

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

75-105

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

ANDA 75-105 APPROVAL SUMMARY

DRUG PRODUCT: Indapamide Tablets USP, 1.25 mg and 2.5 mg

FIRM: Alphapharm Pty., Ltd.

DOSAGE FORM: Tablets

STRENGTH: 1.25 mg and 2.5 mg

cGMP STATEMENT/EIR UPDATE STATUS: EER Acceptable Date May 12, 1997, *FOR 6/24/98*

BIO STUDY: APPROVE, Letter Dated January 28, 1998

VALIDATION: DS and DP are compendial

STABILITY: Nine months accelerated (30°C and 40°C/75%RH) for 100's and 1000's packaging configuration; six months 20°C data for bulk in 20L container; and six months ambient condition (25°C/60% RH) data for bulk in 4L container, provided. The container/closure systems used for the stability study are equivalent to the systems proposed for commercial use. All reported data are within specifications as listed. Thus, a 24 month expiration date is justified.

Tests and specifications for the drug product on stability include: Appearance, Identification (RT matches RS), Related Substances

LABELING: APPROVE, Review Date December 29, 1997

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO BATCH: The bio batch, lot# PJ032, 2.5 mg strength (batch size tablets) is also the test batch for 2.5 mg strength. The DS supplier is is Adequate as of June 16, 1998).

SIZE OF STABILITY BATCHES: Stability batches are the same as the test batches, Lot# PH145 for 1.25 mg, and Lot# PJ032 for 2.5 mg.

PROPOSED PRODUCTION BATCHES: The proposed production batch size is 1 tablets for each of the 1.25 mg and the 2.5 mg product. The manufacturing process for production batches remains the same as that for the test batches.

CHEMIST: *W.A. Bond*

DATE: *6/16/98*

SUPERVISOR: *DSG:ik to vs*

DATE:

6-29-98

Indapamide
1.25 & 2.5 mg tablet
NDA #75-105
Reviewer: J. Lee
75105SA.997

Alphapharm Pty. Ltd
Brisbane, Australia
Submission date:
September 11, 1997

Review of a Study Amendment

This submission addresses the comments and deficiencies conveyed to the sponsor in the review of their bioequivalence study on indapamide 2.5 mg tablet (rev. 7/18/97, J. Lee).

1. The sample, standard and QC preparation and processing procedures were omitted in the original bio-study report.

The procedures were submitted as requested to complete documentation of the assay methodology.

2. The freeze-thaw stability data for indapamide showed a large decline in concentration for the 30 and 240 ng/ml QC samples relative to the 15 and 960 ng/ml QC samples at the third freeze/thaw cycle. The sponsor was asked to explain this and the impact this may have on the clinical sample values.

Response: No frozen clinical samples were thawed more than twice in this study. Reassays utilized the duplicate samples as opposed to a re-thawed original sample. A previous validation of the method (Feb. '92) showed acceptable 3-cycle freeze-thaw data.

3. Long term stability data was not submitted as stated in the submission. Stability data to cover the period equivalent to the duration of the study was requested.

The submitted data showed adequate stability within the variability of the assay.

4. Raw data was not provided in the original study report. All raw data for the analytical runs was provided as requested in this submission. The data further documents the absence of interference at the retention time of the drug peak.
5. The assay methodology associated with dissolution testing and the %CV at each sampling time were omitted in the original dissolution report. The sponsor has provided this information (see attached dissolution summary).
6. Information on the batch sizes of the test products were excluded in the bio-report. That information is now provided:

2.5 mg indapamide tablet, batch # PJ032 (bio-lot)

1.25 mg indapamide tablet, batch #PH145

Comment:

1. The responses to the deficiencies are adequate.
2. Waiver for the 1.25 mg indapamide tablet is granted based on comparable dissolution testing and formulation proportionality with the 2.5 mg product.

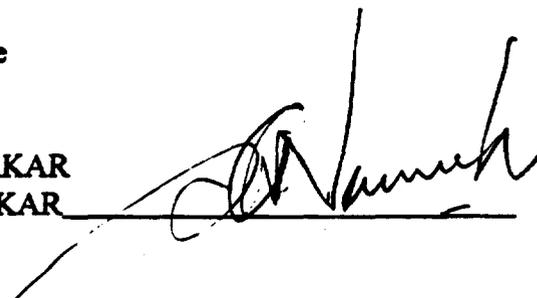
Recommendation:

1. The bioequivalence study conducted by ⁷ for Alphapharm Pty. Ltd. on its indapamide 2.5 mg tablet, batch #PJ032, comparing it to Lozol[®] 2.5 mg tablet has been found acceptable by the Division of Bioequivalence. The study demonstrates that Alphapharm's 2.5 mg indapamide tablet is bioequivalent to the reference product, Lozol[®] 2.5 mg tablet, manufactured by Rhone-Poulenc Rorer.
2. The in-vitro dissolution testing (USP) data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of SGF w/o enzyme at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specification:
3. The Division of Bioequivalence agrees that the information submitted by the sponsor demonstrates that indapamide 1.25 mg tablet falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Alphapharm's indapamide 1.25 mg tablet is deemed bioequivalent to Lozol[®] 1.25 mg tablet, manufactured by
4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

E. Lee 1/27/98

J. Lee
Division of Bioequivalence
Review Branch II

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FT INITIALED SNERURKAR

 1/28/98

Concur: Dale P. Conner Date: 1/28/98

Dale Conner, Pharm. D.
Director, Division of Bioequivalence

JLee/jl/ 01-27-98

cc:

DIVISION OF BIOEQUIVALENCE

11-2-98