CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75211

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 75-211

DRUG PRODUCT: Acyclovir Tablets, 400 mg and 800 mg

FIRM: Mylan Pharmaceutical Inc.

DOSAGE FORM: Tablets

STRENGTHS: 400 mg and 800 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

The dosage form will be manufactured, controlled and processed, packaged and labeled at

Mylan Pharmaceuticals Inc.
P.O. Box 4310
781 Chestnut Ridge Road
Morgantown, WV 26504-4310

(OK on 4-21-98).

Manufacturer-Active Ingredients:

The manufacturer of active ingredient, Acyclovir, USP is listed as follows:

DMF#

(OK on 4-21-98).

Contract Laboratories:

Mylan employed as a contract laboratory for the elemental analysis of Guanine for drug substance.
(OK on 4-21-98).

BIO STUDY:

Satisfactory Per S. Nerukar reviewed 2-23-98 for lot #2C005L (800 mg) and also satisfactory for the dissolution data for 400 mg strength, lot #2C004L, 800 mg strength, lot #2C005L.

400 mg: Lot #2C004L
800 mg: lot #2C005L (Bio batch)

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

Drug dosage form is not compendial. Method validation was requested on 4-27-98 by L. Tang and found acceptable on July 13, 1998 by Baltimore District Laboratory.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability protocol: Satisfactory

Expiration date:

2 years expiration date with 1, 2 and 3 month accelerated stability data (37°C/75% R.H.) and 3,6,9 months room temperature at 25°C - 30°C (27.5°C ± 2.5°C) stability data on lot #2C004L for 100's (120 cc) and 500's (18 oz.) for 400 mg and lot #2C005L for 100's (200 cc) and 500's (36 oz.) for 800 mg.

The stability data includes the following strength and lots:

400 mg: Lot #2C004L
800 mg: lot #2C005L (Bio batch)

LABELING:

Satisfactory per J. White reviewed on 8-5-98.

STERILIZATION VALIDATION (IF APPLICABLE):

NA

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Batch size:

400 mg

a. Tablets (executed batch # 2C004L)
b. Tablets (blank batch record)
c. tablets (blank production batch record)

800 mg

a. Tablets (executed batch # 2C005L)
b. Tablets (blank batch record)
c. tablets (blank production batch record)

DMF has been reviewed and found acceptable per L.Tang on 8-5-98.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The stability batch size:

400 mg

Tablets (executed batch # 2C004L)

800 mg

Tablets (executed batch # 2C005L)

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

The proposed production batch (blank batch):

400 mg

tablets (blank production batch record)

800 mg

tablets (blank production batch record)

CHEMIST: Lucia C. Tang /S/ DATE: 8-5-98 8-31-98

SUPERVISOR: Ubrani Venkataram DATE: 8-13-98 9/9/98

1. CHEMISTRY REVIEW NO. 2

2. ANDA 75-211

3. NAME AND ADDRESS OF APPLICANT

Mylan Pharmaceutical Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,199,574 was expired on April 22, 1997, a New Chemical Entity exclusivity period expired on March 29, 1992, an indication of acute treatment of varicella zoster virus expired on April 26, 1993 and the indication of varicella infections (chickenpox) expired on February 26, 1995.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

9-29-97: Original
12-8-98: Amendment

FDA:

10-22-97: Acknowledgement
1-10-98: 1st NA letter

10. PHARMACOLOGICAL CATEGORY

Antiviral

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

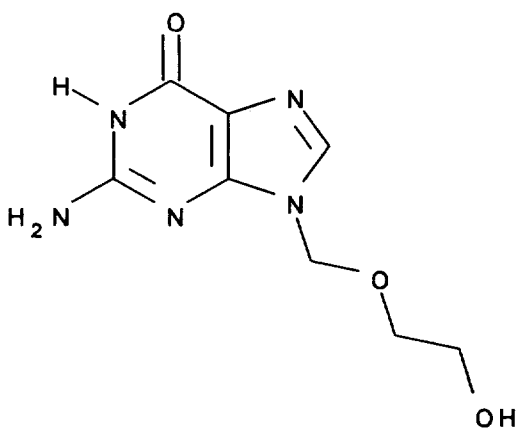
Tablets

14. POTENCY

400 mg & 800 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
$C_8H_{11}N_5O_3$; M.W. = 225.21
CAS [59277-89-3]



1. 9-[(2-Hydroxyethoxy)methyl]guanine.

2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257°. LD_{50} in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Q: 1. We note that the differences between Exhibit and Production size batch records were provided for the specifications of tolerance listed in the final blend and the tablet yield for each strength. We also note that the differences between 400 mg product and 800 mg product were provided for the specifications of tolerance listed in the final blend and the tablet yield. Please provide justification.

A: OK (see response 1 of 7-8-98 amendment).

Q: 2. We note that the assay limits for granulation intermediate is given as %. The in-process specification for Acyclovir should be tighter than the release specification. Please revise.

A: OK (see response 2 of 7-8-98 amendment).

Q: 3. Submit the actual torque test for cap removal covering the 100's and 500's Tablets package sizes for each strength.

A: OK (see response 3 of 7-8-98 amendment).

Status:

a. **EER**: Acceptable

Requested by T. Ames on December 3, 1997 and found acceptable on 4-21-98.

b. MV (method validation):

Drug dosage form is not compendial. Method validation was requested on 4-27-98 by L. Tang and found acceptable on July 13, 1998 by Baltimore District Laboratory.

c. Bio-Review: Satisfactory

Per S. Nerukar reviewed 2-23-98.

d. Labeling review: Satisfactory

Satisfactory per J. White reviewed on 8-5-98.

e. DMFs: satisfactory

Satisfactory per L Tang reviewed on 8-5-98.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 8-6-98