CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84902

ADMINISTRATIVE DOCUMENTS

Promethazine HCl
Suppositories, 50 mg
ANDA 84-902

Alcon Laboratories
Forth Worth, Texas

SUMMARY BASIS OF APPROVAL

I. Background

Promethazine is one of the many widely used phenothiazines for which only limited pharmacokinetic data is available. The instability of promethazine and its low plasma concentrations after therapeutic doses have impaired the development of analytical methods for assaying the drug in serum or plasma. Recently, developed an analytical procedure for promethazine in serum in less than 5 ng/ml concentrations.

Alcon Laboratories conducted a single-dose pilot bioavailability study of a promethazine oral solution to determine that the method was practical for bioequivalence studies. Then, the firm conducted a comparative bioavailability study of promethazine following oral and rectal administration of promethazine dosage forms. They submitted (September 5, 1980) the results of the later study to support their new drug application (ANDA 84-902) for promethazine suppositories, 50 mg.

II. Summary of Pivotal Study

The single-dose three-way crossover study compared promethazine rectal suppositories, 50 mg manufactured by Alcon and Wyeth with an equivalent oral dose of Phenergan Syrup Fortis (Wyeth) in 20 healthy male subjects.

The Table below shows the rate and extent of promethazine absorption in terms of mean pharmacokinetic parameters derived from individual serum concentration-time profiles of 14 subjects who retained both suppository preparations for sufficient time to assure absorption. The mean AUC and C_{max} values were about 100% higher for Alcon's promethazine suppositories than Wyeth's brand. Yet the mean C_{max} value for Alcon's suppositories was 9% more than C_{max} for the solution. Comparison of the uniformity of individual AUC values following Alcon suppositories and Phenergan Syrup Fortis revealed that although the mean AUC values indicate that the Alcon suppositories were 30% more bioavailable, the difference was not statistically significant.

Table

Summary of Promethazine HCl
Bioavailability Study

	Product		
	Wyeth Phenergan$_R$ Suppository, 50 mg Lot #1782592	Alcon Promethazine Suppository, 50 mg Lot #ZE-1424	Wyeth Phenergan Syrup Fortis Lot #1782593
C_{max}, ng/ml	15.1	27.8	25.4
T_{max}, min.	430	267	213
AUC (0-1440 min)	11403	19040	14620

III. Overall Conclusion

The single dose study demonstrated that the Alcon promethazine suppository is significantly more bioavailable than Wyeth's Phenergan brand suppositories, but is bioequivalent to an equivalent oral dose of Phenergan Syrup Fortis.

Prepared by: /S/ Date 11/6/81
Francis R. Pelsor, Pharm.D.
Biopharmaceutics Review Branch

Concur: /S/ Date 11/10/81
Shrikant V. Dighe, Ph.D.
Chief,
Biopharmaceutics Review Branch

Approved by: /S/ Date 11/10/81
Bernard E. Cabana, Ph.D.
Director,
Division of Biopharmaceutics

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 84-902

DATE APPROVAL LETTER ISSUED: OCT 5 1981

TO: Press Relations Staff (HFI-40)

FROM: [XX] Bureau of Drugs [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: [ ] ORIGINAL NDA [ ] SUPPLEMENT TO NDA [XX] ABBREVIATED ORIGINAL NDA [ ] SUPPLEMENT TO ANDA

CATEGORY: [XX] HUMAN [ ] VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG:

Promethacon - promethazine hydrochloride

DOSAGE FORM: suppository

HOW DISPENSED: [XX] Rx [ ] OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)

Promethazine hydrochloride 50 mg.

NAME OF APPLICANT (Include City and State)

Alcon Laboratories
Fort Worth, TX 76101

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

antihistamine

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: Ronald E.Joyce /S/ DATE: 10/2/81

FORM APPROVED BY

NAME: Jack L. Meyer /S/ DATE: 10/2/81

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 2/15/73
FROM: John Gaylor		OFFICE
TO: D.		DIVISION 84-902

SUBJECT: 84-901, 902 / M Seife

SUMMARY

Spoke w. C. O'Brien of subject firm + requested update of stability data + information as to proposed labeling. She said firm would call 10:00 AM tomorrow re same.

Suggest re review of current insert by MO vs. whatever current guidelines we have. I note absence of Reye's syndrome warning in current labeling

SIGNATURE	DOCUMENT NUMBER

FD FORM 2034 (2/72)

Promethazine Suppositories
ANDA 84-902 50 mg
ANDA 84-901 25 mg

Alcon Laboratories
AF #27-736
Meeting Date:
February 3, 1976

MEMORANDUM OF A MEETING

BETWEEN: Richard A. Hamer
Alcon Laboratories
David J. Buddrus, M.D.
Alcon Laboratories

and

Bernard E. Cabana, Ph.D.
Acting Director, Division
of Biopharamceutics
Jerome P. Skelly, Ph.D. (part-time)
Chief, Pharmacokinetics and
Biopharmaceutics Branch
Harold R. Murdock, Ph.D.
Pharmacologist, DB
Gene Knapp (part-time)
Associate Director
Drug Monographs
Dr. Barzilai, Medical Officer
Division of Generic Drug Monographs

The purpose of the meeting was to discuss the bioavailability requirement for the above products.

The company stated that they had done dissolution of their product comparing it with Wyeth's Phenergan. The dissolution was done in dioxane, because they could not do the test in water as the Wyeth product was in a wax base. At a previous meeting with Mr. Hamer he was told that the dissolution was not satisfactory and they should do a bioavailability study. He replied that there was no assay methodology sensitive enough for doing a blood level study. They were asked to document what they had done to develop an assay. To this we got no reply but agreed to the present meeting with other representatives of the company.

The same arguments were raised again at the meeting. The company asked for approval to market the product with the commitment that the bioavailability study would be done as soon as methodology became available. It was pointed out that the pharmacokinetic profile of the product was not known and it would be impossible to write a satisfactory label.

It finally came out that the company had done dissolution studies on other drugs, namely acetaminophen, in a polyethylene glycol base suppository. They were able to show differences in dissolution with different formulations which they claim correlates with bioavailability and they said this should carryover to the promethazine suppositories. They were asked to submit the data in writing to Dr. Cabana who will obtain a decision on whether the dissolution on the other products will apply to this one. The issue of drug metabolism with promethazine was discussed because of the potential of a first pass metabolism.

The company also said that other companies had received approval for oral promethazine products without a bioavailability study. It was pointed out to them that on March 9, 1972 the Bioavailability Committee had made the decision that deferral of bioavailability requirements of promethazine would not apply to special dosage forms such as suppositories.

Dr. Stavchansky said that they could not use Dr. Smolen's pupilometric response because the response became saturated at very low dosages. He was told that Dr. Smolen measured other responses that might be better suited to this drug and they should explore them. The company did not reply to this. In thinking this over, it seems rather imporbable that the pupilometric response would be so quickly saturated when the response does not become saturated by chlorpromazine until the 100 mg dose is reached. The company should be asked to submit their data.

They were advised that in our opinion bioavailability data would be needed to support labeling. They were further advised that the Agency was in the process of documenting bioavailability problems with suppository drug products and that serious considerations was being given to requiring full NDA as stated in June 20, 1975 FEDERAL REGISTER Statement. They were told that their product could be approved under the DESI requirement (ANDA) if they met the bioavailability requirement. Such bioavailability studies could employ a radiotracer to demonstrate bioavailability. The issue of use of animal models was also discussed.

/S/

Harold R. Murdock, Ph.D.

cc: ANDA's ~~orig~~, dupl., trip., hfd-530 (2), hfd-520, hfd-522 (6), af file, ~~chronological~~ file

HRMURDOCK/lj 2/5/76
RD INITIALED BY JPSKELLY & BECABANA
FINAL TYPE INITIALED BY _____

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 1/8/76
FROM: R. E. BARZELAI, M.D. (HFD-530)		OFFICE
TO: B. CABANA, M.D. (HFD-520)		DIVISION
SUBJECT: ANDA's 84-901 and 84-902		

SUMMARY

Subject ANDA's are refered to you in preparation of our 2/3/76 meeting with firm's representative, as apreed today with D Seife and staff.

Thank you

Morris Seife, M.D.

SIGNATURE

/s/

DOCUMENT NUMBER

FD FORM 2034 (2/72)

MEMO RECORD

AVOID ERRORS
PUT IT IN WRITING

11/29/75

FROM: Marvin Seife, M.D.

OFFICE

TO: Division of Biopharmaceutics

DIVISION HFD-530

SUBJECT:

SUMMARY

Attention: Dr. Harold Murdock

NDA 84-902
Promethacon Suppettes 50mg
Alcon Labs.

Please review the bioavailability study on the above drug.

Thank you,

/S/

Marvin Seife, M.D.

SIGNATURE

DOCUMENT NUMBER

FD FORM 2034 (2/72)

MEMO RECORD	AVOID ERRORS PUT IT IN WRITING	DATE 9-17-75
FROM: J. Taylor (thru J.L. Meyer)		OFFICE HFD-530
TO: Mr. David H. Bryant, Office of Compliance		DIVISION HFD-322

SUBJECT: Inspection Request

SUMMARY

In connection with ANDA -

for: 84-901 Prochlorperazine EDI Suppositories, 25 mg
84-902 " " " " 50 mg.

Applicant:

Alcon Laboratories, Inc.
Fort Worth, TX 76101

AF - 17-736

REQUESTED:

[X] 1. Evaluation of compliance with CGMP for:

[X] a. The applicant

[X] b. Others

[X] 2. Recommendation for approval/disapproval of the application/communication/supplement, based on your evaluation of compliance with CGMP

Product will be manufactured, processed, packaged and labeled at:

Alcon Laboratories(Puerto Rico), Inc. (Division of Alcon, Inc.)
P.R. 925 Barrio Jusquitos, Bunasco, P.R. 00661

REMARKS:

Also Q.C.Testing operations.

SIGNATURE	DOCUMENT NUMBER
L. Rubin /S/	