over the peak μg/L at min after infusion ends) and trough μg/L) ranges, which are based on estimates from early clinical trials rather than efficacy or safety data. However, this is the current accepted practice, and the data do not support a change in this practice. The remainder of this discussion concentrates on literature reports (2-5) that discuss vancomycin dosing for premature infants.

McDougal et al. prospectively studied the pharmacokinetic parameters of vancomycin in premature infants receiving multiple doses of vancomycin. Infants received vancomycin at different doses and intervals based on postconceptional age(PCA) groups. The doses and PCA groups were defined as follows: (0) 18 mg/kg every 36 hours for PCA<27 weeks; (I) 16 mg/kg every 24 hours for PCA 27-30 weeks; (II) 18 mg/kg every 18 hours for PCA 31-36 weeks; and (III) 15 mg/kg every 12 hours for PCA ≥37 weeks. The dose was infused over 60 minutes. There were no infants enrolled in group 0. Sixteen, fifteen, and thirteen infants were enrolled in groups I-III, respectively. The results showed that this dosage regimen achieved target peak serum levels in only 64% of infants. There was a tendency to undershoot the target peak concentration, but three patients were at or above the target peak. Unfortunately, the variance in peak serum concentrations is so large that even with a mean serum peak concentration that is in the middle of the target range, a large proportion of the infants would have serum concentrations out of the target range. The data did demonstrate that vancomycin clearance was correlated with postconceptional age($r=0.81$, $p<0.0001$). Even when vancomycin clearance was normalized for weight, there was still a correlation with PCA ($r=0.48$, $p<0.005$). In this study, volume of distribution when normalized for weight does not change with PCA ($r=0.09$, $p=0.59$).

James et al. studied 20 preterm infants with a mean(±SD) gestational age of 26.5(±2.6)weeks. At the time of study, the infants had mean(±SD) postconceptional age of 36.4(±4.5)weeks. The doses used ranged from 9.2 to 18 mg/kg administered over 30 minutes. This study demonstrated a significant negative correlation between vancomycin $t_{\frac{1}{2}}$ and PCA. A significant positive correlation was seen between vancomycin clearance and PCA ($r=0.8$,$p<0.001$). Both $t_{\frac{1}{2}}$ and clearance were also significantly correlated with body weight. No correlation between volume of distribution and PCA or weight was found.

The data from Naqvi et al. was reported in the form of an abstract. Therefore, details regarding methods and results are unavailable. Ten infants were studied and eight were premature. For the premature infants, mean gestational age was 30 weeks (range 24-36 weeks) and mean age was 45 days (range 20-74 days). Eight infants received 10 mg/kg/dose given every eight hours in neonates and every 6 hours in infants >4 weeks of age. Three infants received 15 mg/kg/dose. Vancomycin was infused over one hour. For seven patients receiving 10 mg/kg/dose, mean(±SD) peak and trough concentrations were 28.4(±6.5) and 12.3(±6.7). The authors reported a mean $t_{\frac{1}{2}}$ of 3.9±1.5 hours for infants <3 months and $t_{\frac{1}{2}}$<2 hours for infants >3 months. Eight infants were reported with a mean volume of distribution of 0.48(±0.14) L/kg. Two extremely sick infants had a large volume of distribution and were excluded from the analysis. Comparison of this data with the first two studies is problematic at best without more information about PCA and clearance. However, there is certainly the indication that most of these infants had high trough levels using 6 or 8 hour intervals. The longer $t_{\frac{1}{2}}$ in younger infants suggests similar decreases in clearance to the previous studies, but data relating PCA to clearance are lacking.

The article by Wandstrat et al. was a review of 12 previous studies that involved vancomycin dosing to neonates. The authors indicate that initial dosing regimens were proposed based on data by Schaad et al. Schaad studied 55 pediatric patients, including 21 premature neonates. The majority of the pharmacokinetic data was obtained after a single 10 or 15 mg/kg dose. Elimination half life in the premature infants ranged from 5.9 to 9.8 hours, compared to 4.1 hours for full term infants. Plasma clearance showed a direct positive correlation with chronological age. Schaad recommended that neonates receive 15 mg/kg of vancomycin every twelve hours for those ≤ 7 days and every eight hours for those >7 days. However, the review showed a subsequent study, based on Schaad's recommendations, demonstrating the majority of infants had high peak and trough levels. An association of elevated trough levels with prematurity was suggested in the 2-4 week age group, where 11 of the infants were premature. Wandstrat et al. go on to discuss other individual articles and review their strengths and weaknesses. Their conclusions were that neonates displayed varying pharmacokinetics because of decreased renal clearance and a larger volume of distribution than other infants. They recommended that "regimens should consider PCA as well as body weight".

SUMMARY

The majority of the changes proposed by the sponsor are based on efforts to comply with age categories set forth in the final rule for the pediatric use subsection. However, the inclusion of separate recommendations for premature neonates was also included. Based on the literature presented, there are not enough data provided to make a dosing recommendation for premature infants. However, the data are sufficient to show that renal clearance of vancomycin is altered in premature infants and that high trough levels of vancomycin have been noted when they are given vancomycin at intervals similar to those recommended for neonates in the **DOSAGE AND ADMINISTRATION** section of the product label. Changes in volume of distribution are also reported in some studies, but are not confirmed in other studies. Larger doses of vancomycin (e.g., 18-24 mg/kg) are recommended by some authors based on differences in volume of distribution. The information provided by the sponsor is not sufficient to support particular dosage recommendations or even to make comments about volume of distribution in premature infants.

CONCLUSIONS

The changes proposed by the sponsor to the product label are approvable. The following paragraph shows the proposed changes to the **PRECAUTIONS** section of the label.

The following paragraph shows the proposed changes to the **DOSAGE AND ADMINISTRATION** section of the label. The changes suggested by the medical officer are shown in bold letters.

RECOMMENDATIONS

The sponsor should be notified of the above conclusions.

/S/

John Alexander, M.D.

Concurrence Only:
HFD-520/DIR/Chikami
7/98

CC:
NDA 50-671
HFD-520
HFD-520/CSO/Duvall-Miller
HFD-520/MO/Alexander
HFD-520/SMO/Soreth 7/8/98
HFD-880/Sun
HFD-520/labeling file

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-671/S-002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 50,671, S-002
Vancomycin HCL - Galaxy Plastic Container
Labeling Modification

DATE of SUBMISSION
December 4, 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: Lilly Research Laboratories
Lilly Corporate Center, Indianaplis, Indiana 46285

REVIEWER: HE SUN, Ph.D.

I. INTRODUCTION

The sponsor submitted the application to add specific dose recommendation for premature neonates based on literature reports. The relative pharmacokinetic studies cited in this submission are:

<<Re-evaluation of vancomycin pharmacokinetics in premature infants using high pressure liquid chromatograph (HPLC). SH Naqvi et al. 1984. Abstract.

<<Vancomycin pharmacokinetics and Dose Recommendations for preterm Infants>> Andrew James et al. 1987. Study report.

<<Vancomycin Dosing in Neonatal Patients: The controversy continues>>, Todd L Wandstrat and Stephanie J. Phelps, April, 1994. Review.

<<Vancomycin Pharmacokinetics and Dosing in premature neonates>> Albert McDougal et al. 1995. Study Report.

II. SPECIFIC COMMENTS.

Overall, the following conclusions are drawn:

(1) Reports on the correlation of vancomycin concentrations with efficacy and toxicity are controversial. Commonly believed clinically effective and safe concentrations are C_{max} to be around 30-40 ug/ml and C_{min} should be less than 10 ug/ml.

(2) Dose regimens for premature neonates should consider both post-conceptional age (PCA) and body weight.

(3) In these study reports, number of blood samples from each subject and number of patients participated in each study are small, especially after divided into different age groups. Which caused the PK parameters reported in these reports were controversial, and specific dose recommendations derived from these reports were not solid.

(4) While keeping in mind comments # 3 above, premature neonates < 41 weeks PCA have a larger volume of distribution (per Kg body weight) than older premature neonates. Loading dose of 15 mg/Kg should be given to premature neonates < 41 weeks PCA.

(5) While keeping in mind comments # 3 above, vancomycin clearance significantly and positively correlate with PCA. Due to higher Vd for younger premature neonates patients, the elimination half-life decrease is significant while with a smaller rate as PCA increase. Therefore, longer dosing interval is necessary as PCA decreases.

(6) The intersubject variability of Vd and CL among patients in the same age group are 34% and 35-40%, respectively. There was no report to suggest that vancomycin Vd and CL are dose dependent. Therefore, statistically speaking, only 68% subjects of a given patient population may produce plasma concentrations within ug/ml range if they were dosed based on the mean population pharmacokinetic parameters. Close monitoring of serum concentration of vancomycin and further dose adjustment after initial doses are highly recommended.

(7) Meta analysis or population style data analysis of pooled data may provide better understanding of vancomycin pharmacokinetics and a better dose recommendation in premature neonates.

III. RECOMMENDATION

Specific vancomycin dose recommendation for premature neonates may not be given based on data submitted. A mg/kg loading dose followed by mg/kg maintain dose given as minutes iv infusion proposed by the sponsor is relevant at this time. Longer dosing intervals is necessary as PCA decreases. Close monitoring of serum concentration of vancomycin and further dose adjustment after an initial dose are highly recommended.

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. _____

cc:
NDA 50,671, S-002
HFD-520 (Clinical, CSO)
HFD-340 (Viswanathan)
HFD-880 (Pelsor, Sun)
HFD-880 Div. File NDA 50,671, S-002(Vancomycin)
CDR (Att: Barbara Murphy)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 50-671/S-002

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE
(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 50-671 Supplement # CO2 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-520 Trade and generic names/dosage form: Vancocin HCl (vancomycin injection) Action: AP AE NA

Applicant Eli Lilly Therapeutic Class _____

Indication(s) previously approved MRS infections, penicillin-resistant infections, staph. endocarditis, septicemia, bone infections, lower RTI, skin and skin structure
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Dosing for premature neonates (For supplemen
answer the following questions in relation to the proposed indication.)

✓

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

Project Manager 6/17/97 AE
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 50-671
HFD-520 /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised)

CERTIFICATION

NDA Application No.: **50-671**
Drug Name: **Vancocin**

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Jennifer Stotka, M.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: _____
Jennifer Stotka, M.D.

Title: Director, U.S. Regulatory Affairs

Date: December 04, 1996