CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 62-756 / S-012

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

***Sponsor*:** Merck Research Laboratories

***Approval Date*:** February 18, 1992

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-012

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APPROVAL LETTER

AADA 62-756/S-012

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

FEB 18 1992

Dear Sir:

Reference is made to your supplemental antibiotic drug application submitted pursuant to Section 314.70 of the Regulations, dated July 25, 1991, regarding your abbreviated antibiotic application for Primaxin® ADD-Vantage® (Imipenem-Cilastatin Sodium For Injection, MSD).

The supplemental application provides for addition of the Bacterial Endotoxin Test as an alternate to Pyrogen testing for Imipenem and Cilastatin Sodium drug substance release testing, and for Primaxin® I.V. ADD-Vantage® drug product release testing.

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.

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

Sincerely yours,

Michael G. Beatrice 2/20/92
2/18/92 per KTJ

Michael G. Beatrice
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: AADA # 62-756/S-012
DUP/Division File
HFD-600/RF
HFC-130/JAllen
HFD-635/JHarrison/EDuffy/ EDuffy 2/14/92
HFD-635/MAnderson Mark Anderson 2/14/92
R/D initialed by JHarrison
mw/2/14/92/62756S.012 JHarrison 2/14/92
F/T by mw/2/14/92
SUPPLEMENT APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-012

CHEMISTRY REVIEW

AADA 62-756/S-012

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 applications provide for addition of the Bacterial Endotoxin Test as an alternate to Pyrogen testing for Imipenem, and Ciliastatin Sodium drug substance release testing, and for Primaxin® I.V. ADD-Vantage® drug product release testing.

DATE OF SUBMISSION
July 25, 1991

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	—— mg	——mg
	—— mg	—— mg

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

CONTROLS
The supplement provides for LAL Bacterial Endotoxin Testing as an alternate to Pyrogen Testing for both bulk drug substances (———————— method) and for finished drug product (—— —— method).

PROPOSED LIMITS:
Imipenem - ——EU/mg
Cilastatin Sodium - ——EU/mg
Sodium Bicarbonate - ——EU/mg
Primaxin - ——EU/mg
Rationale: limits based upon max dosage for 70 Kg human of 2000 mg Primaxin (1000 mg Imipenem; 1000 mg/Cilastatin Sodium)

NOTE: the maximum dosage used for this calculation is incorrect - dosage for pts. w/ normal renal, P. aeroginosa, severe/life threatening - 1 g q6h = 4 g/day = 166.6 mg/hr, however this results in a lower EU limit. The *Guideline on the Validation of the Limulus Amoebocyte Lystate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices* limit is 0.7 EU/mg - limit of ——— EU/mg is acceptable

VALIDATION:

Laboratory qualification - acceptable for standard endotoxin range ————————————

Drug substance
Cilastatin Sodium -
- MVC - ————
- Dilution - ————
- MVD - ————

Imipenem -
- MVC - ————
- Dilution - ————
- MVD -————

Sodium Bicarbonate -
- MVC - ————
- Dilution - ————
- MVD - ————

Primaxin (250 mg) -
- MVD - ————

Primaxin (500 mg) -
- MVD - ————

The LAL validation is acceptable.

Revised specifications and testing documentation are provided.

PACKAGING
N/A

STABILITY
Use of the LAL test for stability testing is not explicitly stated - no revised stability testing protocol is provided.

REMARKS AND CONCLUSION
The LAL Bacterial Endotoxin Test limits, validation, and procedures are acceptable.

RECOMMENDATION - APPROVABLE

RECALLS	Reviewer	Date Completed
	Eric P. Duffy	

cc: AADA # 62-756/S-012
Review Chemist's name: Eric P. Duffy EDuffy 2/14/92
Supervisor's name: John D. Harrison

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

YES ✓ NO ___

JDHarrison 2/14/92

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 62-756 / S-012

CORRESPONDENCE

ORIGINAL

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

July 25, 1991

NDA NO. _____ REF. NO. SCI-012
NDA SUPPL FOR CHEMISTRY

OK
J.H. 9/27/91

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

Dear Mr. Harrison:

SPECIAL SUPPLEMENT - CHANGES BEING EFFECTED

ANDA 62-756: PRIMAXIN® I.V. ADD-Vantage®
(Imipenem-Cilastatin Sodium for Injection, MSD)

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

As indicated on the attached Form FDA 356h, the supplemental application provides for changes in Item 3 of the approved New Drug Application for PRIMAXIN® I.V. ADD-Vantage®.

This supplemental application provides for the addition of the Bacterial Endotoxin test by LAL as an alternate to the USP rabbit pyrogen test for end product release for both the bulk drug substance, Imipenem and Cilastatin Sodium and drug product PRIMAXIN® I.V. ADD-Vantage®.

Submitted with this supplement are the validation packages in support of use of the LAL method for the bulk drug substance (Attachment I) and the drug product (Attachment II). Addendum A and B are revised Section 4 (a) and 4 (b) reflecting the addition of Bacterial Endotoxin test as well as the test methods.

RECEIVED
JUL 29 1991
GENERIC DRUGS

The tests were validated following the "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-product Endotoxin test for Human and Animal Parenteral Drugs, Biological Products and Medical Devices". The use of validated LAL test methods following procedures given in the Guideline will give increased assurance that the drug will have the characteristics of purity it purports or is represented to possess. As provided for under 21 CFR 314.70(c), according to the referenced guidelines, these changes will be made concurrently with the submission of this supplement providing for them.

Please note that an identical supplement is also being submitted, under separate cover, to the PRIMAXIN® I.V. (NDA 50-587) and the PRIMAXIN® I.M. (NDA 50-630) filed with the Division of Anti-Infective Drug Products.

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 communications 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 856 788 875