CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74787

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-787

UG PRODUCT: Labetalol Hydrochloride Tablets USP, 100 mg, 200 mg and 300 mg

FIRM: Zenith Goldline Pharmaceutical, Inc. Inc.

DOSAGE FORM: Tablets

STRENGTHS: 100 mg, 200 mg and 300 mg

CGMP STATEMENT/EIR UPDATE STATUS:

Manufacturer-Finished Dosage Form :

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

Zenith Laboratories, Inc.
140 Legrand Avenue
Northvale, NJ 07647

(OK on 4-9-98).

Manufacturer-Active Ingredients:

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

DMF#

(OK on 4-9-98).

Contract Laboratories:

as a contract laboratory for performing all required "microbial limits" testing for inactive ingredients.

(OK on 4-9-98).

BIO STUDY:

Satisfactory per P. Sathe reviewed on September 10, 1996 for lot # ND-241 (200 mg) and also satisfactory for the dissolution data for the 200 mg strength (bio-batch) for the revised lot ND 398 on 4-28-98.

100 mg: Lot #ND-242

200 mg: Original lot #ND-241 [bio-batch] and the revised lot

#ND-398

300 mg: Lot #ND-243

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

Compendial drug substance and drug product.

Methods validation is not required since active ingredients and drug product are monographs in USP 23. Satisfactory per Philadelphia District Laboratory on 9/17/96.

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 (40°C/75% R.H.) and 3,6,9,12,18,& 24 months room temperature at 25°C - 30°C or 25° ± 2° C/60% ± 5% RH stability data on lots ND 241 & ND-398 (200 mg tablets), ND-242 (100 mg tablets), and ND-243 (300 mg tablets) for

LABELING:

Satisfactory per C Park reviewed on 10-7-97.

'ERILIZATION VALIDATION (IF APPLICABLE):

NA

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

Batch size:

100 mg:

a. Tablets (executed batch #ND-242)
b. tablets (blank batch record)

200 mg (Bio batch):
a. Tablets (executed batch #ND-241 [bio-batch] and ND-398 [Executed batch record] submitted on 9-26-97 amendment and 6-5-98 amendment for batch record No. ND-398)
b. tablets (blank batch record)

300 mg:
a. Tablets (executed batch #ND-243)
b. tablets (blank batch record)

DMF has been reviewed and found acceptable per Sema Basaran on 3-27-98.

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

The stability batch size:

100 mg:

Tablets (executed batch #ND-242)

200 mg (Bio batch):
Tablets (executed batch #ND-241 [bio-batch] and ND-398 [Executed batch record] submitted on 9-26-97 amendment and 6-5-98 amendment for batch record No. ND-398)

300 mg:
Tablets (executed batch #ND-243)

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

The proposed production batch (blank batch):

100 mg:

tablets (blank batch record)

200 mg (Bio batch):
tablets (blank batch record)

300 mg:
tablets (blank batch record)

EMIST: Lucia C. Tang /S/ DATE: 6-15-98 & 7-23-98

SUPERVISOR: Ubrani Venkataram DATE: 6-22-98 7/23/98

/S/

74787AAP.P/Tang/6-15-98

1. CHEMISTRY REVIEW NO. 3

2. ANDA 74-787

3. NAME AND ADDRESS OF APPLICANT

Zenith Goldline Pharmaceutical, Inc.
140 Legrand Avenue
Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION

The applicant certifies , that to the best of its knowledge, U.S. Patent No. 4,066,755 expired on January 3, 1995. A New Chemical Entity exclusivity period (Patent No. 1,012,444) will expire on August 2, 1998, an indication of treatment of Hypertension expired on 1-3-95.
Innovator: Normodyne® Tablets from Schering Corporation, Kenilworth, NJ.

5. SUPPLEMENT(s)

N/A

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

Labetalol

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

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

11-14-95: Original Submission
9-26-97: Amendment
6-05-98: Amendment

FDA:

2-9-96: Acknowledgement
7-3-96: 1st NA letter
5-12-98: 2nd NA letter

10. PHARMACOLOGICAL CATEGORY

AntiHypertension

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM

Film Coated Tablets

14. POTENCIES

100 mg, 200 mg, and 300 mg

15. CHEMICAL NAME AND STRUCTURE

Labetalol Hydrochloride USP
$C_{19}H_{24}N_2O_3$ .HCl; M.W. = 364.87
CAS [32780-64-6]
Benzamide, 2-hydroxy-5-[1-hydroxy-2[(1-methyl-3-phenylpropyl)amino]-,monohydrochloride.
5-[1-Hydroxy-2[(1-methyl-3-phenylpropyl)amino]ethyl]-salicylamide monohydrochloride

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Comments:

Q: 1. The certificate of Analysis for batch ND-398 was submitted on September 26, 1997 in support of the theoretical coating weight gain (range). The dissolution results are within the specified limit. Please submit the batch record and 3 months accelerated stability data for lot ND-398 since the 200 mg strength is used for your bioequivalence study batch.

A: See Attachment 1 and response 1 of 6-5-98 amendment.

Q: 2. We note that the test results for containers and containers have been submitted in the original submission and the September 26, 1997 amendment. We also note resin and resin were used to manufacture the package sizes. It is necessary to demonstrate the interchangeability of each resin by compendial testing. Please submit actual test results to demonstrate that and resins meet the current USP 23 requirements for plastics for container. A Certificate of Analysis from the manufacturer of the resin is also acceptable.

A: OK (see response 2 and Attachment 2 of 6-5-98 amendment).

Q: 3. The mater batch record for the 100 mg product appears to include variable process settings on page 35. However on page 36 the in-process control for granulation end-point is specified for one process setting only. Please revise page 35 to specify one process setting based on your executed batch record. Please revise master batch record for 200 mg and 300 mg products also.

A: OK (see response 3 and Attachment 3 of 6-5-98 amendment).

Q: 4. Please submit the release drug product specifications to include the revised description of the drug product for each strength.

A: OK (see response 4 and Attachment 4 of 6-5-98 amendment).

Status:

a. **EER**: Satisfactory

Requested for Zenith, by T.Ames and found acceptable on 4-9-98.

b. MV (method validation): Satisfactory

Active ingredient and drug dosage form are compendial. Method validation is satisfactory, Philadelphia District Laboratory, 9/17/96.

c. Bio-Review: Satisfactory

Satisfactory per P. Sathe reviewed on September 10, 1996 and also satisfactory for the dissolution data for the 200 mg strength (bio-batch) for the revised lot ND 398 on 4-28-98.

d. Labeling review: Satisfactory

Satisfactory per C Park reviewed on 10-7-97.

e. DMFs: Satisfactory

DMF has been reviewed and found acceptable per Sema Basaran on 3-27-98.

18. CONCLUSIONS AND RECOMMENDATIONS

Approval

19. REVIEWER: DATE COMPLETED:

Lucia C. Tang 6-15-98