CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 61-667

Name: Vancomycin Hydrochloride for Oral Solution, USP

Sponsor: Lilly Research Laboratories, A Division of Eli Lilly and Company

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-667

CONTENTS

Reviews / Information Included in this Review

July 13, 1983 Approval Sign-Off	**X**
Tentative Approval Letter	
Labeling	**X**
Labeling Reviews	
Medical Reviews	**X**
Chemistry Reviews	**X**
Bioequivalence Reviews	
Statistical Reviews	
Microbiology Reviews	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-667

July 13, 1983 APPROVAL SIGN-OFF

5004

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

For use of Food and Drug Administration

Date Approved July 13, 1983

Signed John D. Harrison

For the Commissioner of Foods & Drugs

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

July 5, 1983

Section 455.185
No. 61-667

Food and Drug Administration
National Center for Drugs and Biologics (HFN-535)
Attention: Document Control Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6, VANCOCIN® HCl For Oral Use Only M-5105
Vancomycin Hydrochloride For Oral Solution, USP

We are submitting an amendment to the above Form 6 which provides for the manufacture of a 1 g size of Vancomycin Hydrochloride For Oral Solution, USP.

This submission consists of labels and labeling, manufacturing and control information, and a Statement Of Exemption Of Environmental Analysis Report.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:ek

Attachments

011759

RECEIVED
JUL 12 1983

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-667

LABELING

VANCOCIN® HCl

VANCOMYCIN HYDROCHLORIDE FOR ORAL SOLUTION, USP

This preparation is for oral use only. If parenteral vancomycin therapy is desired, use Vancocin® HCl (Sterile Vancomycin Hydrochloride, USP, Lilly), IntraVenous, and consult package insert accompanying that preparation.

DESCRIPTION

Vancocin® HCl (Vancomycin Hydrochloride, USP, Lilly) is a glycopeptide antibiotic derived from *Streptomyces orientalis* which is bactericidal against many gram-positive bacteria.

ACTIONS

Vancocin HCl is poorly absorbed by mouth. Many strains of streptococci, staphylococci, *Clostridium difficile*, and other gram-positive bacteria are susceptible in vitro to concentrations of 0.5 to 5 mcg/ml. Staphylococci are generally susceptible to less than 5 mcg of Vancocin HCl/ml, but a small proportion of *Staphylococcus aureus* strains require 10 or 20 mcg/ml for inhibition. If the Bauer-Kirby method of disc susceptibility testing is used, a 30-mcg disc of Vancocin HCl should produce a zone of more than 11 mm when tested against a vancomycin-susceptible bacterial strain.

INDICATIONS

Vancocin HCl may be administered orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Parenteral antibiotic administration may be used concomitantly. Vancomycin is *not* effective by the oral route for other types of infection.

CONTRAINDICATION

Vancocin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Because of its ototoxicity and nephrotoxicity, Vancocin HCl should be used with care in patients with renal insufficiency. During parenteral therapy, the risk of toxicity is appreciably increased by high blood concentrations or prolonged treatment. If it is necessary to use Vancocin HCl parenterally in such patients, doses of less than 2 g/day usually will provide satisfactory blood levels.

Vancocin HCl should be avoided in patients with previous hearing loss. If it is used in such patients, the dose of Vancocin HCl should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus. The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, tobramycin, and amikacin, requires careful monitoring.

PRECAUTIONS

Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels. All patients receiving the drug should have periodic hematologic studies, urinalyses, and liver and renal function tests.

ADVERSE REACTIONS

Nausea, chills, fever, urticaria, and macular rashes have been associated with the administration of Vancocin HCl. It may also produce eosinophilia and anaphylactoid reactions.

The use of Vancocin HCl may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi appear during therapy with this product, appropriate measures should be taken.

DOSAGE AND ADMINISTRATION

The contents of the 10-g vial may be mixed with distilled or deionized water (115 ml) for oral administration. When mixed with 115 ml of water, each 6 ml provide approximately 500 mg of vancomycin. The contents of the 1-g vial may be mixed with distilled or deionized water (20 ml). When reconstituted with 20 ml, each 5 ml contains approximately 250 mg of vancomycin. Mix thoroughly to dissolve. These mixtures may be kept for 1 week in a refrigerator without significant loss of potency.

Adults—The usual dose is 500 mg every 6 hours or 1 g every 12 hours.

The usual adult dosage for antibiotic-associated pseudomembranous colitis produced by *C. difficile* is 500 mg to 2 g of vancomycin orally/day in 3 or 4 divided doses administered for 7 to 10 days.

Children—The total daily dose is 20 mg/lb of body weight in divided doses.

HOW SUPPLIED

For Oral Solution, equivalent to 10 mg vancomycin (No. M-206) (packages of 1), NDC 0002-2372-37

For Oral Solution, equivalent to 1 g vancomycin (No. M-5105) (Traypak† of 6), NDC 0002-5105-16

Also available:

Vials,* equivalent to 500 mg vancomycin, 10-ml size (No. 657) (vials of 1), NDC 0002-1444-01

*For IV use.

†Traypak™(multivial carton, Lilly).

CAUTION—Federal (U.S.A.) law prohibits dispensing without prescription.

Literature revised June 24, 1983

ELI LILLY AND COMPANY • Indianapolis, IN 46285, U.S.A.

PA 0280 AMP

Printed in U.S.A.

NDC 0002-5105-01

M-5105

℞ Lilly

VANCOCIN® HCl

VANCOMYCIN HYDROCHLORIDE FOR ORAL SOLUTION, USP

Equivalent to

1 g

Vancomycin

FOR ORAL USE ONLY

XWAY 0496 26 VD

Eli Lilly & Co., Indianapolis, IN 46285, U.S.A.

Exp. Date/Control No.

CAUTION—Federal (U.S.A.) law prohibits dispensing without prescription.

Usual Dose—See literature.

Contains Vancomycin Hydrochloride Equivalent to 1 g Vancomycin.

Keep Tightly Closed

Prior to Reconstitution: Store at Controlled Room Temperature 59° to 86°F (15° to 30°C).

After Reconstitution: the solution should be refrigerated and used within one week.

Mix the contents of this vial with distilled or deionized water (20 mL). Mix thoroughly to dissolve.

When reconstituted with 20 mL, each 5 mL contains approximately 250 mg of Vancomycin.

NDC 0002-5105-16 TRAYPAK™

1—6

M-5105

VANCOCIN® HCl

VANCOMYCIN HYDROCHLORIDE FOR ORAL SOLUTION, USP

Equivalent to

1 g

Vancomycin

FOR ORAL USE ONLY

CAUTION—Federal (U.S.A.) law prohibits dispensing without prescription.

Usual Dose—See accompanying literature.

Contains Vancomycin Hydrochloride Equivalent to 1 g Vancomycin.

Keep Bottle Tightly Closed

Prior to Reconstitution: Store at Controlled Room Temperature 59° to 86°F (15° to 30°C)

After Reconstitution: the solution should be refrigerated and used within one week.

Mix the contents of this vial with distilled or deionized water (20 mL). Mix thoroughly to dissolve.

When reconstituted with 20 mL, each 5 mL contains approximately 250 mg of Vancomycin.

SJ 9710 AMS

SJ 9710 AMS

ELI LILLY AND COMPANY, INDIANAPOLIS, IN 46285, U.S.A.

NDC 0002-5105-16 TRAYPAK™

1—6

M-5105

VANCOCIN® HCl

VANCOMYCIN HYDROCHLORIDE FOR ORAL SOLUTION, USP

Equivalent to 1 g Vancomycin

FOR ORAL USE ONLY

Gr. 753 NA

ABCDEFGHIJKL
101131415161718
1920212232425

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-667

MEDICAL REVIEWS

Form 60-180
61-667

February 27, 1980

MEDICAL OFFICER'S REVIEW OF SUPPLEMENT TO ANTIBIOTIC
FORM 60-180 and 61-667

I. General Information

Date of submission of supplement: January 16, 1980

Reason for Submission: Expension of claims to include the use of Vancocin HCl in the treatment of antibiotic-associated pseudomembranous colitis caused by Clostridium difficile.

Applicant: Lilly Research Laboratories
Indianapolis, Indiana 46206

A. Drug Name: generic: vancomycin hydrochloride, sterile USP. (NDA 60-180), and for oral solution (NDA 61-667).

trade: Vancomycin HCl, sterile.
Vancocin HCl, for oral solution.

B. Pharmacologic Category: Vancomycin is an antibiotic produced by streptomyces orientalis and is a glycopeptide related to ristocetin, an antibiotic no longer in use.

C. Proposed Indication: "The usual adult dosage for pseudomembranous colitis produced by C. difficile is 500 mg. of vancomycin orally every 6 hours for a period of 7 to 10 days."

II. Microbiology: See the review of Dr. James King. Review not located.

Recent publications[1-8] have clearly implicated Clostridium difficile and the toxin produced by this organism as an etiologic agent in antibiotic-associated Pseudomembranous Colitis (PMC). In 1977 Larson[1] first reported the presence of a fecal toxin that could be neutralized by C. sordellii antitoxin. Shortly thereafter, George, et al.[2] identified C. difficile as the organism responsible for toxin production in patients with PMC, and in subsequent studies[3-4] they demonostrated the uniform susceptibility of this organism to vancomycin. Of the 39 strains of C. difficile tested, all were susceptible to vancomycin concentrations of 4 mcg or less.[2] In a subsequent report, Larson, et al.[5] confirmed the results of George[2] by isolating C. difficile from four of five PMC patients.

The above findings have also been confirmed by other reports. Burdon, et al.[6] found vancomycin to be active against 37 strains of C. difficile, with MIC ranging from 0.5 to 16 mcg, and a subsequent report by these authors[7] included 20 additional strains with similar MICs, 17 of which were 1 mcg/ml. Fekety[8] has also reported 15 of 15 strains with MICs of 0.2 to 1.6 mcg/ml.

In summary, all of the 111 strains of C. difficile reported in the above studies demonstrated MICs of 16 or less to vancomycin. Most of the strains demonstrated MIC values of 4 or less.

V. Pharmacology: See the review of Dr. George James. Review not located.

Animal Data

The protective effect of vancomycin in the treatment of enterocolitis in laboratory animals has been studied by several investigators.[9-15] Barlett, et al.[9] reported vancomycin prevented death in 49 of 49 Syrian hamsters challenged with clindamycin or lincomycin in an experiment where it was demonstrated that in control animals such challenge was uniformly fatal due to the development of enterocolitis. In a separate report,[10] the same investigators implicated a clindamycin-resistant clostridium species as the agent responsible for the fatal enterocolitis seen in these animals, although C. difficile was not specifically identified. Bartlett, et al.[11] subsequently demonstrated C. difficile in patients with antibiotic-associated enterocolitis, and in animal challenge experiments demonstrated vancomycin to be higly effective in preventing enterocolitis in hamsters treated with clindamycin.

The findings of Barlett were confirmed in the report of Browne, et al.[12] In their study, vancomycin significantly prolonged survival of clindamycin-treated hamsters even if treatment was delayed until 48 hours after clindamycin challenge. Studies of the mechanism of action of vancomycin by Humphrey[13] indicate the suppression of toxin formation in animals is due to antimicrobial activity of the antibiotic rather than to specific toxin neutralization, thus confirming Barlett's suggestions.[11]

Additional confirmation of the protective effect of vancomycin was presented in the report by Katz, et al.[14] who demonstrated the marked protective effect of oral vancomyin in clindamycin-treated rabbits, with concurrent suppression of growth of fecal clostridial species. Subsequent studies by these investigators[15] also showed that clindamycin was uniformly protective in rabbits, and that stool extracts from these animals were not lethal to challenged mice.

In summary, studies in hamsters and rabbits have demonstrated that otherwise fatal clindamycin-induced enterocolitis can be prevented by the administration of oral vancomycin, and that the mechanism of action appears to be by its antibacterial activity against toxin-producing clostridia species, notably C. difficile.

Human Data

Gastrointestinal absorption of vancomycin following oral adminstration is negligible. Thus it should be present in significant concentration in the lower G.I. tract, the site of PMC. This has been confirmed in at least three published reports.[6,21,22]

Burdon[6] reported fecal concentrations of vancomycin in 17 samples from six patients receiving either 125 or 260 mg vancomyin q 6 h. At the higher dose, fecal levels averaged 477 mcg/ml, and 427 mcg/ml at the lower dose. Both are significantly greater than the MICs for C. difficile. Tedesco[21] reported a mean wet weight stool concentration of 3100 ± 400 mcg/gm (range = 905-8760 mcg/gm), and Keighley[22] reported that fecal vancomycin concentrations were at least four times the MIC for C. difficile following oral doses of 125 mg q 6 h on the 2nd and 4th day of therapy.

Clinical Studies

No controlled studies are reported in the literature, and none have been submitted by the sponsor. It would be extremely difficult to conduct a controlled trial since there is no other antibiotic agent that has been studied in the treatment of pseudomembranous colitis produced by C. difficile. Though one can postulate other antibiotic agents that should be efficacious in the treatment of pseudomembranous colitis produced by C. difficile, most studies conducted to date have used vancomycin HCl for several reasons. First, a large number of the human cases of pseudomembranous colitis have ended fatally. Second, once Clostridum difficile had been incriminated as a toxin producing and causative agent, and once vancomycin had been demonstrated to be quite efficacious in mice, hamsters, and rabbits, it was only prudent to treat humans with the antibiotic agent which had been demonstrated in animals to be effective in treating this entity.

A. A review of clinical reports and studies in the literature.

To date, 10 published reports include data on the use of vancomycin in the treatment of antibiotic-associated PMC. A total of 46 patients are included in these reports. A summary of each article is presented below.

Rifkin, et al.[16] reported one patient with ampicillin/gentamicin-induced PMC, diagnosed by sigmoidoscopy. The patient received 500 mg vancomycin orally q.i.d. for 10 days. Diarrhea ceased within 24 hours and the patient was asymptomatic within 48 hours. Pre-vancomycin stool filtrates were lethal to hamsters whereas filtrates collected on the 2nd and 4th days of therapy were nontoxic.

Modigliani and Delchier[17] reported one case of ampicillin-induced PMC diagnosed by barium enema, proctosigmoidoscopy, and biopsy. Vancomycin 2 gm/day, was administered, and diarrhea and fever were absent within 36 hours. Prompt healing of the mucosa occurred (barium enema normal on 4th day).

Kappas, et al.[18] in their report of the clinical course of 28 patients with PMC, state that one patient was treated with vancomycin and improved immediately. No dosage was recorded.

Larson, et al.[19] reported one case of clindamycin-induced PMC, diagnosed by sigmoidoscopy and biopsy. Oral vancomycin, 500 mg q 6 h for five days produced prompt recovery. Both C. difficile and stool toxin disappeared within 48 hours and diarrhea stopped thereafter.

Marrie, et al.[20] reported one case of lincomycin-induced PMC diagnosed by sigmoidoscopy who was treated with conventional therapy without response for three days. Oral vancomycin, 500 mg q 6 h was begun, and the diarrhea had ceased seven days later. Therapy was discontinued after 10 days. Seven days later diarrhea recurred. vancomycin therapy was reinstituted for seven additional days and the patient responded with no further episodes.

Tedesco, et al.[21] treated nine patients with antibiotic-associated PMC diagnosed by sigmoidoscopy and toxin-positive stools. All received oral vancomycin, 500 mg 6 h for seven or more days, and all responded promptly, becoming afebrile within 48 hours. Eight of the nine patients had reduced toxin levels in their stools 3-5 days following onset of therapy, compared to pretherapy levels.

Keighley, et al.[22] reported results in a randomized placebo-controlled trial in which low doses of oral vancomycin were administered (125 mg q 6 h for five days). Diagnosis of PMC utilized sigmoidoscopy, biopsy, and the presence of C. difficile and toxin in fecal samples. Nine patients meeting the criteria for therapy received vancomycin and seven received placebo. Even with the low doses used in the study, eight of the nine vancomycin-treated patients responsed symptomatically and all nine had negative cultures for C. difficile and absent toxin levels. In the placebo group, four patients continued to have positive cultures of C. difficile as well as elevated toxin levels and four patients also continued to exhibit diarrhea. Four placebo patients were subsequently treated with vancomycin, presumably with satisfactory results.

Fekety[8] in his report on the treatment of antibiotic-associated colitis stated he treated nine patients with toxin-positive PMC using oral vancomycin in doses of 500 mg q.i.d. for 7-10 days, excellent response in all nine patients, including reduction of toxin levels as well as cessation of diarrhea, fever, and abdominal pain.

Barlett, et al.[23] in their report on C. difficile colitis, included four patient not previously in the study of Tedesco, et al.[21] Each received 500 mg vancomycin q 6 h for at least seven days with prompt remission of symptoms and a rapid serial decrease in titers of stool toxin.

Bartlett, et al.[24] in their recent report, discussed therapeutic results in 10 patients who received vancomycin for treatment of PMC associated with cephalosporin therapy (one of these may have been previously reported by Tedesco, et al.[21]). The dosage of vancomycin was 500 mg q 6 h for 7-14 days. Cholestyramine was also used in one of these patients. All 10 patients had prompt eradication of systemic symptoms within 48 hours and resolution of diarrhea within 2-10 days. One patient relapsed after the first course of therapy but responded to a second course with no further difficulty.

In summary, all of the 46 patients reported to date in the published literature, having documented diagnoses of antibiotic-associated PMC, have responded to therapy with oral vancomycin. The optimum dosage appears to be 500 mg every six hours for a period of 5-14 days.

Clinical Studies Submitted by the Sponsor

Lilly has submitted under Forms 60-180 and 61-667, the case report forms of 79 patients supplied to Eli Lilly and Company by the Infectious Disease Therapeutics Unit of the Upjohn Company, Kalamazoo, Michigan.

Upjohn has concurrently made a submission of the same case reports with a more detailed clinical summary under Forms 50-162, 50-441, 61-772, and related Puerto Rican Form 6 numbers. This review will apply to both companies' submissions.

Data on 79 patients treated with vancomycin for antibiotic-associated colitis or antibiotic-associated diarrhea have been submitted by John G. Bartlett, M.D., Infectious Disease Research Laboratory, Veterans Administration Hospital, Boston, Massachusetts and Robert Fekety, Jr., M.D., Chief, Division of Infectious Diseases, University of Michigan Medical Center, Ann Arbor, Michigan.

The data was collected by Drs. Bartlett and Fekety and was not the result of a multicenter study. However, the dosage used, length of treatment, and other critical parameters are generally uniform.

The accompanying tables summarize the data. All of the patients had clinical symptomatology compatible with their diagnosis. Most of the patients underwent proctosigmoidoscopy procedures as a diagnostic measure and all but one patient had stool specimens which were positive for Clostridium difficile toxin prior to treatment.

As indicated in Table 2, vancomycin appeared to be efficacious in 77 of the 79 patients. There appeared to be cessation or improvement in their diarrhea as well as improvement in other symptomatology. Eight patients relapsed after treatment with vancomycin but were successfully retreated with vancomycin (7 cases) or cholestyramine (1 case).

The drugs associated or implicated in the development of diarrhea/colitis are listed in Table 3.

TABLE 1

ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

	Case Number	Implicated Antibiotic(s)	Endoscopy Findings	Pretreatment Stool *C. difficile* Toxin Assay	Pretreatment Stool Culture for *C. difficile*	Oral Vancomycin Treatment Dose (mg)	Oral Vancomycin Treatment Duration (days)	Time (days) after initiation of vancomycin treatment for diarrhea to subside
Bartlett Cases	100	clin, oxac, gent	PMC*	+	+	500 q.i.d.	21	5
	101	ceph	PMC	+	+	500 q.i.d.	10	7
	118	clin	PMC	+	ND**	500 q.i.d.	7	5
	120	clin	PMC	+	ND	500 q.i.d.	7	5
	121	ampi	PMC	+	+	250 q.i.d.	10	8
	122	clin	PMC	+	ND	500 q.i.d.	10	4
	124	clin	PMC	+	+	500 q.i.d.	10	6
	125	ampi	PMC	+	+	500 q.i.d.	7	5
	130	clin, naf, ampi, gent	PMC	+	+	500 q.i.d.	14	3
	131	pen	PMC	+	+	250 q.i.d.	10	5
	133	ampi	PMC	+	+	500 q.i.d.	10	5
	134	ceph	PMC	+	+	500 q.i.d.	7	5
	140	clin, gent	PMC	+	+	500 q.i.d.	10	5
	142	S/T	PMC	+	+	500 q.i.d.	10	6
	143	ceph	PMC	+	+	500 q.i.d.	7	5
	144	ceph	PMC	+	+	500 q.i.d.	7	7
	145	clin	PMC	+	+	500 q.i.d.	10	5
	146	ceph	PMC	+	+	500 q.i.d.	7	5
	148	ampi, tobr	PMC	+	+	500 q.i.d.	7	5

Code for antibiotic abbreviations:

clin = clindamycin
oxac = oxacillin
gent = gentamicin
ceph = cephalosporin
ampi = ampicillin
naf = nafcillin
pen = penicillin
tobr = tobramycin
S/T = sulfamethoxazole/trimethoprim
met = metronidazole
ery = erythromycin
amik = amikacin
chlo = chloramphenicol
amox = amoxicillin

PMC* = pseudomembranous colit
ND** = not done

TABLE 1

ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

Case Number	Implicated Antibiotic(s)	Endoscopy Findings	Pretreatment Stool		Oral Vancomycin Treatment		Time (days) after initiation of vancomycin treatment for diarrhea to subside
			C. difficile Toxin Assay	Culture for *C. difficile*	Dose (mg)	Duration (days)	
149	clin	PMC	+	ND	500 q.i.d.	10	6
156	ceph	PMC	+	+	500 q.i.d.	7	3
161	pen	PMC	+	+	250 q.i.d.	10	3
171	S/T	PMC	+	+	500 q.i.d.	10	10
172	ceph	PMC	+	ND	500 q.i.d.	7	3
181	ampi	PMC	+	+	500 q.i.d.	½	expired
184	ceph	PMC	+	+	500 q.i.d.	7	3
186	ceph	PMC	+	+	500 q.i.d.	7	5
194	ceph	PMC	+	+	500 q.i.d.	7	1
206	amox	PMC	+	ND	500 q.i.d.	7	4
213	ampi	PMC	+	+	500 q.i.d.	10	8
214	ampi	PMC	+	-	500 q.i.d.	10	2
216	pen	acute colitis	+	+	500 q.i.d.	10	5
223	ceph	PMC	+	+	500 q.i.d.	7	3 expired
229	pen, clin	PMC	+	+	500 q.i.d.	7	2
243	ceph, oxac	PMC	+	+	500 q.i.d.	10	4
245	ampi, clin, gent	PMC	+	+	500 q.i.d.	7	2
160	ceph	PMC	+	+	500 q.i.d.	10	2-3
170	ampi	PMC	+	+	500 q.i.d.	7	3
173	ampi, met, clin	ND	+	+	500 q.i.d.	7	2

Code for antibiotic abbreviations:

clin = clindamycin
oxac = oxacillin
gent = gentamicin
ceph = cephalosporin
ampi = ampicillin
naf = nafcillin
pen = penicillin
tobr = tobramycin
S/T = sulfamethoxazole/trimethoprim
met = metronidazole
ery = erythromycin
amik = amikacin
chlo = chloramphenicol
amox = amoxicillin

PMC* = pseudomembranous colitis
ND** = not done

TABLE 1

ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

Case Number	Implicated Antibiotic(s)	Endoscopy Findings	Pretreatment Stool		Oral Vancomycin Treatment		Time (days) after initiation of vancomycin treatment for diarrhea to subside
			C. difficile Toxin Assay	Culture for *C. difficile*	Dose (mg)	Duration (days)	
174	ery	PMC	+	+	250 q.i.d.	7	3
177	ceph, amik	ND	+	+	500 q.i.d.	7	1
179	clin, gent	Erythema, Edema	+	-	500 q.i.d.	7	2
186	ceph	PMC	+	+	500 q.i.d.	7	2
197	clin, gent	ND	+	+	500 q.i.d.	7	5
210	ampi, chlo	PMC	+	-	100 q.i.d.	7	2-3
218	ceph	Normal	+	ND	500 q.i.d.	7	3
225	ampi	Normal	+	ND	250 q.i.d.	7	
232	ceph	Negative	+	+	500 q.i.d.	10	4
237	ampi, ceph	ND	+	+	250 q.i.d.	14	6
241	ampi	Erythema	+	ND	500 q.i.d.	7	2-3
242	ampi	Normal	+	ND	500 q.i.d.	7	2
253	clin, gent	Colonic Ulceration	+		500 q.i.d.	10	3
265	bactrim	PMC	+	+	125 q.i.d.	14	10
267	ceph	PMC	+	+	500 b.i.d.	12	2
260	pen, chlo	PMC	+	+	500 q.i.d.	11	2-3
263	ampi	PMC	+	+	?	6	1-2
270	ceph	ND	+	ND	250 q.i.d.	7	1-2
264	oxac	ND	+	ND	500 q.i.d.	7	5

Code for antibiotic abbreviations:

clin = clindamycin
oxac = oxacillin
gent = gentamicin
ceph = cephalosporin
ampi = ampicillin
naf = nafcillin
pen = penicillin
tobr = tobramycin
S/T = sulfamethoxazole/trimethoprim
met = metronidazole
ery = erythromycin
amik = amikacin
chlo = chloramphenicol
amox = amoxicillin

PMC* = pseudomembranous colit
ND** = not done

TABLE 1

ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

Case Number	Implicated Antibiotic(s)	Endoscopy Findings	Pretreatment Stool		Oral Vancomycin Treatment		Time (days) after initiation of vancomycin treatment for diarrhea to subside
			C. difficile Toxin Assay	Culture for *C. difficile*	Dose (mg)	Duration (days)	
159	ampi	ND	+	+	125 q.i.d.	7	2 (20 days to relapse)
159 (relapse)		ND	+	+	500 q.i.d. +125 q.i.d. +125 b.i.d.	14 7 7	3
166	ampi	Normal	+	+	125 q.i.d.	7	1-2 (21 days to relapse)
166 (relapse)		ND	+	+	500 q.i.d.	14	2-3
222	ampi	PMC	+	+	500 q.i.d.	14	3-5 (18 days to relapse)
222 (relapse)		Erythema, Edema	+	+	500 q.i.d. +250 q.i.d. +125 q.i.d. +125 b.i.d.	10 4 2 2	7
254	ampi	PMC	+	+	1000 q.i.d. 500 q.i.d.	2 5	5 (7 days to relapse)
254 (relapse)		ND	+	+	500 q.i.d.	14	1
257	ceph	Focal Ulceration	+	+	500 q.i.d.	7	3 (8 days to possible relapse
257 (relapse)		ND	+	+	None	-	1
247	amox	PMC	+	ND	200 q.i.d.	10	4-5 (4 days to relapse)
247 (relapse)		ND	+	+	200 q.i.d. +100 q.i.d. +100 b.i.d.	6 3 4	2-3 (5 days to relapse)

Code for antibiotic abbreviations:

clin = clindamycin
oxac = oxacillin
gent = gentamicin
ceph = cephalosporin
ampi = ampicillin
naf = nafcillin
pen = penicillin
tobr = tobramycin
S/T = sulfamethoxazole/trimethoprim
met = metronidazole
ery = erythromycin
amik = amikacin
chlo = chloramphenicol
amox = amoxicillin

PMC* = pseudomembranous colit
ND** = not done

TABLE 1

ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

Case Number	Implicated Antibiotic(s)	Endoscopy Findings	Pretreatment Stool: *C. difficile* Toxin Assay	Pretreatment Stool: Culture for *C. difficile*	Oral Vancomycin Treatment: Dose (mg)	Oral Vancomycin Treatment: Duration (days)	Time (days) after initiation of vancomycin treatment for diarrhea to subside
247 (relapse)		ND	+	+	200 q.i.d. +100 q.i.d. +100 b.i.d.	5 3 4	3-4
Fekety Cases							
382-26-4212	naf	PMC	+	ND	500 q.i.d.	5	2 days
RI-1	amox	ulcerative colitis	+	ND	500 q.i.d. 250 q4h	12 2	occasional loose stool at end of treatment
RI-2	ampi	negative	+	ND	500 q.i.d.	14	not mentioned; discharged with normal stools
368-246-450	ampi	PMC	+	ND	500 q6h 500 IV qid	2 7	7
GH-2	ceph	PMC	+	ND	500 q.i.d.	10	1 (?)
GH-1	ceph	PMC	+	ND	250 q.i.d.	4	1½; relapse treated with Questra
1486-466-0	clin, gent	PMC	?	+	500 q.i.d.	15	10
592538	gent, ampi, ceph	PMC	+	ND	500 q6h	10	7
OSU #1	meth naf, dicl, ceph	PMC PMC	+ +	ND ND	500 q.i.d. 500 q.i.d.	10 10	2 10 (8 days to relapse)
OSU #1 (relapse)			+		500 q.i.d.	10	5

Code for antibiotic abbreviations:

clin = clindamycin
oxac = oxacillin
gent = gentamicin
ceph = cephalosporin
ampi = ampicillin
naf = nafcillin
pen = penicillin
tobr = tobramycin
S/T = sulfamethoxazole/trimethoprim
met = metronidazole
ery = erythromycin
amik = amikacin
chlo = chloramphenicol
amox = amoxicillin
meth = methicillin
dicl = dicloxacillin

PMC* = pseudomembranous colit
ND** = not done

TABLE 1

ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

Case Number	Implicated Antibiotic(s)	Endoscopy Findings	Pretreatment Stool: *C. difficile* Toxin Assay	Pretreatment Stool: Culture for *C. difficile*	Oral Vancomycin Treatment: Dose (mg)	Oral Vancomycin Treatment: Duration (days)	Time (days) after initiation of vancomycin treatment for diarrhea to subside
1296-786-1	ceph	ND	+	+	125 t.i.d.	2	(patient was also receiving vanco. I.V. for endocarditis)
					500 q.i.d.	14	2
1567-167-1	5-fluorouracil	colitis	+	+	250 t.i.d.	7	2
	5-fluorouracil	ND	+	+	125 t.i.d.	2	2
					250 t.i.d.	14	
TC 1	Macrodantin, clin, gent, ceph	PMC	+	+	125 q8h	10	3
1534-985-2	ampi, kana	ND	+	ND	1200/M^2/day	15	"quickly"
BC-1	clin	pale mucosa	+	ND	500 q.i.d.	10	2
0744-134-4	ampi	normal	+	ND	500 q.i.d.	4	"prompt"

Code for antibiotic abbreviations:

clin = clindamycin
oxac = oxacillin
gent = gentamicin
ceph = cephalosporin
ampi = ampicillin
naf = nafcillin
pen = penicillin
tobr = tobramycin
S/T = sulfamethoxazole/trimethoprim
met = metronidazole
ery = erythromycin
amik = amikacin
chlo = chloramphenicol
amox = amoxicillin
meth = methicillin
dicl = dicloxacillin

PMC* = pseudomembranous colitis
ND** = not done

TABLE 2

SUMMARY OF ANTIBIOTIC-ASSOCIATED DIARRHEA/COLITIS CASES WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

	J. Bartlett	P. Fekety	Total
Total Cases	64	15	79
PMC by endoscopy	47	8	55
Endoscopy not PMC	10	5	15
Endoscopy not done	7	2	9
Toxin positive	64	14	78
Toxin not mentioned	0	1	1
Culture positive	47	4	51
Culture negative	3	0	3
Culture not done	13	11	24
Culture data unknown	1	0	1
*Doses 500 mg. p.o. q.i.d.	51	8	59
250 mg. p.o. q.i.d.	7	1	8
125 mg. p.o. q.i.d.	3	0	3
125 mg. p.o. t.i.d.	0	2	2
misc.	4	5	9
Dose duration (days)	7-21	4-15 mean 9.7	
Time for diarrhea clear (days)	1-10	1½-10 mean 3.9	
Relapses (one)	5	2	7
(two)	1	0	1
Fatalities	2	0	2
Vancomycin apparently efficacious	63[a]	14[b]	77

*Some patients had more than one dosage regimen.

[a]One patient died after two doses; laparotomy showed multiple colonic perforations; patient expired post-op.

[b]One patient suffered a relapse that was treated with Questran®.

TABLE 3

DRUGS IMPLICATED IN CASE REPORTS OF THE DEVELOPMENT OF DIARRHEA/COLITIS WITH TOXIN POSITIVE STOOLS TREATED WITH VANCOMYCIN

Individual Drugs Implicated	No. of Cases
cephalosporins alone	21
ampicillin alone (inc. amoxicillin)	21
clindamycin alone	7
penicillin alone (inc. semi-synthetics)	6
sulfa or sulfatrimeth. alone	3
erythromycin alone	1
5-fluorouracil	1

Combination Therapy Implicated	
clindamycin + gentamicin	6
clindamycin + ampicillin + others	3
ampicillin + others	5
cephalosporins + others	4
penicillin + clindamycin	1
penicillin + chloramphenicol	1
clindamycin + others	1

Summary*	
cephalosporins (alone or in combination)	25
ampicillin (alone or in combination)	29
clindamycin (alone or in combination)	18
penicillin (alone or in combination)	8
others	5

* There is some overlap in these groupings.

Conclusions:

Ths sponsor has submitted satisfactory evidence that vancomycin HCl is effective in the treatment of antibiotic associated pseudomembranous colitis produced by Clsotridium difficile.

Recommendations:

1. Under the "Indications" section of 60-180 and 61-667, the addition of "and pseudomembranous colitis produced by Clostridium difficile." should be changed to read: "and antibiotic associated pseudomembranous colitis produced by Clostridium difficile."

2. It is recommended that the following claim in the "For Oral administration" section of "Dosage and Administration" of 60-180 and in "Dosage and Administration....Adults" of 61-667:

   "The usual adult dosage for pseudomembranous colitis produced by C. difficile is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days."

   be modified to read:

   "The usual adult dosage for antibiotic associated pseudomembranous colitis produced by C. difficile is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days."

3. The inclusion of [redacted] (b) (4) under Actions should not be approved. The sponsor has only submitted data to substantiate the inclusion of Clostridium difficile. The inclusion of Clostridium difficile in the Actions section is found approvable.

4. All other suggested changes in labeling for 60-180 and 61-667 are found to be acceptable.

George R. Stanley

George R. Stanley, M.D.
Medical Officer
Division of Anti-Infective
Drug Products

cc:
ORIG. FORM 61-180
ORIG. FORM 61-667
HFD-535/Harrison
HFD-140
HFD-140/GRStanley/sj/3/11/80
HFD-140/CSO
HFD-140/James
HFD-140/King
HFD-140/Norton
HFD-180
HFD-332
R/D init. by: TGReed/2/27/80 "See Group Leader's Comments"

References

1. Larson, H. E., and Price, A. B.: [illegible] Presence of Clostridial Toxin. Lancet, December 24 and 31, 1977.

2. George, R. H.; Symonds, J. M.; Dimock, F.; Brown, J. D.; Arabi, Y.; Shinagawa, N.; Keighley, M. R. B.; Alexander-Williams, J.; and Burdon, D. W.: Identification of Clostridium difficile as a Cause of Pseudomembranous Colitis. British Med. Journal, 1:695, 1978.

3. George, W. L., Sutter, V. L., and Finegold, S. M.: Toxigenicity and Antimicrobial Susceptibility of Clostridium difficile, A Cause of Antimicrobial Agent-Associated Colitis. Current Microbiology, 1:55-58, 1978.

4. George, W. L.; Kirby, B. D.; Sutter, V. L.; and Finegold, S. M.: Antimicrobial Susceptibility of Clostridium difficile. Microbiology - 1979, pp. 267-271, American Society for Microbiology, Washington, D.C., 1979.

5. Larson, H. E.; Price, A. B.; Honour, P.; and Borriello, S. P.: Clostridium difficile and the Aetiology of Pseudomembranous Colitis. Lancet, May 20, 1978.

6. Burdon, D. W.; Brown, J. D.; George, R. H.; Arabi, Y.; Alexander-Williams, J.; and Keighley, M. R. B.: Pseudomembranous Colitis Caused by Clostridia. (Letter) New England Journal of Medicine, 299:48, 1978.

7. Burdon, D. W.; Brown, J. D.; Young, D. J.; Arabi, Y.; Shinagawa, N.; Alexander-Williams, J.; Keighley, M. R. B.; and George, R. H.: Antibiotic Susceptibility of Clostridium difficile. J. Antimicrob. Chemother., 5:307-310, 1979.

8. Fekety, R.: Prevention and Treatment of Antibiotic-Associated Colitis. Microbiology - 1979, pp. 276-279, American Society for Microbiology, Washington, D.C., 1979.

9. Bartlett, J. G., Onderdonk, A. B., and Cisneros, R. L.: Clindamycin-Associated Colitis in Hamsters: Protection with Vancomycin. Gastroenterology, 73:772-776, 1977.

10. Bartlett, J. G.; Onderdonk, A. B.; Cisneros, R. L.; and Kasper, D. L.: Clindamycin-Associated Colitis Due to a Toxin-Producing Species of Clostridium in Hamsters. J. Infect. Dis., 136:701, 1977.

11. Bartlett, J. G., Chang, T., and Onderdonk, A. B.: Comparison of Five Regimens for Treatment of Experimental Clindamycin-Associated Colitis. J. Infect. Dis., 138:81-86, 1978.

12. Browne, R. A.; Fekety, R.; Silva, J.; Boyd, D. I.; Work, C. O.; and Abrams, G. D.: [illegible] Clindamycin-Induced Colitis. 141:183-192, 1980.

13. Humphrey, C. D.; Condon, C. W.; Cantey, J. R.; and Pittman, F. E.: Partial Purification of a Toxin Found in Hamsters with Antibiotic-Associated Colitis: Reversible Binding of the Toxin by Cholestyramine. Gastroenterology, 74:1045, 1978.

14. Katz, L.; LaMont, J. T.; Trier, J. S.; Sonnenblick, E. B.; Rothman, S. W.; Broitman, S. A.; and Rieth, J.: Experimental Clindamycin-Associated Colitis in Rabbits: Evidence for Toxin-Mediated Mucosal Damage. Gastroenterology, 74:246-252, 1978.

15. LaMont, J. T., Sonnenblick, E. B., and Rothman, S.: Role of Clostridial Toxin in the Pathogenesis of Clindamycin Colitis in Rabbits. Gastroenterology, 76:356-361, 1979.

16. Rifkin, G. D.; Fekety, F. R.; Silva, Jr., J.; and Sack, R. B.: Antibiotic-Induced Colitis: Implication of a Toxin Neutralized by Clostridium sordellii Antitoxin. Lancet, 2:1103-1106, 1977.

17. Modigliani, R., and Delchier, J. C.: Vancomycin for Antibiotic-Induced Colitis. Lancet, 1:97-98, 1978.

18. Kappas, A.; Shinagawa, N.; Arabi, Y.; Thompson, H.; Burdon, D. W.; Dimock, F.; George, R. H.; Alexander-Williams, J.; and Keighley, M. R. B.: Diagnosis of Pseudomembranous Colitis. Brit. Med. J., 1:675-678, 1978.

19. Larson, H. E., Levi, A. J., and Borriello, S. P.: Vancomycin for Pseudomembranous Colitis. Lancet, 2:48, 1978.

20. Marrie, T. J.; Faulkner, R. S.; Badley, B. W. D.; Hartlen, M. R.; Comeau, S. A.; and Miller, H. R.: Pseudomembranous Colitis: Isolation of Two Species of Cytotoxic Clostridia and Successful Treatment with Vancomycin. Canadian Medical Association Journal, 119:1058-1060, 1978.

21. Tedesco, F.; Markham, R.; Gurwith, M.; Christie, D.; and Bartlett, J. G.: Oral Vancomycin for Antibiotic-Associated Pseudomembranous Colitis. Lancet, 2:226-228, 1978.

22. Keighley, M. R. B.; Burdon, D. W.; Alexander-Williams, J.; Thompson, H.; Young, D.; Johnson, M.; Bentley, S.; George, R. H.; and Mogg, G. A. G.: Randomised Controlled Trial of Vancomycin for Pseudomembranous Colitis and Postoperative Diarrhoea. British Medical Journal, 2:1667-1669, 1978.

23. Bartlett, J. G.; Chang, T.; Taylor, N. S.; and Onderdonk, A. B.: Colitis Induced Clostridium difficile. Rev. Infect. Dis., 1:370-378, 1979.

24. Bartlett, J. G.; Willey, S. H.; Chang, T.; and Lowe, B.: Cephalosporin-Associated Pseudomembranous Colitis Due to Clostridium difficile. J.A.M.A., 240(2503 (December 15), 1978.

Form 60-180
Form 61-667

February 27, 1980

GROUP LEADER'S COMMENTS ON MEDICAL OFFICER'S REVIEW
dated February 27, 1980

Applicant: Lilly Research Laboratories

Name of Drugs: VANCOCIN HCl Vials No 657 (Sterile vancomycin hydrochloride, USP)
VANCOCIN HCl for Oral Solution M-206 (Vancomycin hydrochloride for oral solution, NF)

Date of Amendment: January 16, 1980

The applicant wishes to amend its vancomycin HCl labeling to add a new claim, the use of vancomycin HCl in the treatment of antibiotic-associated pseudomembranous colitis caused by Clostridium difficile. Other minor revisions are made.

Recommendations: I agree with the medical officer's recommendations except for one minor change. The letters HCl should follow the name vancomycin where appropriate.

1. My most important recommendation is related to the fact that there is a potential for adverse cardiovascular effects with rapid intravenous administration of concentrated vancomycin HCl. Newfield and Roizen "retrospectively evaluated 76 monitored patients who had undergone intracranial surgery and found that administration of 1 g of vancomycin in 10 mL of crystalloid over 10 min was quickly followed in 11 patients by a 25% to 50% decrease in systolic pressure lasting 2 to 3 min." These authors subsequently gave the drug in dilute form over 30 min to more than 100 patients and hypotension was not noted (Ann. Int. Med.: Vol 91, No 4, Oct. 1979, 581).

Therefore, the Precautions section of the package insert for Sterile vancomycin HCl vials should be revised to add the following paragraph: "A 25% to 50% decrease in systolic blood pressure has been reported following rapid intravenous administration (over a 10 minute period) of the concentrated formulation."

2. The following reactions should be added to the Adverse Reactions sections of labeling for both products: ototoxicity and deafness, nephrotoxicity, and tinnitis. Reactions for this section of the labeling for the sterile vial should include: pain at the injection site, and thrombophlebitis.

3. Delete the "Actions" heading and add a "Clinical Pharmacology" heading in its place.

4. Add a "Microbiology" subheading at the end of the "Clinical

Pharmacology" heading and transfer the third (second) sentence of the first paragraph and the remainder of the first paragraph, now under the "Actions" heading, to the "Microbiology section. This section will read, "Many strains of streptococci -------" through "_____when tested against a vancomycin-susceptible bacterial strain."

The applicant should be requested to review the final rule regarding the content and format for prescription drug labeling published in the FEDERAL REGISTER on June 26, 1979 (Vol 44, No 124, pages 37434-37467) since other changes in this labeling will be made in the future to comply fully with this rule.

Theresa Greene Reed
Theresa Greene Reed, M.D., M.P.H.

cc
Orig Form 60-180
Orig Form 61-667
HFD-140/Vancomycin file
HFD-140/Reed
HFD-140/Stanley
HFD-140/Norton
HFD-180
HFD-535/Powers
HFD-332
HFD-140/Joyce

MRS 3/4/80

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-667

CHEMISTRY REVIEWS

DRUG CONTROL REVIEW NOTES

1. TYPE ☐ IND ☒ 6 ☐ 5

2. NO. 61-667 ~~60-480~~

3. SPONSOR Eli Lilly & Company

ATT: F.B. Peck, Jr., MD Director Medical plans and Regulatory Affairs

4. ADDRESS Indianapolis, Indiana 46206

5. SUBMISSIONS REVIEWED

a. ORIGINAL DATED

b. AMENDMENTS DATED 10/8/71, 4/11/72

5c. PROVIDING FOR Repackaging vancomycin HCl in 10gm vials for oral use

6. NAME(S)

a. TRADE: Vancocin HCl For Oral Use

b. NON-PROPRIETARY: Vancomycin HCl

c. CHEMICAL:

d. ESTAB: Vancomycin HCl

e. USAN: Vancomycin HCl XVII

f. WHO:

7. STRUCTURAL FORMULA

8. DOSAGE FORM: Oral solution - 10gm.

9. ☒ RX ☐ OTC

10. FAMILY OR TYPE OF DRUG: Antibiotic

11. RELATED NDA, IND, MF, FORM 5's

148s.1

12. REMARKS

No stability data was submitted but a 36 month expiration date for the dry ~~intravenous~~ vial and a 2 week period at room temperature under refrigeration has been approved for the ~~reconstituted~~ intravenous vial. Lilly has requested 36 months on unreconstituted material and 1 week under refrigeration for the reconstituted oral suspension.

13. CONCLUSIONS

Controls are adequate.

14. DATE REVIEWED 7-20-72

15. REVIEWER J. Eckert

FORM FDH-1742 5/65

COPY TO: 1. Original IND
2. Duplicate IND
3. Triplicate IND

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 61-667

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Noted
10/12/71
KES

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

October 8, 1971

Section 148s.1
No. 60-180

Alan E. Smith, M.D.
Division of Anti-Infective Drug
Products
Office of Scientific Evaluation
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Smith:

Approximately three months ago, during one of my visits, I discussed with you, Dr. Gibson, and Dr. Lockhart our desire to meet a need for an oral dosage form of vancomycin.

As you may recall, we have been approached on numerous occasions by institutions involved in "Life Island" therapy to provide them "bulk" vancomycin for oral use, since the present 0.5 Gm. I.V. ampoule presents a distinct handicap in preparing from 10-50 Gm. of material daily. Amounts of this magnitude are used routinely in such institutions as the National Cancer Institute, [redacted] (b) (4) Hospital, and [redacted] (b) (4); and individual doses prepared from bulk solutions are dispensed by the hospital pharmacy for use in patients undergoing "Life Island" therapy.

During our conversation, it was agreed that perhaps the best answer would be to make available an oral form suitably labeled and packaged in a container that would clearly not be mistaken for a parenteral preparation. A 10-Gm. vial was suggested, and this proposal is satisfactory to those institutions subsequently contacted.

Consequently, under separate cover we have submitted a Form 6 Amendment, a desk copy of which is enclosed with this letter. It provides for a 10-Gm. screw-capped vial suitably labeled in bold face red ink "FOR ORAL USE ONLY." We have also revised the current package literature for the intravenous product to an insert we feel clearly spells out that the new form is for oral use only. This has been accomplished by a warning box below the label and by deleting all dosage references for the I.V. product.

We hope that by providing this dosage form we can be of service to institutions requesting such a product form and will look forward to your comments. Please do not hesitate to call me if there are any questions.

Very truly yours,

ELI LILLY AND COMPANY

F. B. Peck, Jr. (rc)

F. B. Peck, Jr., M.D.
Director, Medical Plans
and Regulatory Affairs

FBP:llg

Enc.

A-6
Eisler

THE LILLY RESEARCH LABORATORIES

61-667

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

October 8, 1971

PERSONALLY SUBMITTED BY
Gerald S. Kantrowe
Rec'd by B. Owens
10-12-71

Section 148s.1
No. [redacted]

Department of H.E.W.
Food and Drug Administration
Division of Anti-Infective Drug
Products
Certification Services Branch
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only, M-206, Vancomycin Hydrochloride

We are submitting in triplicate pertinent sections of Form FD-1675 to amend the Antibiotic Regulation Section 148s.1 to provide for the certification of vancomycin hydrochloride for oral use only. This will be a non-sterile product and will be packaged in 10 Gm. vials which are identical in composition to the material used for our approved Ampoule No. 657, vancomycin hydrochloride.

In addition, we have prepared a proposed amendment to Section 148s.1 to include this non-sterile oral dosage form. The labeling in this submission is in final printed form and differs from that of the Intravenous product.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

F. B. Peck, Jr. (ms)

F. B. Peck, Jr., M.D.
Director, Medical Plans
and Regulatory Affairs

FBP:llg

Attachment

RECEIVED
OCT 12 1971
BUREAU OF DRUGS

RECEIVED
FOOD & DRUG ADM.
OCT 14 1971
DIVISION OF
CERTIFICATION
SERVICES

2351

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
FOOD AND DRUG ADMINISTRATION
WASHINGTON, D.C. 20204

Form Approved
Budget Bureau No. 57-R009.2

ANTIBIOTIC APPLICATION

(Check applicable item below)

FORM 5 REQUEST UNDER 146.10 TO PROVIDE FOR CERTIFICATION OF A NEW ANTIBIOTIC OR ANTIBIOTIC-CONTAINING PRODUCT. ☐

FORM 6 DATA TO ACCOMPANY OR PRECEDE EVERY INITIAL REQUEST UNDER 146.2 FOR CERTIFICATION OF AN ANTIBIOTIC DRUG COVERED BY EXISTING REGULATIONS.
SECTION _____. ☐

FORM 5 AMENDMENT. REGULATION SECTION _____ IF KNOWN. ☐

FORM 6 AMENDMENT. REGULATION SECTION 148s.1 ☒

FOR USE OF FOOD AND DRUG ADMINISTRATION

DATE APPROVED | ACCOUNT NO.

SIGNED

FOR THE COMMISSIONER OF FOOD AND DRUGS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NAME OF APPLICANT
ELI LILLY AND COMPANY

ADDRESS *(Include Zip Code)*
P. O. BOX 618, INDIANAPOLIS, INDIANA 46206

DATE OF APPLICATION
October 8, 1971

NAME OF DRUG
VANCOCIN® HCl For Oral Use, M-206, Vancomycin Hydrochloride

Commissioner
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C. 20204

Attention: Division of Antibiotics and Insulin Certification

In accordance with regulations promulgated under Section 507 of the Federal Food, Drug, and Cosmetic Act, as amended, we hereby submit this application with respect to an antibiotic product.

Attached hereto, in triplicate (except for the information required under item 9 (a) through (f) which is submitted in single copy) and constituting a part of this application are the following:

1. A full list of the articles used as components of the drug. This list should include all substances used in the fermentation, synthesis, extraction, purification or other method of preparation of any antibiotic and in the preparation of the finished dosage form, regardless of whether they undergo any change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

2. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per milliliter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

3. A complete description of the methods and processes used in manufacturing, packing and labeling of the drug to preserve its identity, strength, quality, and purity in conformity with good manufacturing practices including:

(a) Name and location of each plant conducting the operations.

(b) Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

(c) Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material used in the fermentation, synthesis, extraction, and purification of the drug and for each ingredient used in the manufacture of the drug that is to be dispensed.

(d) If it is a drug produced by fermentation:

(i) Source and type of microorganism used to produce the drug.

(ii) Composition of media used to produce the drug.

(iii) Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.

(iv) Name and composition of preservative, if any, used in the broth.

(v) A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, demulsifiers, and all other agents used.

(vi) If the drug is produced by a catalytic hydrogeneration process, *(such as tetracycline from chlortetracycline)*, a complete description of the process, including the name of the catalyst used, how it is removed, and how the drug is extracted and purified.

(e) If it is a drug that is synthesized by chemical processes, a detailed description of each chemical reaction with graphic formulas used to produce the drug, including the names and amounts of all substances used in the process.

(NOTE: If the applicant is not the manufacturer of the antibiotic used in making the drug, in lieu of the information required in 3(a) through 3(e), he should include the name and address of the manufacturer.)

(f) Method of preparation of the master formula records and individual batch records and manner in which these records are used.

(g) Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

RECEIVED
OCT 12 1971
FOOD AND DRUGS

(b) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up the batch according to the formula card, and at what stage and by whom this is done.

(i) At what point in the process the drug is mixed homogeneously and a description of the equipment used for this purpose and its total capacity in terms of pounds, kilograms, gallons, or liters of the drug and the maximum quantity of the drug that is mixed in such equipment.

(j) A description, where applicable, of the equipment used in the fermentation, synthesis, extraction, purification, filtration, sterilizing, grinding, blending, mixing, tableting, encapsulating, filling, packaging, and labeling of the drug.

(k) If it is a sterile drug, a description of the methods used to insure the sterility of each batch and the controls used for maintaining its sterility, including a detailed description of the sterile areas where the drug is produced and packaged.

(l) Additional procedures employed which are designed to exclude contaminants *(e.g., other drug substances, extraneous materials, etc.)* and otherwise assure proper control of the product.

(m) Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug container to insure their suitability for the intended use.

(n) Controls used in the packaging and labeling of each batch to insure the standards of identity, strength, quality and purity of the drug.

(o) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.

(p) Precautions to insure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling, storage, and inventory control.

(q) Copies of all printed forms used by the applicant in the manufacture, packaging, and labeling of a batch.

(r) The name of each person responsible for each of the above operations and information concerning his scientific training and experience.

4. A complete description of the tests and methods of assay and other controls used during the manufacture of the batch and after it is packaged.

(a) Details of analytical procedures for all active ingredients. The analytical procedures should be capable of determining the active components and of assuring the identity of such components.

(b) Standards used for acceptance of each lot of the finished drug.

(c) A detailed description of the collection of the samples to be tested by the applicant and by the Food and Drug Administration.

(d) Copies of all printed forms used by the applicant in the laboratory control of raw ingredients and the finished batch.

(e) A complete description of the laboratory facilities used in such controls, including:

(i) The location of the laboratory in relation to the plant where the drug is manufactured,

(ii) A description of the laboratory equipment available for performing tests and assays, and

(iii) The names of the persons who will be responsible for conducting the required laboratory tests and information concerning their scientific training and experience.

(f) If the applicant uses the services of a consulting laboratory, the name and address of such laboratory and a statement from such laboratory that includes the information required under 4(a), (b), and (e).

(g) An explanation of the exact significance of any batch numbers used in the manufacturing, processing, packaging, and labeling of the drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

(h) A complete description of, and data derived from, stability studies of the potency and physical characteristics of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new antibiotic, for the finished dosage form of the drug in the container including a multiple-dose container in which it is to be marketed, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed.

(i) The expiration date needed to preserve the identity, strength, quality, and purity of the drug until it is used.

5. The following samples shall be submitted with the application or as soon thereafter as they become available:

(a) If it is a new antibiotic: 10 grams of the applicant's reference standard if an official standard has not been designated, plus 5 grams from each of three separate batches. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

(b) If it is a dosage form: 6 immediate containers (or 30 tablets or capsules) from each of three separate batches, except that if it is a sterile drug 30 containers shall be submitted from each of three batches.

(c) Include for samples submitted pursuant to items 5(a) or 5(b) detailed results of all laboratory tests made to determine the identity, strength, quality and purity of the batch represented by the sample.

(d) Additional samples shall be submitted on request.

(e) The requirements of items 5(a) or 5(b) may be waived in whole or in part on request of the applicant, or otherwise, when any such samples are not necessary.

6. Each copy of the application shall contain a copy of each label and all other labeling to be used for the drug.

(a) Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

(b) The labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use, or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to laymen.

(c) If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purpose for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with 1.106(b) or (c).

(d) If no established name exists for a new antibiotic, the application shall propose a nonproprietary name for use as the established name for the substance.

(e) Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not be approved prior to the submission of the final printed label and labeling of the drug. No application may be approved if the labeling is false or misleading in any particular. *(If the article is a prescription drug, copies of proposed advertising may be submitted optionally for comment or approval).*

7. State whether the drug is *(or is not)* limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

8. It is understood that the labeling, and advertising for the antibiotic drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will also contain substantially the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions, contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until an amendment providing for a change is approved by the Food and Drug Administration.

9. Full reports of investigations that have been made to show whether or not the drug is safe for use and efficacious in use.

If this is a Form 5 application submit one copy of (a) through (f) below

(a) An application may be found unsatisfactory unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the proposed labeling and includes all the following:

(i) Detailed reports of the preclinical investigations, including studies made on laboratory animals, in which the methods used and the results obtained are clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short - or long - term administration or whether it is to be used in infants, children, pregnant women, or premenopausal women.

(ii) Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

(iii) All information pertinent to an evaluation of the safety and efficacy of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application or pertinent information about any relevantly related drug. An adequate summary may be acceptable in lieu of a reprint of a published article which only supports other data submitted. Include any evaluation of the safety or efficacy of the drug that has been made by the applicant's medical department, expert committee, or consultants.

(iv) If the drug is a combination of previously investigated or marketed drugs an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

(b) An application may be found unsatisfactory unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the efficacy of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(c) The complete composition and/or method of manufacture of the drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in item 1, 2, 3, or 4 of the application in any way that would bias an evaluation of the report.

(d) An application shall include a complete list of the names and post office addresses of all investigators who received the drug.

(e) The information required by 9(a) through 9(d) may be incorporated in whole or in part by specific reference to information submitted under the provisions of §130.3.

(f) Explain any omission of reports from any investigator to whom the investigational drug has been made available. The unexplained omission of any reports of investigations made with the drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, that would bias an evaluation of the safety of the drug or its efficacy in use constitutes grounds for finding the application unsatisfactory.

(g) **If this is a Form 6 application,** in lieu of the information required in 9(a) through 9(f) it should include data adequate to demonstrate that the drug is comparable to the drug for which certification has previously been provided.

10. If this is an amendment, full information on each proposed change concerning any statement made in the approved application. After an application is approved, an amendment may propose changes. An amendment should be submitted for any change beyond the variations provided for in the approved application. An amendment may omit statements made in the approved application concerning which no change is proposed. Any mailing or promotional piece used after the drug is placed on the market is labeling requiring an amendment. An amendment should be submitted for proposed changes in labeling. If a change is made in the components, composition, manufacturing methods, facilities or controls, or in the labeling or advertising from the representations in an approved application and the drug is marketed before an amendment is approved for such change, certification of the drug may be suspended.

Very truly yours,

ELI LILLY AND COMPANY
(Applicant)

Per F. B. Peck, Jr. (rc)

F. B. Peck, Jr., M.D., Director
Medical Plans and Regulatory Affairs
(Indicate Authority)

This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States. The data specified under the several numbered headings should be on separate sheets or sets of sheets, suitably identified. The sample of the drug, if sent under separate cover, should be addressed to the attention of the Division of Antibiotics and Insulin Certification and identified on the outside of the shipping package with the name of the applicant and the name of the drug as shown on the application. **All applications and correspondence should be submitted in triplicate except for the information required under item 9 (a) through (f) which should be submitted as a single copy attached to the originial copy of the application.**

61-667

NDA ~~60-180~~

AF 9-577

JAN 11 1972

Eli Lilly and Company
Attention: F. B. Peck, Jr., M.D.
Indianapolis, Indiana 46206

Gentlemen:

Reference is made to your Form 6 amendment 60-180 Vancocin HCl for Oral Use Only (Vancomycin hydrochloride) dated October 8, 1971.

The following sentence should be added to the vial, carton, and insert immediately following the directions for reconstitution of the drug:

"When reconstituted with (b)(4) milliliters each 6 milliliters contain 500 milligrams of vancomycin".

On the vial and carton labels, the vial size, 10 grams, should be more prominently displayed.

Samples of the 10 gram vial should be submitted to the National Center for Antibiotics Analysis as soon as they are available.

A copy of the proposed certification monographs is enclosed for your review and comment. In § 148s.11, the sample preparation for the potency assay may need revision after our laboratories have tested some samples. Also the number of samples required may need adjustment.

Sincerely yours,

for Merle L. Gibson, M.D.
Director
Division of Anti-Infective
Drug Products
Office of Scientific Evaluation
Bureau of Drugs

Enclosure

cc:
CIN-DO
Orig NDA
Dup NDA
~~Trip NDA~~
BD-100
BD-22
BD-242
BD-401
BD-430
BD-140
BD-140/JEckert:dd 1/7/72

R/D init by RNorton 1/5/72
R/D init by MLGibson 1/6/72
J Eckert 1/10/72

A-6
Eckert

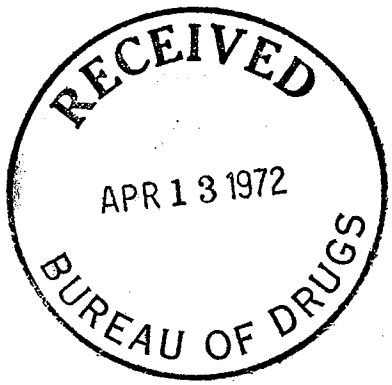
THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

PERSONALLY SUBMITTED BY
Gerald S. Kantorow
Reid by B Owens
4-13-72

April 11, 1972

Section 148s.1
No. ~~60-100~~ 61-667.



Department of H.E.W.
Food and Drug Administration
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only, M-206, Vancomycin Hydrochloride

In reply to Dr. Merle L. Gibson's letter of January 11, 1972, we are submitting in triplicate the data he requested.

The reconstitution statement has been changed to read as follows:

> "When mixed with 110 ml. of water, each 6 ml. provide approximately 500 mg. of vancomycin."

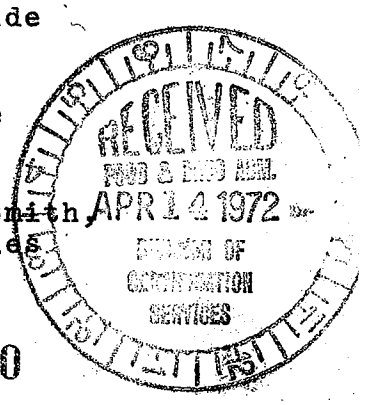
The vial and carton labels have also been revised to include this statement. In addition, the "10 Gm." has been made larger on the labels.

In regard to the proposed certification monographs, they have been reviewed, and we have the following comments:

> The portion of Section 148s.11 (a) (1) pertinent to reconstitution should read as follows: "When reconstituted with 110 milliliters of distilled or deionized water as directed in the labeling (providing a total volume of 117 milliliters) each milliliter contains vancomycin hydrochloride equivalent to 85.5 milligrams of vancomycin."

With this one exception, the proposed monographs are satisfactory.

In accord with a request received from Dr. Alan E. Smith, we have included stability data on vancomycin ampoules after dilution.



5390

Samples of the 10 Gm. vial are being submitted to the National Center for Antibiotic Analysis.

Very truly yours,

ELI LILLY AND COMPANY

F. B. Peck, Jr., M.D.
Director, Medical Plans
and Regulatory Affairs

FBP:llg

Attachment

61-667

Form 6 #~~60-180~~

JUN 19 1972

AF 9-577
Eli Lilly and Company
Attention: F.B. Peck, Jr., M.D.
Indianapolis, Indiana 46206

Gentlemen:

Reference is made to your Form 6 amendment #60-180 Vancocin HCl for Oral Use Only (Vancomycin hydrochloride) dated October 8, 1971 and amended April 11, 1972.

The following phrase "equivalent to 10 gm. vancomycin" should be added to the front panel of the vial and carton labels immediately below "Vancomycin hydrochloride, U.S.P."

A copy of the revised certification monographs are enclosed. Please note the following changes:

1. In § 148s.2, the word "nonsterile" has been deleted in the heading and in the first sentence of paragraph (a)(1) to conform with U.S.P. nomenclature.

2. In § 148s.11:

a. In paragraph (a)(1), the terminal phrase "packaged in a suitable dispensing container" was added to the first sentence and the sentence pertaining to reconstitution has been deleted.

b. In paragraph (a)(3)(ii(b), the number of immediate containers required on the batch was reduced from "12" to "6".

c. In paragraph (b)(1), the sample preparation for the potency assay was revised. This is subject to change pending the report from our laboratories.

You should point out to U.S.P. that with the addition of the nonsterile bulk, vancomycin hydrochloride monograph, to the antibiotic regulations, their monograph of the same name no longer conforms to the sterile bulk and a change is required in the "Usual dose" section. Also, the "Category and Dose" section of their "Sterile vancomycin hydrochloride will need revision.

cc: Orig. Form 6 (BD-145)
Dup. Form 6 (BD-145) BD-100
BD-140 BD-106 BD-242 BD-1
BD-401 BD-430 CA-226
JEckert/BD-140/6/16/72
yy/typed final: 6/16/72
R/D init.: RNorton 6/16/72

Enclosure

Sincerely yours,

MLG

Merle L. Gibson, M.D., Director
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs

To Lilly 6-19-72

§ 148s.11 Vancomycin hydrochloride for oral solution.

(a) Requirements for certification --- (1) Standards of identity, strength, quality, and purity. Vancomycin hydrochloride for oral solution is vancomycin hydrochloride packaged in a suitable dispensing container. Its potency is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of [redacted] grams of vancomycin that it is represented to contain. Its moisture content is not more than 5 percent. Its pH in an aqueous solution containing 50 milligrams per milliliter is not less than 2.5 and not more than 4.5. The vancomycin hydrochloride used conforms to the standards prescribed by § 148s.2(a)(1).

(2) Labeling. It shall be labeled in accordance with the requirements of § 148.3 of this chapter.

(3) Requests for certification; samples. In addition to complying with the requirements of § 146.2 of this chapter, each such request shall oontain:

(i) Results of tests and assays on:

(a) The vancomycin hydrochloride used in making the batch for potency, safety, moisture, pH, factor A content, and identity.

(b) The batch for potency, moisture, and pH.

(ii) Samples required:

(a) The vancomycin hydrochloride used in making the batch: 12 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of 6 immediate containers.

(b) Tests and methods of assay (1) Potency. Proceed as directed in § 141.110 of this chapter, preparing the sample for assay as follows: Empty the contents into an appropriate-sized ~~volumetric~~ flask and dilute to volume with sterile distilled water. Further dilute an aliquot with 0.1M potassium phosphate buffer, pH 4.5 (solution 4), to the reference concentration of 10 micrograms of vancomycin per milliliter (estimated).

(2) Moisture. Proceed as directed in § 141.502 of this chapter.

(3) pH. Proceed as directed in § 141.503 of this chapter, using a solution containing 50 milligrams per milliliter.

A-6
POR-EAS.

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

PERSONALLY SUBMITTED BY
Gerald D. Kantorow
Read by B Owens
7-14-72

July 12, 1972

Section 148s.11
No. 60-180

Date Approved 7-25-72

Account No.

Signed Albert Smith M.D. Dep. Dir. BD/KO
For the Commissioner of Food and Drugs
Department of Health, Education and Welfare

Department of H.E.W.
Food and Drug Administration
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride

We are submitting in triplicate vial and carton labels revised in accord with Dr. Merle L. Gibson's letter of June 19, 1972.

We have reviewed the revised certification monographs and find that they are acceptable.

In regard to the last paragraph in Dr. Gibson's letter, the appropriate individual in our company will advise the U.S.P. of the necessary changes in their vancomycin hydrochloride monograph.

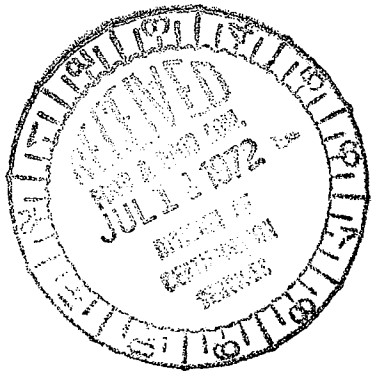
Very truly yours,

ELI LILLY AND COMPANY

F. B. Peck, Jr., M.D.
Director, Medical Plans
and Regulatory Affairs

FBP:llg

Attachments: XU 5992 AMX
SG 5302 AMS



6864

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

July 24, 1972

Our reference:
Form 6 ~~#60-180~~ 61-667.

AF 9-577

Eli Lilly and Company
Attention: F. B. Peck, Jr., M.D.
Indianapolis, Indiana 46206

Gentlemen:

We acknowledge receipt of your submission dated July 12, 1972 for Form 6 #60-180 Vancocin HCl for Oral Use Only (Vancomycin hydrochloride).

The information and labeling specimens submitted are satisfactory. An approved copy of the Form 6 application is being returned for your files.

Under authority of section 507(a) of the Act, the National Center for Antibiotics Analysis may now accept samples of this drug with a view to release of batches complying with the standards of the enclosed monograph. After the applicable regulation has been published in the FEDERAL REGISTER, samples may be submitted for certification.

We have no objection to your use of an expiration period of 36 months for the dry powder and one week for the reconstituted drug when stored under refrigeration.

Sincerely yours,

Merle L. Gibson, M.D., Director
Division of Anti-Infective Drug Products
Office of Scientific Evaluation
Bureau of Drugs

cc: DET-DO
BD-145
BD-145/OD
BD-140
BD-430/lab.
J.Eckert BD-140
MLGibson: Enclosure
hb

August 15, 1972

Our reference:
61-667

Eli Lilly and Company
Attention: F. B. Peck Jr., M.D.
Medical Plans and Regulatory Affairs
Indianapolis, Indiana 46206

Gentlemen:

This is in reference to your Form 6 for Vancocin (Vancomycin Hydrochloride) For Oral Use.

Please continue to use #60-180 as reference number for Vancomycin Hydrochloride Intravenous. We have assigned #61-667 to Vancocin For Oral Use. This number should be used on all future correspondence pertaining to this drug.

Sincerely yours,

William E. Magner
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products

cc:
BD-145
BD-145/OD
BD-430/lab.
WEMagner:hb

A-6
Eisler

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

June 13, 1973

Section 148s.11
No. 61-667

Date Approved 6/22/73

Account No.

Signed John L. Harrison
For The Commissioner of Food and Drugs
Department of Health, Education and Welfare

Department of H.E.W.
Food and Drug Administration
Division of Anti-Infective Drug
Products
Certification Services Branch
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use
Only M-206, Vancomycin Hydrochloride, U.S.P.

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachments

RECEIVED JUN 15 1973 BUREAU OF DRUGS

RECEIVED FOOD & DRUG ADM JUN 2 3 1973

9527

June 22, 1973

Our reference:
61-667 (148s.11)

Lee G. Cromwell
Regulatory Affairs Associate
Eli Lilly and Company
Indianapolis, Indiana 46206

Dear Mr. Cromwell:

This will acknowledge receipt of your letter of June 13, 1973, with which you provided stability data for Vancomycin Hydrochloride, U.S.P. for Oral Use Only.

The data appear to be satisfactory and will be added to the file for this product.

At the next time data point, in addition to running the base assay following reconstitution, the product should be assayed again following refrigeration storage for seven days.

A signed copy of your June 13, 1973 submission is enclosed.

Sincerely yours,

Milton Eisler
Certifiable Drug Review Staff (BD-145)
Division of Anti-Infective Drug Products

Enclosure

cc: DET-DO

BD-145
BD-145/OD
BD-430/lab.
MEisler:hb

(1)

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

October 3, 1973

[redacted] Approved 10/11/73

Applicant No. [redacted]

Signed John O. Haines
For The Commissioner of Food and Drugs
Department of Health, Education and Welfare

Section 148s.11
No. 61-667

Department of H.E.W.
Food and Drug Administration
Division of Anti-Infective Drug Products
Certification Services Branch
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206, Vancomycin Hydrochloride, U.S.P.

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment

RECEIVED
FOOD & DRUG ADM.
OCT 10 1973
DIVISION OF
CERTIFICATION
SERVICES

1651

A-6

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

March 28, 1974

Date Approved 4/5/74

Section 148s.11
No. 61-667

Account No.

Signed John D Harrison
For the Commissioner of Food and Drugs
Department of Health, Education and Welfare

Department of H.E.W.
Food and Drug Administration
Division of Anti-Infective Drug Products
Certification Services Branch
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206, Vancomycin Hydrochloride, U.S.P.

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment

RECEIVED FOOD & DRUG ADM. APR 3 1974 DIVISION OF CERTIFICATION SERVICES

RECEIVED APR2 1974 BUREAU OF DRUGS

4225

6-A

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

June 13, 1974

Section 455.185
No. 61-667

Department of H.E.W.
Food and Drug Administration
Certifiable Drug Review Staff
(HFD-145)
Division of Anti-Infective Drug
Products
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use
Only M-206, Vancomycin Hydrochloride, U.S.P.

We are submitting in triplicate a proposed amendment to Regulation 148s.11 (455.185) to provide for a new upper potency limit of [redacted] (b) (4) percent for the above product.

Accordingly, the new potency limit in the regulation will read as follows:

> Its potency is satisfactory if it is not less than 90 percent and not more than [redacted] (b) (4) percent of the number of grams of vancomycin that it is represented to contain.

This change is in keeping with the limits established for some other oral antibiotics.

We would appreciate an approved copy returned for our files at your earliest convenience.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

5484

Sold
Rejection letter
issued / copy
w/B Sorenson

THE LILLY RESEARCH LABORATORIES

ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

August 12, 1974

Mr. Bernard Arret
Mr. W. T. Robinson

This is your unofficial desk copy. Please destroy when review is completed.

L.G.C.

Section 455.185
No. 61-667

Department of H.E.W.
Food and Drug Administration
Certifiable Drug Review Staff
(HFD-145)
Division of Anti-Infective Drug
Products
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use
Only M-206, Vancomycin Hydrochloride, U.S.P.

In accordance with a discussion on July 29, 1974, between Mr. W. T. Robinson and our Dr. (b) (6) and Mr. (b) (6), we are submitting in triplicate revised labeling for the above product. The revision in this labeling is in the preparation where the contents of the vial are reconstituted in distilled or deionized water containing 115 ml. rather than the previous amount which was 110 ml.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachments: YB 1191 AMX
SG 5303 AMS
PA 6515 AMP

A6
Powers

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

August 12, 1974

Date Approved 11/6/74

Accession No.

Signed

For the Secretary of Health, Education and Welfare

Section 455.185
No. 61-667

Department of H.E.W.
Food and Drug Administration
Certifiable Drug Review Staff
(HFD-145)
Division of Anti-Infective Drug
Products
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use
Only M-206, Vancomycin Hydrochloride, U.S.P.

In accordance with a discussion on July 29, 1974, between Mr. W. T. Robinson and our Dr. (b) (6) and Mr. (b) (6), we are submitting in triplicate revised labeling for the above product. The revision in this labeling is in the preparation where the contents of the vial are reconstituted in distilled or deionized water containing 115 ml. rather than the previous amount which was 110 ml.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachments: YB 1191 AMX
SG 5303 AMS
PA 6515 AMP

6288

AUG 14 1974

Personally submitted by G Flora 12-20-74 Carl Chap

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

December 18, 1974

Section 455.185
No. 61-667

Date Approved 12/23/74

Account No.

Signed [signature]
For the [illegible]
Department of Health, Education and Welfare

Department of H.E.W.
Food and Drug Administration
Certifiable Drug Review Staff
(HFD-145)
Division of Anti-Infective Drug Products
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206, Vancomycin Hydrochloride, U.S.P.

We are submitting in triplicate a revised package insert for use with the above preparation. The subsection "Children" under "DOSAGE AND ADMINISTRATION" has been changed to read as follows: "The total daily dose is 20 mg. per pound of body weight in divided doses."

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment: PA 6516 AMP

RECEIVED
DEC 20 1974
BUREAU OF DRUGS

RECEIVED
DEC 20 1974

8320

Gen Robinson

ELI LILLY AND COMPANY

INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

December 18, 1974

Revised insert appr'd no reply needed - JRR 12/31/74

Mr. William T. Robinson, Chief
Certification Services Branch [HFD-332]
Division of Drug Product Quality
5600 Fishers Lane
Rockville, Maryland 20852

Dear Mr. Robinson:

Per our telephone conversation, I am reporting the steps we have taken in correcting a typographical error in our package insert literature for M-206 VANCOCIN®, vancomycin hydrochloride, U.S.P., 10 Gm. for Oral Use.

The error consisted of a misprint in the Dosage and Administration of the insert. The Children line reads "The total daily dose is 200 mg. per pound of body weight in divided doses". The correct dosage is 20 mg. This insert was submitted for F.D.A. approval on August 12, 1974, and approved on November 6. A copy of the erroneous portion of the insert is enclosed.

The incorrect insert was used on only one batch of M-206, VANCOCIN®, bearing batch number 8JF62. This batch was certified on December 6, 1974, under F.D.A. number VA7809H. Of the (b)(4) vials listed on the Form 7, (b)(4) were finished for marketing. Investigation revealed that (b)(4) of these vials were still in house, (b)(4) had been shipped to the (b)(4) Hospital in (b)(4), 2 vials sent to the (b)(4) Hospital in (b)(4), (b)(4) and 1 vial to the (b)(4) Hospital in (b)(4). By physical count, the (b)(4) shipment was still intact and was impounded. A Lilly representative is being sent to (b)(4) tomorrow to replace the inserts with corrected ones. One of the two vials sent to (b)(4) had been used at a dose of 500 mg. 3 times per day on a 41-year old female patient and the second was being administered to the same patient. This dosage is in accordance with the recommended dose for adults. The one vial shipped to (b)(4) has not arrived yet. A Lilly representative will correct this insert when it arrives.

New package insert literature has been printed which bears the correct children's dosage. It will be used to replace the incorrect insert and all of the erroneous material will be accounted for and destroyed. A copy of the correct insert will be submitted for your files.

Very truly yours,

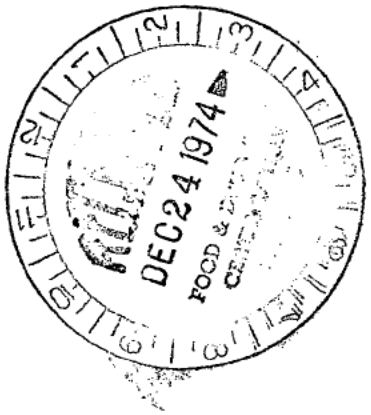
8348

ELI LILLY AND COMPANY

R. B. Bourne, Manager
Receiving and Distribution
Quality Control

RBB:nkh

Enclosure



21-667

(1)

Powers

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

June 10, 1975

(For use of Food and Drug Administration)
Date approved 6/16/75
Account No.
Signed [signature]
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20852

OK to signout
[signature] 6/16/75

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride, USP

We are submitting in triplicate a revised package insert for use with the above preparation. The following sentence has been added to the section on "WARNINGS": "Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, and tobramycin, should be avoided." The generic title in this insert has been changed to conform with the new USP XIX.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment: PA 6517 AMP

11084

RECEIVED JUN 13 1975 FOOD & DRUG ADMIN. CERTIFICATION SERVICES

(1)

A-6

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

September 22, 1975

(For use of Food and Drug Administration)
Date approved 9/29/75
Account No.
Signed M. D. Harmon
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate a revised package insert for use with the above preparation. The generic title in this insert has been changed to conform with the new NF XIX.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee L. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment: PA 6518 AMP

RECEIVED
SEP 26 1975
FOOD AND DRUG ADM.
CERTIFICATION
SERVICES

(1)

A-6
~~Powers~~

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 636-2211

October 21, 1975

ok to sign out
GDP 10/24/75

Section 455.185
No. 61-667

(For use of Food and Drug Administration)
Date approved 10/24/75
Account No.
Signed John D. Thomson
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate a revised bottle label for use with the above preparation. The generic title on this label has been changed to conform with the new NF XIV.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY 00963

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment: YB 1192 AMX

RECEIVED
OCT 24 1975
FOOD & DRUG ADM.
CERTIFICATION
SERVICES

OK MLL 12/3/75 H-6 ~~Eisler~~

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

December 1, 1975

Date Approved 12/3/75

Account No.

Signed
For The Commissioner of Food and Drugs
Department of Health, Education and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

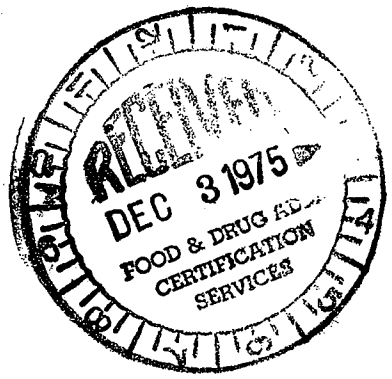
Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment

01666



OK NLA 12/17/76 N-6

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

December 13, 1976

Section 455.185
No. 61-667

Date Approved 12/17/76

Account No.

Signed John D. Harrison

For The Commissioner of Food and Drugs
Department of Health, Education and Welfare

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20852

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment

C07208

H-6
Powers

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

March 31, 1977

Section 455.185
No. 61-667

Date Approved 4/5/77

Account No.

Signed John D. Harris
For the Commissioner of Food and Drugs
Department of Health, Education and Welfare

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate a revised package insert for use with the above preparation. The "HOW SUPPLIED" section has been changed to a tabular form for clarification.

We would appreciate an approved copy returned for our files.

Very truly yours,

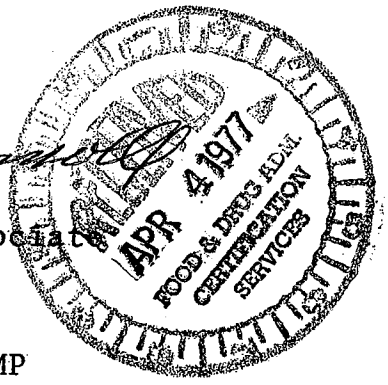
ELI LILLY AND COMPANY

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

LGC:11g

Attachment: PA 6519 AMP



008691

(1)

A-6
~~Product~~ S

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

August 25, 1977

(For use of Food and Drug Administration)
Date approved 8/30/77
Accession No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health Education, and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

OK to signout
DBP 8/30/77

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate a revised carton for use with the above preparation. The generic title has been changed to conform with the NF XIV, and the following storage statement has been added: "Prior to Reconstitution: Store at Controlled Room Temperature 59° to 86°F. (15° to 30°C.)."

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

010530

Lee G. Cromwell

Lee G. Cromwell
Regulatory Affairs Associate

RECEIVED
AUG 29 1977
FOOD & DRUG

LGC:llg

Attachment: SJ 3030 AMS

OK mg 10/11/77 A-6 Eisler

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

October 4, 1977

Date Approved 10/11/77

Account No.

Signed
For The Commissioner of Food and Drugs
Department of Health, Education and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell 000071

Lee G. Cromwell
Regulatory Affairs Associate

LGC:11g

Attachment

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: FORM 6 – #61-667

DATE APPROVAL LETTER ISSUED: 10/11/77

TO: Press Relations Staff (HFI-40)

FROM: ☐ Bureau of Drugs ☐ Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: ☐ ORIGINAL NDA ☐ SUPPLEMENT TO NDA ☐ ABBREVIATED ORIGINAL NDA ☐ SUPPLEMENT TO ANDA

CATEGORY: ☐ HUMAN ☐ VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

VANCOCIN HCl FOR ORAL USE ONLY; VANCOMYCIN HYDROCHLORIDE

DOSAGE FORM: POWDER FOR ORAL SOLUTION

HOW DISPENSED: ☑ RX ☐ OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

VANCOMYCIN HYDROCHLORIDE
10 GRAMS/CONTAINER

NAME OF APPLICANT *(Include City and State)*

LILLY RESEARCH LABORATORIES
INDIANAPOLIS, INDIANA

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

ANTIBACTERIAL (ANTIBIOTIC)

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

ADDITIONAL STABILITY DATA

FORM PREPARED BY

NAME: [signature]

DATE: Oct. 11, 1977

FORM APPROVED BY

NAME: John R. Darrow

DATE: 10/11/77

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

(1)

A-6

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

January 10, 1978

OK to sign and DSP 1/13/78

(For use of Food and Drug Administration)
Date approved 1/13/78
Control No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate a revised bottle label for use with the above preparation. The following storage statement has been added to this label: "Prior to Reconstitution: Store at Controlled Room Temperature 59° to 86°F. (15° to 30°C.)."

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

Lee G. Cromwell
Regulatory Affairs Associate

LGC:llg

Attachment: YB 1193 AMX

001107

RECEIVED
JAN 12 1978
Documentation Services

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 61-667

DATE APPROVAL LETTER ISSUED: 1/13/78

TO: Press Relations Staff (HFI-40)

FROM:
- [x] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [ ] ORIGINAL NDA
- [x] SUPPLEMENT TO ~~NDA~~ FORM 6
- [ ] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [x] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

VANCOMYCIN HYDRO CHLORIDE

DOSAGE FORM: FOR ORAL SOLUTION

HOW DISPENSED
- [x] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

VANCOMYCIN HCl - 10grams/vial

NAME OF APPLICANT *(Include City and State)*

ELI LILLY + CO.
INDIANAPOLIS, IND.

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

ANTIBACTERIAL

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

REVISED LABEL

FORM PREPARED BY

NAME: J. David Powers — DATE: 1/13/78

FORM APPROVED BY

NAME: John D. Harris — DATE: 1/13/78

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

(1)

H6

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 261-2000

December 3, 1979

(For use of Food and Drug Administration)
Date Approved 12/10/79
Account No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section ~~455~~.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

OK to sign out
12/10/79

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate a revised carton for use with the above preparation. The words "After Reconstitution" have been added preceding the following storage statement: "The solution should be refrigerated and used within one week."

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows
Regulatory Affairs Associate

EAB:11g

Attachment: SJ 3031 AMS

FDA/BD/HFD-535
DEC 5 2 58 PM '79
RECEIVED

011089

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

January 16, 1980

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution
M-206, Vancomycin Hydrochloride For Oral Solution, NF

We are submitting in triplicate an amendment to the above Form 6 to provide for an additional indication. We feel that the clinical data included in this amendment will support the expansion of claims to include the use of VANCOCIN HCl in the treatment of antibiotic-associated pseudomembranous colitis caused by Clostridium difficile.

In addition, the third paragraph under "WARNINGS" in the package insert has been revised to include "amikacin."

Minor editorial changes also have been made in this insert.

After you have had an opportunity to review this submission and we have received your comments, we will submit twelve copies of the package insert in final printed form for approval.

Very truly yours,

ELI LILLY AND COMPANY

F. B. Peck, Jr., M.D.
Director
Regulatory Affairs

FBP:llg

Attachment

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 1/21/80
FROM: Certifiable Drug Review Staff (HFD-535)		OFFICE
TO: Dr. Theresa G. Reed (HFD-145)		DIVISION
SUBJECT: Eli Lilly & Company - Vancomycin HCl for Oral Solution		

SUMMARY

Form 6# 61-667

Labeling supplement 1/16/80

The submitted information makes approvable to amend the previously approved package insert for VANCOCIN (oral) by adding a recommendation for using vancomycin HCl for treating antibiotic - associated pseudomembranous colitis caused by Clostridium difficile. Certain other minor editorial changes are also proposed.

All proposed labeling changes approvable in light of information received?

SIGNATURE John D. Harrison (HFD-535)

DOCUMENT NUMBER 011549

FORM FDH-2034 (11/66)

NDA-537

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

April 4, 1980

Our reference:
60-180
61-667

NOTE orig. submission dated 9/16/80 not rec'd back by FDA 4/9/80

F. B. Peck, Jr., M.D.
Director
Regulatory Affairs
Eli Lilly and Company
Indianapolis, Indiana 46206

Dear Dr. Peck:

Reference is made to your Form 6 amendments of February 16, 1980 for Vancocin (vancomycin) HCl dosage forms wherein an additional indication was proposed- the parenteral form administered orally for treatment of pseudomembranous colitis produced by Clostridium difficile. Medical staff in the Division of Anti-fective Drug Products has reviewed the clinical data and medical literature submitted in support of the proposal and finds the additional indication to be approvable.

However, before the amendments can be approved, the wording in the "Indications" and "Dosage and Administration" sections should be revised to appear as recommended in the reviewing medical officers "Recommendations" which follow:

Recommendations:

1. Under the "Indications" section of 60-180 and 61-667, the addition of "and pseudomembranous colitis produced by Clostridium difficile." should be changed to read: "and antibiotic associated pseudomembranous colitis produced by Clostridium difficile."

2. It is recommended that the following claim in the "For Oral Administration" section of "Dosage and Administration" of 60-180 and in "Dosage and Administration.....Adults" of 61-667:

   "The usual adult dosage for pseudomembranous colitis produced by C. difficile is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days."

   be modified to read:

   "The usual adult dosage for antibiotic associated pseudomembranous colitis produced by C. difficile is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days."

2- Dr. F. B. Peck, Jr., M.D.

60-180
61-667

3. The inclusion of [redacted] (b) (4) under Actions should not be approved. The sponsor has only submitted data to substantiate the inclusion of Clostridium difficile. The inclusion of Clostridium difficile in the Actions section is found approvable.

4. All other suggested changes in labeling for 60-180 and 61-667 are found to be acceptable.

When the package inserts are revised as indicated above and in final printed form, please submit twelve copies of each for approval of the amendments.

Sincerely yours,

I. David Powers

I. David Powers
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs

cc:
HFD-535
HFD-535/OD
HFD-430/lab.
HFD-140/Dr.Stanley
IDPowers:hb

(1)

A6

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 261-2000

OK pigment
DF 5/28/80

May 23, 1980

(For use of Food and Drug Administration)
Date Approved 5/28/80
Account No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section ~~455~~.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution
M-206, Vancomycin Hydrochloride For Oral Solution, USP

We are submitting in triplicate a revised bottle label for use with the above preparation. The generic title has been changed to conform with USP XX which will become official on July 1, 1980. The zip code has been changed from "46206" to "46285," and "10 Gm." has been changed to "10 g." Minor editorial changes also have been made in the copy.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:11g

Attachment: YB 1194 AMX

FDA/BD/HFD-535
MAY 27 2 11 PM '80
RECEIVED

013457

(1)

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 261-2000

(For use of Food and Drug Administration)
Date Approved 6/20/80
Account No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

June 17, 1980

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

OK & signature
6/20/80

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution
M-206, Vancomycin Hydrochloride For Oral Solution, USP

We are submitting in triplicate a revised carton for use with the above preparation. The generic title has been changed to conform with USP XX which will become official on July 1, 1980. The zip code has been changed from "46206" to "46285" in the signature, and "10 Gm." has been changed to "10 g." Minor editorial changes also have been made in the copy.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:11g

Attachment: SJ 3032 AMS

RECEIVED
JUN 19 11 00 AM
FDA/BB/HFD-95

013772

(1)

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE (317) 261-2000

June 18, 1980

(For use of Food and Drug Administration)
Date Approved 6/24/80
Account No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section 455.285a
No. 60-180

Mr. I. David Powers
Food and Drug Administration
Certifiable Drug Review Staff
(HFD-535)
Division of Generic Drug
Monographs
Bureau of Drugs
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Powers:

Re: Form 6 Amendment, VANCOCIN® HCl Vials No. 657,
Sterile Vancomycin Hydrochloride, USP

In accordance with your letter dated April 4, 1980, we are submitting in final printed form twelve copies of a revised package insert to include a new claim, i.e., "antibiotic-associated pseudomembranous colitis produced by Clostridium difficile."

As requested in your letter, the following additional changes have been made in this insert:

1. Under the section on "ACTIONS," "[redacted] (b) (4)," has been changed to "Clostridium difficile."

2. In the subsection "For Oral Administration" under "DOSAGE AND ADMINISTRATION," the second sentence has been changed to read as follows: "The usual adult dosage for antibiotic-associated pseudomembranous colitis produced by C. difficile is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days."

In addition, the title "AMPOULES (VIALS)" has been changed to "VIALS," and minor editorial changes have been made in this insert.

RECEIVED
JUN 23 3 25 PM '80
FDA/BD/HFD-535

013837

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:11g

Attachment: PA 1714 AMP

VIALS

VANCOCIN® HCl

STERILE VANCOMYCIN HYDROCHLORIDE, USP

INTRAVENOUS

DESCRIPTION

Vancocin® HCl (Sterile Vancomycin Hydrochloride, USP, Lilly), IntraVenous, is a glycopeptide antibiotic derived from *Streptomyces orientalis* which is bactericidal against many gram-positive bacteria. It should be administered intravenously, in dilute solution (*see* Dosage and Administration).

ACTIONS

Vancocin HCl is poorly absorbed by mouth, but an intravenous dose of 1 g produces serum levels averaging 25 mcg/ml at 2 hours. Its half-life in the circulation is about 6 hours. Many strains of streptococci, staphylococci, *Clostridium difficile*, and other gram-positive bacteria are susceptible in vitro to concentrations of 0.5 to 5 mcg/ml. Staphylococci are generally susceptible to less than 5 mcg of Vancocin HCl per ml, but a small proportion of *Staphylococcus aureus* strains require 10 or 20 mcg/ml for inhibition. If the Bauer-Kirby method of disc susceptibility testing is used, a 30-mcg disc of Vancocin HCl should produce a zone of more than 11 mm when tested against a vancomycin-susceptible bacterial strain.

Clinically effective concentrations of this antibiotic in the blood are usually achieved and maintained by its intravenous administration; moreover, inhibitory concentrations can be demonstrated in pleural, pericardial, ascitic, and synovial fluids and in urine. This antibiotic does not readily diffuse across normal meninges into the spinal fluid. However, when the meninges are inflamed as a result of infection, Vancocin HCl penetrates into the spinal fluid.

About 80% of injected Vancocin HCl is excreted by the kidneys. Concentrations are high in the urine. Impairment of renal function results in delayed excretion and in high blood levels associated with an increase in drug toxicity.

INDICATIONS

Vancocin HCl is indicated in potentially life-threatening infections which cannot be treated with another effective, less toxic antimicrobial drug, including the penicillins and cephalosporins.

Vancocin HCl is useful in therapy of severe staphylococcal* infections in patients who cannot receive or who have failed to respond to the penicillins and cephalosporins or who have infections with staphylococci that are resistant to other antibiotics, including methicillin.

Vancocin HCl has been used successfully alone in the treatment of staphylococcal* endocarditis. Its effectiveness has been documented in other infections due to staphylococci,* including osteomyelitis, pneumonia, septicemia, and soft-tissue infections. When staphylcoccal infec-

*Including methicillin-resistant staphylococci.

tions are localized and purulent, antibiotics are used as adjuncts to appropriate surgical measures.

The parenteral form may be administered orally for treatment of staphylococcal enterocolitis and antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Parenteral antibiotic administration may be used concomitantly. Vancomycin is *not* effective by the oral route for other types of infection.

CONTRAINDICATION

Vancocin HCl is contraindicated in patients with known hypersensitivity to this antibiotic.

WARNINGS

Because of its ototoxicity and nephrotoxicity, Vancocin HCl should be used with care in patients with renal insufficiency. The risk of toxicity is appreciably increased by high blood concentrations or prolonged therapy. If it is necessary to use Vancocin HCl in such patients, doses of less than 2 g/day usually will provide satisfactory blood levels.

Vancocin HCl should be avoided in patients with previous hearing loss. If it is used in such patients, the dose of Vancocin HCl should be regulated, if possible, by periodic determination of the drug level in the blood. Deafness may be preceded by tinnitus. The elderly are more susceptible to auditory damage. Experience with other antibiotics suggests that deafness may be progressive despite cessation of treatment.

Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly streptomycin, neomycin, kanamycin, gentamicin, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, tobramycin, and amikacin, requires careful monitoring.

PRECAUTIONS

Patients with borderline renal function and individuals over the age of 60 should be given serial tests of auditory function and of vancomycin blood levels.* All patients receiving the drug should have periodic hematologic studies, urinalyses, and liver and renal function tests.

Vancocin HCl is very irritating to tissue and causes necrosis when injected intramuscularly; it must be administered intravenously. Pain and thrombophlebitis occur in many patients receiving Vancocin HCl and are occasionally severe. The frequency and severity of thrombophlebitis can be minimized if the drug is administered in a volume of at least 200 ml of glucose or saline solution and if the sites of injection are rotated.

ADVERSE REACTIONS

Nausea, chills, fever, urticaria, and macular rashes have been associated with the administration of Vancocin HCl. It may also produce eosinophilia and anaphylactoid reactions.

*Vancomycin serum levels may be determined by use of the modified Rammelkamp serial twofold-dilution technique with streptococcus C203 as the indicator organism.

VANCOCIN® HCl (vancomycin hydrochloride, Lilly)

The use of Vancocin HCl may result in overgrowth of nonsusceptible organisms. If new infections due to bacteria or fungi appear during therapy with this product, appropriate measures should be taken.

DOSAGE AND ADMINISTRATION

Adults—The usual intravenous dose is 500 mg (in 0.9% Sodium Chloride Injection or 5% glucose in Sterile Water for Injection) every 6 hours or 1 g every 12 hours. The majority of patients with infections caused by organisms susceptible to the antibiotic show a therapeutic response by 48 to 72 hours. The total duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In staphylococcal endocarditis, therapy for 3 weeks or longer is recommended.

Children—The total daily dosage of Vancocin HCl, calculated on the basis of 20 mg per pound of body weight, can be divided and figured in with the child's 24-hour requirement of fluid.

PREPARATION OF SOLUTION:

At the time of use, add 10 ml of Sterile Water for Injection to the vial of dry, sterile Vancocin HCl powder.

FURTHER DILUTION IS REQUIRED. READ INSTRUCTIONS WHICH FOLLOW:

1. Intermittent Infusion (the preferred method of administration)
   The above solution (containing 500 mg Vancocin HCl) can be added to 100-200 ml of 0.9% Sodium Chloride Injection or 5% glucose in Sterile Water for Injection. This intravenous infusion may be given over a period of 20 to 30 minutes every 6 hours.
2. Continuous Infusion (should be used only when intermittent infusion is not feasible).
   Two to 4 vials of the above (1 to 2 g) can be added to a sufficiently large volume of 0.9% Sodium Chloride Injection or 5% glucose in Sterile Water for Injection to permit the desired daily dose to be administered slowly by intravenous drip over a 24-hour period.

For Oral Administration—The contents of 1 vial (500 mg) may be diluted in 1 ounce of water and given to the patient to drink, or the diluted material may be administered via nasogastric tube. The usual adult dosage for antibiotic-associated pseudomembranous colitis produced by *C. difficile* is 500 mg of vancomycin orally every 6 hours for a period of 7 to 10 days. For convenience of oral administration, Vancocin HCl is also available in a screw-cap container (No. M-206).

STABILITY OF PREPARED SOLUTION

After reconstitution, the solution may be stored in a refrigerator for 96 hours without significant loss of potency.

HOW SUPPLIED

Vials, equivalent to 500 mg vancomycin, 10-ml size (No. 657)—1
Also available:
For Oral Solution, equivalent to 10 g vancomycin (No. M-206)—1

Literature revised April 17, 1980

PRINTED IN U.S.A

ELI LILLY AND COMPANY • Indianapolis, IN 46285, U.S.A.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

June 25, 1980

Our reference:
60-180
61-677

E. A. Burrows
Regulatory Affairs Associate
ELI LILLY AND COMPANY
Indianapolis, Indiana 46206

Dear Mr. Burrows:

The package inserts submitted in final printed form with your letters of June 18, 1980 for Vancocin HCl vials (sterile vancomycin hydrochloride) and Vancocin HCl (vancomycin hydrochloride) for Oral Solution are satisfactory. Approved copies are enclosed for your records.

Approval of these inserts constitutes approval of your Form 6 amendments of February 16, 1980 to provide for an additional indication for these drugs - oral administration to treat antibiotic-associated pseudomenbranous colitis produced by Clostridium difficile.

Sincerely yours,

I. David Powers
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs

Enclosures (2)

cc:
HFD-535
HFD-535/OD
HFD-430/lab.
IDPowers:hb

1

A6
E

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

(For use of Food and Drug Administration)
Date Approved 2/11/81
Account No.
Signed John D. Harrison
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

February 4, 1981

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206, Vancomycin Hydrochloride For Oral Solution, USP

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:gw

Attachment

FDA/BD/HFD-535
FEB 9 5 33 PM '81
RECEIVED

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

ok to sign out Dan 5/29/81

A-6 magnum

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

April 20, 1981

For use of Food and Drug Administration
Date Approved 5/29/81
Signed John O Harrison
For the Commissioner of Food & Drugs
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution M-206, Vancomycin Hydrochloride For Oral Solution, USP

We are submitting herewith an amendment which provides for the production of M-206 Vancomycin Hydrochloride for Oral Solution, USP at our new small-volume parenteral manufacturing facility (Building 105) in Indianapolis, Indiana. This application is representative of the continuing program to shift production of many of Lilly's small-volume parenterals from their present production areas to new and improved production areas within Building 105. Other submissions providing for the production of other Lilly products in Building 105 are currently being submitted or will be submitted to the Agency in the coming months.

Reference is made to previous correspondence (see attached) between Lilly and FDA relative to Building 105 and to FDA's expressed interest in providing expeditious review of submissions covering the new facility.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:ek

Attachment

FDA/BD/HFD-535
APR 22 3 09 PM '81
RECEIVED

002205

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date April 24, 1981

From Certifiable Drug Review Staff, HFD-535

Subject Requester's Name: William E. Magner Phone: 34340
ESTABLISHMENT EVALUATION REQUEST

To Division of Drug Manufacturing, HFD-320

NDA, ANDA, AND SUPPLEMENT NUMBER: 61-667
DRUG TRADE MARK (if any): Vancocin
DRUG NONPROPRIETARY NAME: Vancomycin hydrochoride for oral solution
DOSAGE FORM AND STRENGTH(s) 10 gram
DRUG CLASSIFICATION: N/A A or B IC Other: Liq PROFILE CLASS CODE
(Priority)
APPLICANT'S NAME: Lilly Research Laboratories
ADDRESS: Indianapolis, Indiana

FACILITIES TO BE EVALUATED: (Name, Full Address, DMF# (if any), and Responsibility):

Lilly Labs

Building 105

Comments: ( ) See attached
( ) Actual on-site inspection requested.

Reason: We need a GMP evaluation on the new facilities.

For HFD-320 USE ONLY:
Request Rec'd _____ Date Inspection Requested _____ Date
EIR Rec'd _____ Date Fwd _____ Date
Reviewing CSO _____ Approval _____ Non-approval _____

cc: HFD-535/OD
HFD-535
HFD-332

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date MAY 26, 1981

From Manufacturing Review Branch, HFD-322
Division of Drug Manufacturing

Subject APPROVABLE Form 6 61-667 VANCOMYCIN HCl FOR ORAL SOLN

To Director
Division of CERTIFIABLE DRUG REVIEW STAFF (HFD 535)
Drug Products
Attn: WILLIAM E. MAGNER

APPLICANT: LILLY RESEARCH LABS, INDIANAPOLIS, IN
MANUFACTURING;
ELI-LILLY AND CO, BUILDING 105, INDIANAPOLIS, IN

We have evaluated the operations of ELI-LILLY AND CO as they relate to compliance with Current Good Manufacturing Practice Regulations (21 CFR 211) with the exception of expiration dating (211.137) and stability testing (211.166) for the referenced application(s). Since you evaluate the applicants' submission of stability data and proposed expiration date, you should make the determination that the stability testing is adequate to support the proposed expiration date. If you desire, you can include appropriate references to (211.137) and (211.166) as deviations directly into your non-approvable letter if you conclude the stability testing is inadequate. Otherwise, we conclude there is no reason to withhold approval of the subject application(s) insofar as CGMP compliance of this/these firm(s) is concerned for the type of operations as specified in this/these pending application(s).

Our evaluation is based in part on Establishment Inspection and Quality Assurance Profile information.

Seymour Fishman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 10, 1981

Our reference:
61-667

E.A. Burrows
Regulatory Affairs Associate
LILLY RESEARCH LABORATORIES
307 East McCarty Street
Indianapolis, Indiana 46285

Dear Mr. Burrows:

This is in reference to the product labeling contained in your Antibiotic Form 6 for VANCOCIN HCl (vancomycin hydrochloride) FOR ORAL SOLUTION.

For treatment of antibiotic associated pseudomembranous colitis produced by Clostridium difficile we are recommending a dosage range rather than the current prescribed fixed dosage of 500 mg vancomycin orally every 6 hours. In the "Warnings" section of the labeling for antibiotic products known to precipitate antibiotic associated colitis we are adding recommendations for treating the adverse reaction with oral vancomycin.

The labeling for your company's "Vancocin HCl for Oral Solution" should be revised at the next printing to recommend the same dosage as follows:

> "The usual adult dose is 500 mg. to 2 grams of vancomycin orally per day in three to four divided doses administered for 7 to 10 days."

Enclosed is s copy of an article from the British Medical Journal (16 December 1978) which reported the efficacy of lower doses of oral vancomycin.

Sincerely yours,

John D. Harrison

John D. Harrison
Antibiotic Drug Review Branch (HFD-535)
Division of Generic Drug Monographs

Enclosure

cc:
HFD-535
HFD-535/OD
HFD-430/lab
JDHarrison:

A-6

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

December 15, 1981

For use of Food and Drug Administration
Date Approved 12/23/81
Account No.
Signed
For the Commissioner of Food and Drugs
Food and Drug Administration
Department of Health, Education, and Welfare

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206, Vancomycin Hydrochloride For Oral Solution, USP

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

005439

EAB:ek

Attachment

RECEIVED
DEC 21 9 46 AM '81
FDA/BD/HFD-535

A6
RJ

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

OK to sign out RJ 7/20/82

July 14, 1982

For use of Food and Drug Administration

Date Approved 7/20/82

Signed [signature]

For the Commissioner of Foods & Drugs

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Section 455.185
No. 61-667

Food and Drug Administration
Bureau of Drugs, HFD No. 535
Attention: Document Control
Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution
M-206, Vancomycin Hydrochloride For Oral Solution, USP

We are submitting in triplicate a revised label and carton for use with the above preparation. This labeling has been revised to reflect a change in the wording of the mixing instructions. In order to clarify this procedure the instructions have been changed to read:

"Mix the contents of this vial with distilled or deionized water (115 ml). Mix thoroughly to dissolve."

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

[signature]

007836

E. A. Burrows
Regulatory Affairs Associate

EAB:ek

Attachments: YC 8171 AMX
SJ 6811 AMS

S-001

H

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

For use of Food and Drug Administration

Date Approved 11/1/82

Signed John D. Harrison

For the Commissioner of Foods & Drugs

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

October 28, 1982

Section 455.185
No. 61-667

Food and Drug Administration
National Center for Drugs and Biologics
HFD-535, Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Solution M-206,
Vancomycin Hydrochloride For Oral Solution, USP

Reference is made to Mr. John D. Harrison's letter dated September 10, ~~1982~~ 1981 concerning labeling with respect to Vancomycin Hydrochloride For Oral Solution.

We are submitting a revised package insert for use with the above preparation which incorporates the following change in the DOSAGE AND ADMINISTRATION section, as requested by Mr. Harrison:

> "The usual adult dosage for antibiotic-associated pseudomembranous colitis produced by C. difficile is 500 mg to 2 g of vancomycin orally/day in 3 or 4 divided doses administered for 7 to 10 days."

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows
Regulatory Affairs Associate

EAB:ek

Attachment: PA 6512 AMP

FDA/BD/HFD-535
NOV 1 1 52 PM '82
RECEIVED

~~008989~~
008989

1

Lilly

S.002

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

For use of Food and Drug Administration

Date Approved 12/7/82

Signed John D Harrison

For the Commissioner of Foods & Drugs

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

December 1, 1982

Section 455.185
No. 61-667

Food and Drug Administration
National Center for Drugs and Biologics
HFD No. 535, Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206
Vancomycin Hydrochloride For Oral Solution, USP

We are submitting in triplicate additional stability data to further substantiate the dating period now given the above preparation.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:ek

Attachment

009285

RECEIVED
DEC 6 9 19 AM '82
FDA/BD/HFD-535

5.003 H

Lilly

Lilly Research Laboratories
A Division of Eli Lilly and Company

307 East McCarty Street
Indianapolis, Indiana 46285
(317) 261-2000

For use of Food and Drug Administration

Date Approved June 28, 1983

Signed [signature]

For the Commissioner of Foods & Drugs

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES

June 20, 1983

Section 455.185
No. 61-667

Food and Drug Administration
National Center for Drugs and Biologics (HFN-535)
Attention: Document Control Room No. 12B-20
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: Form 6 Amendment, VANCOCIN® HCl For Oral Use Only M-206
Vancomycin Hydrochloride For Oral Solution, USP

We are submitting an amendment to the above Form 6 to provide for an increased storage period for the reconstitued drug.

We would appreciate an approved copy returned for our files.

Very truly yours,

ELI LILLY AND COMPANY

E. A. Burrows

E. A. Burrows
Regulatory Affairs Associate

EAB:ek

Attachment

RECEIVED
JUN 27 1983

011578

Our reference:
61-667 (455.185)

June 28, 1983

Lilly Research Laboratories
Attn: E. A. Burrows
307 East McCarty Street
Indianapolis, Indiana 46285

Dear Mr. Burrows:

We have examined the data submitted with your letter of June 20, 1983, pertaining to your Vancomycin Hydrochloride for Oral Solution U.S.P., and providing for an increase in the storage period for the subject drug following reconstitution and refrigeration, from seven (7) days to fourteen (14) days.

The data appear to support your request. We therefore authorize that the discard statement on the subject drug be increased from seven (7) to fourteen (14) days following reconstitution and refrigeration.

When final printed satisfactory labeling submit becomes available, i.e., container cartons, package insert, as appropriate, 12 copies of each to this office.

A signed copy of your June 20, 1983, submission is enclosed for your files.

Sincerely yours,

Milton Eisler
Antibiotic Drug Review Branch (HFN-535)
Division of Generic Drug Monographs

Enclosures

cc:
HFN-535
HFN-535/OD
R/D MEisler
HFN-530 (Dr. Seife)
ft

mw

6/28/83

w7340B