CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 62-756 / S-015

***Name*:** Primaxin® ADD-Vantage®
(Imipenem-Cilastatin Sodium for Injection)

***Sponsor*:** Merck Research Laboratories

***Approval Date*:** August 31, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-015

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-015

APPROVAL LETTER

AADA 62-756/S-015

AUG 3 1 1992

Merck Sharp & Dohme Research Laboratories
Attn: Ronald A. Salerno, Ph.D.
Sumneytown Pike
West Point, PA 19486

Dear Sir:

Reference is made to your supplemental antibiotic drug application submitted pursuant to Section 314.70 of the Regulations, dated April 10, 1992, regarding your abbreviated antibiotic application for Primaxin® ADD-Vantage® (Imipenem-Cilastatin Sodium for Injection, MSD)

The supplemental application provides for use of ——— ——————— stopper as an alternate.

We have completed the review of this supplemental application and it is approved. Our letter of January 8, 1987 detailed the conditions relating to the approval of this abbreviated application.

It is recommended that you provide sterility and particulate data in addition to the usual stability parameters, preferrably at annual test stations, but at least at expiry (and at the end of the accelerated stability test period) in future stability reports. Note that the recommended accelerated conditions are as 40° C and 75% relative humidity.

The material submitted is being retained as part of your application.

Sincerely yours,

Robert A. Jemini for 8/28/92

Acting Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA # 62-756/S-015
DUP/Division File
HFD-600/RF
HFD-635/RF

Endorsements:
HFD-635/EDuffy/8-25-92 EDuffy 8/27/92
HFD-635/JHarrison/NSager for JDH 8/25/92 NSager 8/27/92
HFD-635/MAnderson/8/25/92 Mark Anderson 8/27/92
B:MSD15S62.756
B:62756S.015
F/T by mw/8/26/92
SUPPLEMENT APPROVAL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-015

CHEMISTRY REVIEW

AADA 62-756/S-015

NAME AND ADDRESS OF APPLICANT:

Merck Sharp & Dohme Research Laboratories
Attn: Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Liason
Sumneytown Pike
West Point, PA 19486

Contact:
Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Liason
(215) 834-2958
or
Kenneth R. Brown, M.D.
(215) 834-2552

PURPOSE OF AMENDMENT/SUPPLEMENT
The supplemental application provides for use ——— ——————— stopper as an alternate.

DATE OF SUBMISSION
April 10, 1992

PHARMACOLOGICAL CATEGORY
Antibiotic

TRADE NAME
Primaxin® I.V. ADD-Vantage®

NONPROPRIETARY NAME
Imipenem-Cilastatin Sodium

DOSAGE FORM
Powder for reconstitution

POTENCY
250, 500 mg

RX OR OTC
℞

SAMPLES	RELATED IND/NDA/DMF
N/A	50-587 Primaxin® IV
	50-630 Primaxin® IM

STERILIZATION
N/A

LABELING
N/A

BIOEQUIVALENCY STATUS
N/A

ESTABLISHMENT INSPECTION
N/A

COMPONENTS, COMPOSITION, MANUFACTURING

COMPOSITION

COMPONENT	250/250	500/500
STERILE IMIPENEM MONOHYDRATE	—— mg *	—— mg *
STERILE CILASTATIN SODIUM	—— mg *	—— mg *
STERILE SODIUM BICARBONATE	10 mg	— mg
	— mg	—— mg

* equivalent to 250 mg and —— % overage for Imipenem & Cilastatin
* equivalent to 500 mg and —— % overage for Imipenem & Cilastatin

CONTROLS
N/A

PACKAGING
N/A

STABILITY
Acceptable stability data (room temperature, and 40° C through 12 months) are provided from one lot using the proposed ———————————— stopper, and one lot using the approved ———— stopper.

Telecon 7/17/92: EDuffy/HFD-635 to Ron Salerno/Merck - inquired whether the "accelerated" stability conditions were 40° C and 75% RH or 40° C as is indicated in the stability report. RESPONSE: the conditions are 40° C.

Note that sterility and particulate data are not provided.

The firm commits to provide stability data from three early production batches.

REMARKS AND CONCLUSION

1. The "sister" application 50-587 received the same supplement - APPROVED 7/17/92 (copy attached).

2. The cover letter incorrectly refers to the stopper part # ——— rather than ———.

3. Type III DMF ——— was reviewed - found deficiencies which do not warrant NA of the supplement.

4. It is recommended that the firm provide sterility and particulate data in addition to the usual stability parameters in future stability reports, and that accelerated conditions be 40° C and 75% relative humidity.

RECOMMENDATION - APPROVABLE

RECALLS	Reviewer	Date Completed
	Eric P. Duffy	

cc: AADA # 62-756/S-015
DUP/Division File
Endorsements:
HFD-635/EDuffy/8-25-92 E Duffy 8/27/92
HFD-635/JHarrison/NSager for JDH 8/25/92 8/27/92
B:MSD15S62.756
B:62756S.015
F/T by mw/8/26/92

The application covered by this review was taken in date order of receipt.

YES _X__ NO ___

NDA 50-587/S-037

Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Affairs
Merck Sharp & Dohme Research Laboratories
Sumneytown Pike
West Point, Pennsylvania 19486

JUL 17 1992

Dear Dr. Salerno:

Reference is made to your supplemental Antibiotic Drug Application (ADA) dated April 10, 1992, submitted pursuant to Section 507 of the Federal Food, Drug, and Cosmetic Act for Primaxin I.V. (imipenem-cilastatin sodium).

The supplemental application provides for the addition of the ———————————— gray stopper for Imipenem and cilastatin sodium for injection.

We have completed our review and the supplemental application is approved effective as of the date of this letter.

We acknowledge your commitment to place the first three production batches of Primaxin 500mg and Primaxin 250mg with the———————————— gray stopper on stability and recall any batch that fails to meet the currently approved specifications. Please provide the stability data with the next annual report.

This approval affects only those changes specifically submitted in this supplemental application. Other changes that may have been approved or are pending evaluation are not affected.

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

Sincerely yours,

WD 7/17/92

Wilson H. De Camp, Ph.D.
Supervisory Chemist
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

JUL 15 1992

NDA SUPPLEMENT REVIEW

CHEMIST'S REVIEW | **1. ORGANIZATION** DAIDP (HFD-520) | **2. NDA NUMBER** 50-587

3. NAME & ADDRESS OF APPLICANT
Merck Sharp & Dohme Research Laboratories
Sumneytown Pike
West Point, PA 19486

4. AP NUMBER

5. SUPPLEMENT(s)

NUMBER(s)	DATE(s)
SCP-037	4/10/92

6. NAME OF DRUG
Primaxin[R]

7. NONPROPRIETARY NAME
Imipenem-Cilastatin Sodium

8. SUPPLEMENT(s) PROVIDES FOR:

SCS-037 The addition of the ———— ———— gray stopper for Imipenem and Cilastatin sodium for injection.

9. AMENDMENTS AND OTHER (REPORTS, etc.) DATES

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. HOW DISPENSED
XXX
Rx OTC

12. RELATED IND/NDA/DMF(s)
DMF ————

13. DOSAGE FORM(s)
Recon. powder for I.V.

14. POTENCY(ies)
≈250mg Imipenem/Cilastatin sodium
≈500mg Imipenem/Cilastatin sodium

15. CHEMICAL NAME AND STRUCTURE

Imipenem — $C_{12}H_{17}N_3O_4S.H_2O$

(5R,6S)-3-[[2-(formimidoylamino)ethyl]thio]-6-[(R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid monohydrate

m.w. 317.36 CAS Registry No. 74431-23-5

Cilastatin Sodium — $C_{16}H_{25}N_2NaO_5S$

Sodium (Z)-7-[[(R)-2-amino-2-carboxyethyl]-thil]-2-[(S)-2,2-dimethylcyclopropanecarboxamido]-2-heptenoate

m.w. 380.43 CAS Registry No. 81129-83-1

16. RECORDS AND REPORTS

	Yes	No
CURRENT	XX	
REVIEWED	XX	

17. COMMENTS
This drug is not the subject of a USP monograph.

18. CONCLUSIONS AND RECOMMENDATIONS
The supplement is approvable. An approval letter may be issued.

cc: Orig: NDA 50-587
HFD-520
HFD-520/Buko
HFD-520/SBRoy
HFD-520/Soprey
HFD-520/Chapman
HFD-520/WHDeCamp:R/D initialed 7/15/92

19. NAME	REVIEWER SIGNATURE	DATE COMPLETED
Suva B. Roy, Ph.D.		6/24/92

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Redacted 2 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW

MEMORANDUM OF A TELEPHONE CONVERSATION

June 24, 1992

Between: Ronald A. Salerno, Ph.D
Merck-Sharp and Dohme
(215)-834-2958

And: Suva B. Roy, Ph.D.
Review chemist, HFD-520

Subject: NDA 50-587/ SCP-036

I called Dr. Salerno to verify

- The correct part number for the stopper. The DMF ——— referenced in the supplement states the stopper to be ———. The supplement cover letter refers to the stopper as ———.
- Whether the supplement is to add the ——— ——— stopper as an alternate to the currently approved ——— stopper.

Dr. Salerno said he would verify and call back.

Dr. Salerno called back with the responses later in the day.

- The correct part number is ———. The cover letter is in error.
- The stopper will be in addition to the currently approved ——— stopper.

The conversation ended amicably.

cc: Orig: NDA 50-587
HFD-520
HFD-520/Soprey
HFD-520/Buko
HFD-520/Chapman
HFD-520/SBRoy
HFD-520/WHDeCamp:R/D initialed __

DMF CHECKLIST FOR ANDA/AADA # 62-756/S-015

DMF #	DMF SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED	COMMENTS
—	—		DEF	8/25/92	Def for —

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under "Comments").

PAGE 1 OF 1 Erin P. Duffy Reviewer Signature 8/25/92 Date

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-015

CORRESPONDENCE

These copies are OFFICIAL FDA Copies
not desk copies.

Noted: 2/1
review in turn
Mona Anderson
4/17/92

MERCK SHARP & DOHME RESEARCH LABORATORIES
DIVISION OF MERCK & CO., INC.
WEST POINT, PENNSYLVANIA 19486

RONALD A. SALERNO, PH.D.
ASSOCIATE DIRECTOR
REGULATORY AFFAIRS

(215) 834-2958
(215) 661-5000
FAX (215) 834-2962

April 10, 1992

NDA NO._____ REF. NO. SC-015
NDA SUPPL FOR Control Revision

Mr. John D. Harrison, Chief
Antibiotic Drug Review Branch
HFD-635, Room 17B-31
Division of Generic Drugs
Office of Generic Drugs (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

RECEIVED
APR 14 1992
GENERIC DRUGS

Dear Mr. Harrison:

ANDA 62-756: PRIMAXIN ADD-Vantage
(Imipenem-Cilastatin Sodium for Injection)

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act and in accordance with 21 CFR 314.50 and 21 CFR 314.70.b, we submit for your approval a supplement to ANDA 62-756.

As indicated in the attached Form 356h, the supplemental application provides for changes in item 3 of the approved New Drug Application for PRIMAXIN ADD-Vantage.

This supplemental application provides for the addition of the _____ gray as an approved stopper for the product. Attached is a letter of authorization from _____ (DMF ____) to refer to their Drug Master File.

To evaluate their acceptability, USP Physico-Chemical Tests for Elastomeric Closures were performed to compare the current and proposed stopper. Results of this testing are outlined in the attached Table I and show that the stoppers compare favorably with no significant differences. In addition, the current and proposed stoppers were stored at room temperature and 40°C for 12 months. All results for Test samples compare favorably with the Control samples (Refer to Table II).

Merck commits to incorporate samples of three early production batches, produced under this change, into its existing drug product stability testing program. Results of testing will be routinely provided to the Agency. Any deviations will be investigated. Appropriate action, including recall, will be taken based upon the findings of the investigation.

Lims
4-16-92

Please note that an identical suppiement is also being submitted, under separate cover, to PRIMAXIN I.V. (NDA 50-587) filed with the Anti-Infective Drug Division.

We consider the filing of this supplemental New Drug Application to be a confidential matter, and request the Food and Drug Administration not to make its content, nor any future communication in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Questions concerning this supplemental application should be directed to Ronald A. Salerno, Ph.D. (215/834-2958) or, in my absence, to Kenneth R. Brown, M.D. (215/834-2552).

Sincerely yours,

Ronald A. Salerno, Ph.D.
Associate Director
Regulatory Affairs

ALS/cat
75H

Attachments

Certified No. P 712 125 865