CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

84902

BIOEQUIVALENCY REVIEW(S)

Promethazine Suppositories, 50 mg
ANDA 84-902

Alcon Laboratories
Ft. Worth, TX
Submission Dated: 7/7/81
July 7, 1981

REVIEW OF DISSOLUTION DATA

The purpose of this study was to determine the dissolution profile of several experimental Alcon promethazine suppository formulations, and Phenergan (Wyeth) suppositories using dioxane as the dissolution medium and modified USP Method I procedures. These data were first submitted to the Agency on October 31, 1975. At that time, Dr. Albert Mattocks (Expert, HFD-522) reviewed the study and recommended that it was unacceptable as a demonstration of bioequivalence of the two products. The firm was advised that an in vivo comparative bioavailability study was required to meet the Bioavailability/Bioequivalence Requirement.

Alcon Laboratories submitted (September 5, 1980) results of a three-way crossover study which compared equivalent doses of their suppositories to Phenergan suppositories, and a promethazine oral solution. The study was found acceptable to the Division of Biopharmaceutics. Further, the Division recommended that the firm be advised that their application fulfilled all necessary elements of the Bioavailability/Bioequivalence Requirements.

In order to establish a complete record of the in vitro and in vivo bioavailability of the Alcon promethazine suppositories, the results of the dissolution study are summarized in Table I below.

COMMENTS:

1. Figure I (attached) shows the solubility of promethazine HCl in dioxane-water mixtures.

2. The firm noted that attempts to study the dissolution profile of Phenergan 25 mg and 50 mg suppositories using However, the firm's Promethacon 50 mg suppositories dissolve % in water in 15 minutes. It should be noted that the Alcon's formulations employ the ase system. In addition, ascorbic acid and water are included in the formulation to improve dispersion of promethazine HCl. Whereas, Phenergan suppositories employ an oil base.

3. In 100% dioxane, Promethacon 25 mg and 50 mg suppositories dissolve % and % in 30 minutes, respectively. At 60 minutes, the respective strengths dissolve % and %. Both strengths of Phenergan supporistories dissolve about %% in 30 minutes and at 60 minutes they dissolve at least %.

4. The results of the in vivo study showed that Alcon's promethazine 50 mg suppositories were 1.7 times as bioavailable as Phenergan 50 mg suppositories. Using dioxane as the medium, the dissolution test results do not appear to correlate positively with the results in vivo.

5. The firm should be informed that the Agency has no dissolution test requirement for promethazine suppositories. However, the Agency encourages the firm to develop dissolution test methodology and specifications in water and/or buffer which resemble biological fluids.

RECOMMENDATIONS:

The Dissolution Study No. PRZ 7750140 submitted July 7, 1981, (original submission dated: 10/31/75) and conducted by the has been reviewed by the Division of Biopharmaceutics.

The Division of Biopharmaceutics has determined that your application has fulfilled all the necessary elements of the Bioavailability/Bioequivalence Requirement.

The above recommendation as well as comments (#5) should be forwarded to the firm.

/S/ 8/24/81

Francis R. Pelsor, Pharm. D.
Biopharmaceutics Review Branch

FPELSOR/vmp/8/21/81(0514W)

cc: ANDA 84-902 orig., HFD-530(4), HFD-522 (Pilsor), HFD-503 (Mr. Hare), Chron File, Drug File, Review File.

RD INITIALED BY SVDIGHE for CMISE
FT INITIALED BY SVDIGHE for CMISE 8/24/81

Table I

Milligrams (Average) Promethazine HCl Dissolved*

	Strength			
	25 mg		50 mg	
Time, min	Alcon Promethacon Lot #165-21-4	Wyeth Phenergan Lot #1750758	Alcon Promethacon Lot #165-21-2	Wyeth Phenergan Lot #1750829
2.5	1.76 (93)**	.66 (14)	1.98 (25)	3.47 (88)
5	2.88 (48)	2.51 (31)	5.59 (4)	5.52 (83)
7.5	4.13 (35)	4.28 (27)	9.33 (7)	9.74 (42)
10	5.46 (19)	6.43 (3)	13.29 (2)	12.81 (26)
15	9.20 (22)	9.18 (9)	22.36 (8)	16.46 (26)
20	12.08 (17)	11.50 (10)	26.66 (7)	21.94 (16)
25	14.36 (13)	12.45 (7)	32.90 (5)	28.86 (13)
30	15.78 (8)	14.89 (0)	36.02 (4)	29.47 (15)
40	18.58 (7)	17.51 (5)	41.93 (4)	36.92 (21)
50	18.92 (7)	20.15 (3)	42.26 (4)	41.27 (14)
60	19.18 (9)	21.69 (8)	42.47 (4)	45.96 (12)
75	19.74 (4)	23.80 (12)	41.93 (1)	46.44 (14)
90	19.74 (4)	24.80 (2)	41.29 (0)	
105	23.22 (4)			
120	23.87 (0)			

* Dissolution tests were conducted on 2 suppositories each (except Lot #1750829, n = 3) in 100 ml dioxane (100%). The USP basket was lowered to 2 cm from the bottom of the 200 ml beaker and run at 50 rpm.

** % CV.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date . August 13, 1981

From Director (HFD-530)
Division of Generic Drug Monographs

Subject Bioavailability for ANDA 84-902, Promethacon (promethazine HCl) Suppositories, 25 mg.

To C. M. Ise (HFD-522)

Dr. Pelsor's review of ANDA 84-902, Promethacon, 50 mg., concluded that bioequivalence had been demonstrated. Can this conclusion be extrapolated to the 25 mg. suppository?

The composition of each suppository is given below:

Component	mg/supp	mg/supp
Promethazine HCl		
Polyethylene glycol 1000		
Polyethylene glycol 4000		
Ascorbyl palmitate		
Ascorbic acid		
Purified water		
Blue food color		
TOTAL WEIGHT:	mg.	mg.

/S/
Marvin Seife, M.D. 8/13/81

cc:
ANDA's (84-901, 84-902)
HFD-535 (R.Joyce) 8/13/81
RJ/MS/wh/8-13-81
8/13/81

Promethazine
Suppositories, 50 mg
ANDA 84-902

Alcon Laboratories, Inc.
FT Worth, TX 76101
Submission Dated:
June 25, 1981

REVIEW OF A BIOAVAILABILITY STUDY

The purpose of this submission was to communicate the firm's response to comments given by the Division of Biopharmaceutics on their promethazine suppository comparative bioavailability study. The firm included additional data to document the validity of the assay they employed to measure promethazine (See deficiencies #1, 2, 3, F. Pelsor's review, submission dated: 9/5/80).

The firm's response point-by-point to the reviewer's comments are:

1. The firm exhibited chromotograms to show that any unidentified peaks (including any on the shoulder of the promethazine peak) did not interfere with the detection of promethazine. Therefore, the analyst was not required to subtract a blank value from unknown samples.

2. For serum samples demonstrating drug levels on the order of 1 ng/ml, the coefficient of variation was in the range of %. A 1 ng/ml standard yielded a signal equivalent to about % of full-scale response. Therefore, 1 ng/ml was the lower limit of detection of the assay. Values below 1 ng/ml were reported as 0.

3. The products from the reaction between trichloroethylchloroformate (TCEF) and promethazine, triflupromazine and phenothiazine were analyzed by mass spectrometry (See Report attached).

4. Concerning large within-subject variation, the firm pointed out that in 4 subjects where individual C_{max} values for the suppository exceeded those of the syrup by more than 30%, the C_{max} value for the suppository, in all cases, was less than additional subjects demonstrated for the syrup. The firm contends therefore, that product safety is not an issue.

   The firm further compared the uniformity of AUC values of the test suppositories to the uniformity of those of the reference solution (Pittman Morgan F test). With this evaluation significant differences for the Alcon suppository over the Phenergan solution were not found.

5. The firm believes greater bioavailability of the suppository should be expected since the rectal route of administration circumvents the first-pass effect of the oral route of administration. At the same time the firm points out that the Alcon suppositories, although more bioavailable, are not significantly different from the solution (Pittman Morgan F test).

RESULTS

The firm submitted additional data to document the sensitivity and recovery of the assay. With regard to the method, the firm conducted an additional study, "Comparision between Methods for the Determination of Promethazine Hydrochloride in Human Serum."

Method:

Sensitivity: the 1 ng/ml and 1.3 ng/ml sample responses were calculated to be % of full scale.

Recovery: Recovery studies were accomplished by spiking serum with 10 ng/ml of promethazine and extracting according to the procedure. The peak height obtained after extraction was compared to the peak height obtained from a solution of promethazine HCl in methanol. The mean percent recovery of promethazine HCl serum was % (n = 5 samples).

Method:

Standard Curve:
Slope: 0.9866 vs 0.9948; t = .309 (ns)
Intercept: -1.188 vs 0.1416; t =-1.163 (ns)

Spiked Promethazine HCl in Serum (ng/ml)	Experimental Promethazine HCl in Serum* (X)	(Y)
2.5	3.40(0.793)**	2.24(0.679)
5.0	5.01(0.829)	5.12(0.659)
15.0	13.45(2.62)	11.71(1.42)
30.0	31.01(4.07)	27.43(4.41)
90.0	89.60(11.82)	88.16(6.87)

Correlation Equation: 0.9914 X - 1.3196 = Y
* Mean N = 6
** Standard Deviation

In summary, the data indicates that the methods are precise, linear in the concentration range studied and that no bias exists between them.

COMMENTS

1. The firm has supplied sufficient data concerning the assay methods employed to remove the deficiencies identified previously. (See F. Pelsor's review, submission dated 9/5/80).

2. Concerning the firm's response to the comment on large within-subject variation, the problem was not an issue of safety vis-a-vis the 70/70 rule. The issue was bioequivalence. In this case where oral and rectal absorption are confounding promethazine product comparison, strict adherence to the rule does not now seem appropriate. Where a drug like promethazine is subject to large first-pass effect following oral administration, one could reasonably expect a large proportion of subject bioavailability comparisons to lay beyond the range when the true bioavailability of the suppository is % greater than the solution.

3. This reviewer has determined that the firm conducted dissolution studies on their suppositories. The data will be reviewed shortly so that the Division may retain the information for reference. However, there are no dissolution test requirements for promethazine HCl suppositories.

RECOMMENDATION

The bioavailability study (submission dated: September 5, 1980) conducted by has been found acceptable to the Division of Biopharmaceutics as partial fulfillment of the Bioavailability/Bioequivalence Requirements. The Division of Biopharmaceutics has determined that your application has fulfilled all the necessary elements of the Bioavailability/Bioequivalence Requirement.

The above recommendations should be forwarded to the firm.

/S/ , 7/21/81

Francis R. Pelsor, Pharm.D.
Biopharmaceutics Review Branch

cc: ANDA 84-902 orig., HFD-530(4), HFD-522 (Pelsor), Drug File, Review File, Chron File

FPELSOR/pag/7/16/81 FT: vmp 7/17/81(3504E)

RD INITIALED BY CMISE
FT INITIALED BY CMISE C.M.

Promethazine HCl
50 mg Suppository
ANDA 84-902

Alcon Laboratories
Forth Worth, Texas
Submission Dated:
September 5, 1980

ADDENDUM TO A REVIEW OF A BIOAVAILABILITY STUDY

In my initial review of the bioavailability study the mean values listed for C_{max}, T_{max}, and AUC under the Alcon 50 mg Suppository Lot ZE-124 were 27.8(84), 267(36) and 15114(113), respectively. These values are incorrect. The correct values are as follows:

C_{max}(ng/ml)	2.42(95)
T_{max}(min)	263(37)
AUC (0-1440 min)	15114(113)

To reflect the correct values, paragraph 2 under Results should read as follows:

Table I shows the mean promethazine serum concentration and derived pharmacokinetic parameters for each of the products tested in all 20 subjects. For 40 through 360 minutes, the Alcon suppositories resulted in significantly higher concentrations than the Wyeth suppositories. Further, the Alcon suppositories showed significantly higher results for AUC and C_{max}. T_{max} was significantly longer for the Wyeth suppositories. The Alcon suppositories and Phenergan Syrup Fortis do not differ by more than % as determined by comparing the mean values for AUC and; by no more than % by comparing mean C_{max} values. On the other hand, the Alcon suppositories differ from the Wyeth suppositories by as much as % when mean values for AUC and C_{max} are compared.

These corrections do not change any previous recommendations. The application has fulfilled all the necessary elements of the Bioavailability/Bioequivalence Requirements.

/S/ 12/2/81

Francis R. Pelsor, Pharm.D.
Biopharmaceutics Review Branch

cc: Orig., HFD-530 (4), HFD-522 (Dr. Pelsor), Drug File, HFD-503 (Mr. Hare), HFD-522 (Dr. Ise), Review File, Chron File

FRP/vmp/11/16/81 (7517E) RD
FRP/vmp/11/19/81 FT

RD INITIALED BY CMISE
FT INITIALED BY CMISE C.M. Ise 12-2-81

Promethazine HCl
50 mg Suppository
ANDA 84-902

Alcon Laboratories
Fort Worth, Texas
Submission Dated:
September 5, 1980

REVIEW OF A BIOAVAILABILITY STUDY

The purpose of this study was to compare the bioavailability of promethazine suppositories, 50 mg manufactured by Alcon and Wyeth, and the reference solution: Phengergan Syrup Fortis (Wyeth). The study was conducted at the
under the direction of Serum promethazine assays were performed by

PROTOCOL:

Twenty (20) male subjects, aged 21-33, participated in the study. All subjects were given a general physicial examination, including anoscopy, prior to initiation of the study. Consent was obtained from all subjects prior to the study.

Following an overnight fast, each subject received a single 50 mg dose of promethazine on day 1 of the study. All suppositories were inserted by a physician; all Alcon suppositories were moistened with water before insertion; the Phenergan brand were not premoistened. After insertion of the suppositories, the subjects were maintained for 30 minutes in a standing position, then the subjects were ambulatory for the remainder of the study period. All subjects received 200 ml of water at the time of treatment regardless of dosage form administered. An additional 200 ml of water was given 2 hours post-dose. At 3 hours after each rectal dose, the anal sphincter of each subject was examined; and at 4 hours post-dose, subjects were allowed to eat and drink according to a specific diet. Blood samples (15 ml) were collected at 0, 20, 40, 60 minutes, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after drug administration. Samples were allowed to coagulate; then centrifuged. Serum was harvested and flash frozen for storage until time of analysis. The procedures of day 1 were repeated on days 7 and 14 to complete phase 2 and phase 3 of the crossover study.

An method developed by was used to analyze serum samples for promethazine concentration. The method is based on

(internal standard);

For this study, the relationship between peak-height ratio of drug to internal standard and concentration of drug in serum was linear over the range ng/ml. Based on replicate analysis of a 15 ng/ml sample, the coefficient of variation (CV) for all assays was % and within days was %. The day-to-day variation was %.

Pharmacokinetic and statistical analysis of the average promethazine serum concentration-time curves were performed by AUTOAN and NONLIN. The major bioavailability parameters (C_{max}, T_{max}, AUC) were subjected to ANOVA using OMNITAB II.

RESULTS:

Serum levels of promethazine were determined for each sample drawn from all subjects who participated in the study. However, values from 6 subjects who eliminated a portion of the Alcon suppository, one of which also eliminated a portion of the Phenegeran suppository, in their bowel contents were not included in the study evaluation.

Table I shows the mean promethazine serum concentration and derived pharmacokinetic parameters for each of the products tested. For 40 thru 360 minutes, the Alcon suppositories resulted in significantly higher concentrations than the Wyeth suppositories. Further, the Alcon suppositories showed significantly higher results for AUC and C_{max}; T_{max} was significantly longer for the Wyeth suppositories. The Alcon suppositories and Phengeran Syrup Fortis do not differ by more than % as determined by comparing the mean values for AUC and; by no more than % by comparing mean C_{max} values. On the other hand, the Alcon suppositories differ from the Wyeth suppositories by almost % when mean values for AUC and C_{max} are compared.

Table II shows the C_{max}, T_{max}, and AUC for only 14 subjects who retained both suppository preparations for sufficient time to assure absorption. Using each subject as his own control, the Alcon suppositories are 1.4 times as bioavailable as Phengeran Syrup Fortis and 1.8 times as bioavailable as the Wyeth suppositories.

COMMENTS:

1. The report stated that spiked serum samples and drug-free serum yielded unidentified peaks, one on the shoulder of the promethazine peak. The firm should indicate whether the promethazine concentration reported reflects any within-or between-subject variation in this unidentified peak. For example, did the analyst subtract a blank value from unknown sample values for the same subject.

2. The firm should state the decision rules for reporting a sample promethazine concentration as zero (0).

3. The firm should show the extent to which the promethazine-trichloroethylchloroformate product was characterized.

4. The study shows large within subject variation. For example, when each subject was used on his own control, C_{max} following administration of the Alcon suppositories was 1.1 times that following Phengeran Syrup Fortis. However, less than % (8/14) of the subjects were in the range (proposed Phenothiazine Bioequivalence Requirements, Federal Register, p. 56832, August 26, 1980). Only 4 of 14 subjects were in the range when subjects were evaluated for the relative bioavailability of the test suppositories (Alcon) and reference solution.

5. Given that the assay method is valid, the study shows that the Alcon suppositories are 1.4 times as bioavailable as the Phenergan Syrup. Further, 7 of 14 subjects exhibited a relative bioavailability $\geq$ 1.4. These results indicate that the Alcon suppositories are certainly more bioavailable than the innovator's suppositories; they were 0.9 times as bioavailable as the syrup.

RECOMMENDATION:

The firm should be informed of the comments. The submission is incomplete due to the following deficiences:

DEFICIENCIES:

/S/ 1/29/81
Francis R. Pelsor, Pharm.D.
Biopharmaceutics Review Branch

cc: ANDA 84-902 orig., HFD-530(4), HFD-522 (Dr. Pelsor), Chron File, Drug File, Review File

FPelsor/vmp/1/21/81 (0590E)
RD INITIALED BY CMISE
FT INITIALED BY SVDIGHE C. M. Ise

TABLE I

MEAN PROMETHAZINE SERUM LEVELS (ng/ml)
AND DERIVED PHARMACOKINETIC PARAMETERS FOLLOWING A 50 mg DOSE

Parameter	Wyeth 50 mg Suppository Lot 1782592	Wyeth Syrup Fortis Lot 1782593	Alcon 50 mg Suppository Lot ZE-1424
Time, Minutes			
20	0.3(367)	0.3(167)	1.3(263)
40	0.7(286)	3.6(117)	4.7(143)
60	1.1(227)	8.5(114)	9.7(144)
90	2.1(157)	15.8(107)	13.0(118)
120	2.9(145)	22.5(103)	16.6(104)
180	5.9(120)	26.2(84)	24.7(96)
240	9.6(142)	24.7(86)	25.6(86)
360	12.1(94)	21.5(97)	23.7(94)
480	11.6(88)	16.4(98)	18.9(99)
720	8.5(75)	8.9(130)	12.7(100)
1440	3.5(131)	1.4(136)	4.3(147)
C_{max}	14.0(96)	28.9(82)	27.8(84)
T_{max}	364(34)	198(27)	267(36)
AUC(0-1440 min)	10103(84)	16094(97)	19040(100)

%CV.

TABLE II

PROMETHAZINE RELATIVE BIOAVAILABILITY

	Wyeth(A) Suppository			Wyeth(B) Syrup Fortis			Alcon(C) Suppository			Ratio (AUC)	
Subject	C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC	C/B	C/A
2	10.6	367	10565	14.7	248	6579	34.3	241	13478	2.05	1.28
3	59.5	245	33522	70.7	239	50681	92.1	181	70924	1.40	2.12
4	3.6	490	2734	7.5	183	5146	2.3	360	1705	0.33	0.62
5	22.3	481	18031	26.7	184	14510	46.2	189	30939	2.13	1.72
7	5.1	723	3473	19.2	180	10878	19.5	362	5828	0.54	1.68
9	4.5	480	3755	51.9	180	31709	29.4	184	19223	0.61	5.12
10	12.4	358	9082	10.5	185	3168	15.7	183	10057	3.17	1.11
12	17.0	476	14410	32.8	182	15054	33.3	237	24302	1.61	1.69
14	7.5	363	7300	6.4	190	4462	8.1	250	4802	1.08	0.66
15	8.9	480	5309	23.4	180	8399	22.0	240	16513	1.97	3.11
17	5.2	362	3645	13.5	185	7558	10.9	502	8575	1.13	2.35
18	8.5	360	5329	12.5	239	8446	11.8	250	7578	0.90	.142
19	9.5	480	7629	10.4	240	5858	13.7	194	7476	128	0.98
22	37.2	361	34861	55.2	362	32233	49.5	360	45175	1.40	1.30

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

Alcon Laboratories
Fort Worth, Texas
Submission Dated:
September 5, 1979

REVIEW OF A BIOAVAILABILITY PROTOCOL

In a review of the initial protocol submitted by the firm on June 20, 1979, I raised questions concerning subject sample size, volume of blood collected per subject, validity of the analytical method, and sample collection times.

During a telephone conversation on August 31, 1979, Mr. Roger Metzler, (Alcon Labs) indicated that the firm was aware of some of these problems. Subsequently, the firm responded by submission of this revised protocol.

STUDY DESIGN

The study design remains the same as that described in my review of June 20, 1979 submission with the following exceptions:

1. The number of subjects was increased from 12 to 24.

2. The estimated total volume of blood collected over the three-week test period was reduced from 720 to 540 ml per subject. This was accomplished by reducing the volume of sample collected at each time interval from 20 to 15 ml.

RECOMMENDATION

The protocol is approved provided the firm incorporates Comments 1 and 2 into the study design and submits the data described in Comment 3 at a later date.

Comments:

1. The total volume of blood collected over the three-week test period is estimated to be 540 ml per subject. Again, this is in excess of the 450 ml per 1 month per subject specification imposed by the agency. The volume of the sample collection at 30 minutes could be substituted for collections at 20 and 40 minutes. This would reduce the total volume collected per subject to 495 ml.

2. A sample (.suppositories) of the same lot as used in the bioavailability study should be forwarded to:

Angela C. Gresham, R. Ph.
Bureau of Drugs (HFD-522)
Food and Drug Administration
Department of Health, Education, and Welfare
5600 Fishers Lane
Rockville, Maryland 20857

3. The analyst must demonstrate that the method for promethazine is sensitive, specific, and reliable when used for pharmacokinetic studies following the rectal administration of suppository preparations.

/S/ 10/25/79

Francis R. Pelsor, Pharm. D.
Biopharmaceutice Review Branch

cc: ANDA 84-901 - 902, HFD-530 (3), HFD-522 (Pelsor Malinwoski), Chron File, Review File, HFD-525

PELSOR/pcg 10-19-79 (1437P)
RD INITIALED BY SVDIGHE
FT INITIALED BY CMISE C. M Ise

Promethazine HC1 Suppositories
25mg and 50mg
ANDRA 84-901 - 25mg
ANDRA 84-902 - 50mg

Alcon Laboratories
Ft. Worth, Texas
Submission Dated:
June 20, 1979

REVIEW OF A BIOAVAILABILITY PROTOCOL

1. The objective of the proposed study is to compare the bioavailability of promethazine HC1, 50 mg rectal suppositories (Alcon) to the reference products, Phenergan, 50 mg rectal suppositories (Wyeth), and Phenergan Syrup Fortis, 50 mg/10 ml oral solution (Wyeth), in humans. The three-way crossover study will be performed at the
under the direction of
Chemical analysis on plasma samples will be conducted by

2. A sufficient number of subjects will be pre-screened to insure that 12 will enter the study. Subjects will be normal healthy male volunteers, age 21 through 35 years, selected from the student population at the Subjects must conform to height and weight of the Metropolitan Life Insurance Company with the weight range not to exceed 30 Kg. In addition to the medical history, physical assessment, SMA 12/60, CBC with differential and urinalysis; all subjects will be given an anoscopic examination. The consent form will explain potential adverse reactions and permit the subjects to withdraw from the study at any time. Subjects will not have consumed any drugs for 2 weeks prior to the initial test day and during the study period. Subjects will be required to fast for 8 hours prior to dosing and will remain fasted until after the 4th hour blood sample is collected, at which time the subject will be allowed to eat and drink according to a specific diet.

3. Each subject will insert rectally a 50 mg suppository or ingest orally 10 ml of syrup, according to random assignment, along with 200 ml of water. After insertion of the suppositories, the subjects will be maintained for 30 minutes in a standing position then they will be ambulatory. At 3 hours after each rectal dose, subjects will again receive an anoscopic examination. Each subject will receive an additional 200 ml of water every 2 hours while fasting is still being maintained. Blood samples (20 ml) will be drawn at 0, 0.3, 0.7, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dosing. Following a one week washout period, the procedure will be repeated with each subject being dispensed an alternate medication. Each blood sample collected will be immediately coded, centrifuged, plasma separated and frozen.

4. Promethazine levels in plasma will be determined using an method developed by . will be used as the internal standard. The method is based

The recovery of promethazine was stated to be % with a quantitation limit of 1 ng promethazine per 1 ml of plasma. The method was used to determine the following promethazine levels in human plasma after an oral dose of 50 mg:

Time (HRS)	Plasma Level (mg/ml)
0	0.22
0.3	3.21
0.6	4.6
1.0	7.8
1.5	13.0
2.0	17.9
2.5	19.4
3.0	23.8
4.0	22.6
6.0	16.3

Assay results will be decoded and tabulated. The data will be analyzed using . In the event that the oral dose form gives grossly different results, the two rectal forms will be compared separately. Data analyses will be performed for the following comparisons: plasma level at each time interval post dose; area under the curve; peak concentration (Cmax); and time to peak (Tmax).

COMMENTS

1. A sample size of 12 may not be sufficient to assure a meaningful study. It is the experience of the Division of Biopharmaceutics that bioavailability studies of suppository preparations are at best difficult to conduct. For example, one study of suppository preparations of a different drug entity showed that % of the subjects did not retain the suppository preparation for the time necessary to complete absorption of the drug.

2. The total volume of blood collected over the three week test period is estimated to be 720 ml per subject. This is in excess of the 450 ml per one month per subject specification imposed by the agency. The volume of the sample must be decreased or the washout period prolonged in order to comply with the agency specification.

3. The analyst must demonstrate that the method for promethazine is sensitive, specific, and reliable when used for pharmacokinetic studies in humans following the rectal administration of suppository preparations.

4. Sample collection points during the 3-8 hour interval may not be sufficient to accurately determine the Cmax and Tmax following rectal administration of promethazine.

RECOMMENDATION

The company should be informed of Comments 1, 2, 3 and 4. Further, the protocol is not acceptable. The company should conduct a feasibility study on three or four subjects to assure the assay is satisfactory, the sampling times are correct, and the proper number of subjects are used.

/S/ 10/23/79

Francis R. Pelsor, Pharm. D.
Biopharmaceutics Review Branch

cc: ANDA 84-901 - 902, HFD-530 (3), HFD-522 (Pelsor Malinowski)
HFD-525, Chron File, Review File

PELSOR;pcg 10-23-79 (1345P)
RD INITIALED BY SVDIGHE
FT INITIALED BY CMISE C. M. Ise

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

Alcon Laboratories
Fort Worth, Texas
AF #27-736
Submission Dated:
October 31, 1975

REVIEW OF A BIOAVAILABILITY STUDY

INTRODUCTION:

This submission is a comparison of dissolution curves for Promethazine Suppositories (Alcon Labs) and Phenergan Suppositories (Wyeth Labs), the reference product. The study was performed by

RECOMMENDATION:

The relative rates at which promethazine suppositories dissolve in dioxane has not been shown to be related bioavailability in humans, and this study cannot be recommended as a demonstration of bioequivalence of the two products.

COMMENTS:

In a memorandum dated March 9, 1972 the Division of Actions Implementation/DESI stated that deferral of bioavailability requirements (for conventional types of oral dosage forms) of promethazine would not apply to special dosage forms such as suppositories. A bioavailability study is required for approval.

If the sponsor wishes to discuss this matter in greater detail we shall be glad to meet with them for this purpose.

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Expert, Biopharmaceutics Review Branch/DB

cc: ANDA's orig., dupl., trip., hfd-530, hfd-520, hfd-522, af file, chronological file

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