CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-933
20-636/SE1-009

CHEMISTRY REVIEW(S)

DIVISION OF ANTIVIRAL DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA #: **20,933** –

CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** 25-Aug-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	17-Apr-98	20-Apr-98	27-Apr-98
Amendment	29-Jul-98	30-Jul-98	31-Jul-98
Amendment	20-Aug-98	21-Aug-98	25-Aug-98
Amendment	31-Aug-98	31-Aug-98	31-Aug-98

NAME / ADDRESS OF APPLICANT: Boehringer Ingelheim Corporation
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

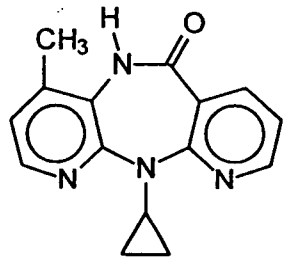
DRUG PRODUCT NAME

Proprietary: VIRAMUNE® Oral Suspension
Nonproprietary: nevirapine oral suspension
Code Name/#: BIRG 587 BS

PHARMACOLOGICAL CATEGORY: Antiviral
INDICATION: Anti-HIV
DOSAGE FORM/STRENGTH: Suspension, 50 mg/5 mL
ROUTE OF ADMINISTRATION: Oral

CHEMICAL NAME / STRUCTURAL FORMULA:

11-cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one hemihydrate



Registry Number [129618-40-2]

$C_{15}H_{14}N_4O$ Formula Weight: 266.30 (anhydrous)
275.31 (hemihydrate)

SUPPORTING DOCUMENTS:

NDA 20,636 VIRAMUNE® (nevirapine) Tablets, 200 mg

RELATED DOCUMENTS:

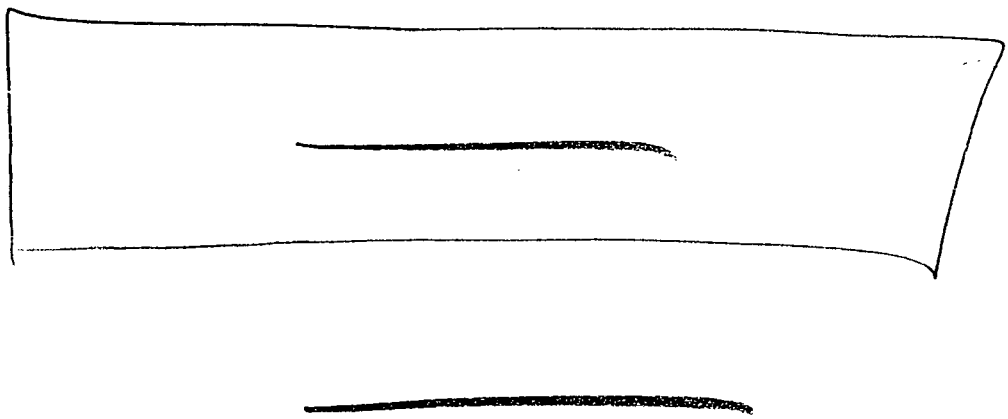
Chemistry Reviews of NDA 20,636

CONSULT REVIEWS: None

REMARKS/COMMENTS:

DRUG SUBSTANCE: ***Satisfactory***

Nevirapine hemihydrate is a non-nucleoside inhibitor of HIV-1 reverse transcriptase. Nevirapine has been approved for use in the form of 200 mg tablets. The dosage form in this Application is an oral suspension for pediatric use.



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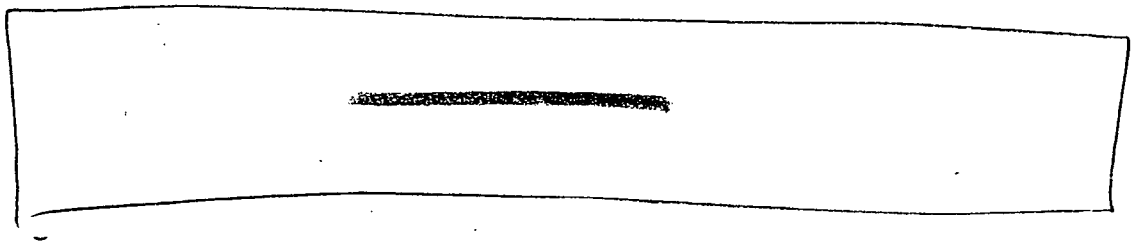

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One batch failed to meet the particle size specification at the 6 month and later time points. This coincided with a change in the particle size analysis method which might have been expected to result in slightly lower values. Had the particle size been determined with the original methods at

the earlier time points the batch would probably have failed specification then also. Thus there is no trend towards larger particles. Otherwise all specifications were met and no trends were observed.

The Applicant commits to continue the stability studies on the primary stability batches stored at 25°C/60% RH for 5 years. These batches will fulfill the stability requirements for the first 3 production batches. Additionally, the Applicant commits to carry out stability testing on at least one batch per year.

DRUG PRODUCT: ***Satisfactory***

The drug product is a 50 mg/5 mL oral solution containing nevirapine hemihydrate, carbomer 934P, polysorbate 80, sorbitol sucrose, methylparaben, propylparaben, sodium hydroxide, and purified water. All excipients are compendial.

The specifications include description, identification , pH, uniformity, assay for nevirapine, methylparaben, and propylparaben, degradants, dissolution, viscosity, particle size, microbial controls, and preservative effectiveness testing. The release pH control (5.5-6.0) is more restrictive than the shelf life pH control (5.4-6.0). The uniformity control applies to samples taken from a single bottle. An in-process control will provide for inter-bottle dose uniformity. Control of the suspension stability is provided primarily by the viscosity and particle size specifications. Test suspensions with viscosities greater than specification and which met the particle size specification were stable and homogeneous and showed no sedimentation over 14 months. Preservative efficacy is only applicable to the first three batches subsequent to the primary stability batches and will only be performed at the beginning, middle, and end of shelf life. After that determination the parabens will provide a control on the preservative efficacy. The acceptance criteria are appropriate and the analytical test methods are fully described and validated.

Three batches of nevirapine oral suspension have been manufactured at the proposed commercial site according to the proposed commercial formulation and to the proposed commercial scale. All specifications are met.

Stability data are available for the following time periods (in months).

Other specification	1	12	-	6	6	6

A statistical analysis has been carried out by the sponsor. Apart from some spurious results caused by improperly packaged drug product few trends were observed and the batches remained within their specifications. There was a slight decline in the levels of the parabens over time but their values still remained above the levels required for preservative efficacy

Based on the primary stability data of 12 months for the recapped bottles, 18 months for the non-recapped bottles, and supportive real-time data for clinical batches a provisional shelf-life of 24 months is recommended.

The sponsor commits to performing stability testing on at least one marketed batch produced during each year of manufacture. The bottles will be [redacted] and testing for appearance, pH, nevirapine assay, methylparaben assay, propylparaben assay, degradants, dissolution, particle size, and viscosity will be carried out at 0, 3, 6, 9, 12, 36, 48, and 60 months. A random sampling plan will be used. Any batch that does not meet specifications will be withdrawn from the market.

ENVIRONMENTAL ASSESSMENT: ***Satisfactory***

The sponsor has requested a categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) in 62 FR 40570 on the basis that the Environmental Introduction concentration will be less than 1 ppb.

METHODS VALIDATION: ***Pending***

[redacted]

Validation of the analytical methodology is not anticipated prior to the approval decision for this application.

LABELING: ***Satisfactory***

The labels are analogous to those for the nevirapine tablets. The labels and the box contain the same information.

The labels read VIRAMUNE® (nevirapine) Oral Suspension 50 mg/5 mL. Each 5 mL contains 50 mg of nevirapine as nevirapine hemihydrate. Rx only. The instructions are "Shake gently before dispensing. Store at 15°C-30°C (59°F-86°F)."

Dosage Instructions [redacted]

The draft package insert was submitted in Pediatric Supplement S-009 to NDA 20-636 on 3/13/98.

ESTABLISHMENT INSPECTION: ***Satisfactory***

The Establishment Evaluation Request was submitted on 5/8/98. Boehringer Ingelheim Chemicals, Inc., Petersburg VA, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield CT, [redacted] were found to be acceptable based on profile. After inspections

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

60 pages

CDER Establishment Evaluation Report
for August 05, 1998

Application: NDA 20933/000 Priority: P Org Code: 530
Stamp: 20-APR-1998 Regulatory Due: 20-OCT-1998 Action Goal: District Goal: 10-JUL-1998
Applicant: BOEHRINGER INGELHEIM PHARMS Brand Name: VIRAMUNE (NEVIRAPINE) SUSPENSION

NO CITY, , XX

Established Name:
Generic Name: NEVIRAPINE
Dosage Form: SUS (SUSPENSION)
Strength: 50 MG/5 ML

FDA Contacts:
T. CRESCENZI (HFD-530) 301-827-2335 , Project Manager
G. LUNN (HFD-530) 301-827-2393 , Review Chemist
S. MILLER (HFD-530) 301-827-2392 , Team Leader

Overall Recommendation:

ACCEPTABLE on 04-AUG-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1119657
BOEHRINGER INGELHEIM CHEMIC
2820 NORTH NORMANDY DR
PETERSBURG, VA 23805

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 08-MAY-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 08-MAY-1998
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Responsibilities: [redacted]

Establishment: 1510690
ROXANE LABORATORIES INC
1809 WILSON RD
COLUMBUS, OH 43228

DMF No:
AADA No:

Profile: LIQ OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date 04-AUG-1998

Responsibilities: DRUG SUBSTANCE OTHER TESTER
FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **1527529**
ROXANE LABORATORIES INC
330 OAK ST
COLUMBUS, OH 43216

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **04-AUG-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **DRUG SUBSTANCE RELEASE TESTER**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **08-MAY-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

APPEARS THIS WAY ON ORIGINAL