

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
75-366

BIOEQUIVALENCE

Sotalol Hydrochloride Tablets

80mg, 120mg, 160mg & 240mg

ANDA #75-366

Reviewer: Sikta Pradhan

XWP #75366S2W.598

Eon Labs Manufacturing Inc.

Laurelton New York

Submission Date:

May 22, 1998

September 9, 1998

**Review of two Bioequivalence Studies
Dissolution Data and Waiver Requests****Background:**

Sotalol hydrochloride is a beta-adrenoreceptor blocking agent with additional class III antiarrhythmic properties. Sotalol hydrochloride is a racemic mixture of d- and l-sotalol. Both isomers have similar Class III antiarrhythmic effects, while the l-isomer is responsible for virtually all of the beta-blocking activity. In healthy subjects, the oral bioavailability of sotalol hydrochloride is 90-100%, indicating negligible first-pass effect in the liver. The plasma levels are proportional to the single oral dose administered in the range of 80 to 320 mg. After 160 mg single oral doses, peak plasma Sotalol concentrations were observed between 1.4 and 1.7 mcg/mL at 2 to 3 hours after administration. Food may decrease the bioavailability of sotalol. No active metabolites of the drug have been identified.

Sotalol is commercially available as 80 mg, 120 mg, 160 mg and 240 mg Betapace^R oral tablets manufactured by Berlex Laboratories. Betapace^R oral tablet, 320 mg has recently been discontinued. The recommended initial oral dosing schedule for adults is 80 mg Betapace^R twice daily at approximately 12 hour intervals. The dose should be increased at 3 day intervals to 160 mg BID, 240 mg BID, and if necessary to 320 mg BID. Unusual patients with life-threatening refractory arrhythmia may require doses as high as 960 mg/day. Dosage should not exceed 960 mg/day.

I. Bioequivalence Study under Fasting Conditions:

Objective: The purpose of this single dose, two-way crossover study in healthy volunteers under fasting condition is to determine the bioequivalence of the test tablet, Sotalol HCl, 160 mg relative to the reference Betapace^R 160 mg tablet marketed by Berlex Laboratories. The firm has recently received the Agency approval for using 160 mg dose instead 240 mg dose in the bioequivalence study. It should also be mentioned here that, the

Agency has recently selected 160 mg Sotalol tablet as the RLD for the bioequivalence study.

Study Sites: Clinical - Anapharm Inc., Sainte-Foy, Qc, Canada
Analytical Laboratory Facility - Same as above

Principal Investigator: MarLeBel, Pharm.D.

Medical Investigator: -----

Analytical Director:

Pharmacokinetic and Statistical Director: Zohreh Abolfathi, Ph.D.

Protocol: #ANA-97-135

Study Design: This was a randomized, single oral dose, two-way crossover design comparing the test tablets with the reference tablets in twenty-four (24) healthy male volunteers under fasting conditions.

Subject Selection:

The study was conducted in two groups. In Group I, twenty-four (24) plus two (2) subjects were selected for this study after signing informed consent and meeting Inclusion Criteria of the study protocol. In Group II, four (4) were dosed to replace the dropouts.

Dosing Dates:

Group I (Subjects 1-26)	Period 1 October 17, 1997 Period 2 October 24, 1997
Group II (Subjects 27, 28, 29, 30)	Period 1 November 2, 1997 Period 2 November 9, 1997

Treatments:

- A. 1x160 mg Tablets of Sotalol (test product) of Eon Lab., Lot #970901; Lot size tablets; Potency: 100.1%
- B. 1x160 mg Tablets of Betapace^R (Reference product) manufactured by Berlex, Lot #W70049; Potency: 100.3%; Exp. Date: April, 2000.

Dose Administration:

A single oral dose of one 160 mg sotalol tablet (test or reference) was administered with 240 mL of water following a 10 hour fast.

Drug Washout Period:

The two treatments were separated by a seven (7) days washout period.

Meal and Food Restrictions: All volunteers fasted for 4 hours after drug administration. No fluid except that given with drug administration was allowed within 1 hour of dosing. Standard meal was served during the in-house confinement period. No caffeine-containing food or beverages were served during the study. All subjects were confined in the Clinical live-in facility from the evening before dosing until after the 24-hours blood draw.

Safety Monitoring: Subjects were monitored for medical (heart rate, blood pressure, ECG, etc.) events throughout the study. There were no significant or unexpected adverse events.

Blood Samples Collection: Blood samples were collected in tubes containing EDTA as anticoagulant at predose (0 hour), and at 0.5, 1.0, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 60 hours post-dosing. The plasma samples were separated and kept frozen at -80°C until analysis.

Assay Methodology:

Method: The plasma samples were analyzed for sotalol concentration by _____ with

Sotalol was extracted from an aliquot of human plasma using a _____ extraction, then injected into the

All stock solutions were prepared on **October 24, 1997** and stored at -80°C. QC samples were prepared on **October 30, 1997**. A total of 1008 samples were analyzed from **November 13, 1997 to November 28, 1997**.

Specificity:

No interference was observed at the retention times of sotalol and internal standard (Atenolol).

Linearity:

The standard plots were linear in the concentration range of, 4.40 to 2600.0 ng/mL, for sotalol with a mean value of 0.995 for correlation coefficient.

Sensitivity:

The lower limit of quantitation (LLOQ) was 4.40 ng/mL (inter/intra-batch CV=1.78%) for sotalolol. Any value below this limit was reported as zero.

Precision:

Precision was defined as the coefficient of variation of individual replicates from the calculated values.

A. Pre-study validation:

Intra day Precision from QC Samples:

(N = 8)

- 6.21% (CV) at 4.40 ng/mL
- 1.34% (CV) at 22.0 ng/mL
- 1.46% (CV) at 790.0 ng/mL
- 2.51% (CV) at 2100.0 ng/mL
- 3.03% (CV) at 2600.0 ng/mL

Interday Precision from QC Samples:

(N = 16)

- 4.37% (CV) at 22.0 ng/mL
- 3.34% (CV) at 790.0 ng/mL
- 4.17% (CV) at 2100.0 ng/mL

B. Within-study validation:

Interday Precision from Standards:

- 2.41% (CV) at 5 ng/mL; N=16
- 4.62% (CV) at 59.09 ng/mL; N=15
- 2.24% (CV) at 1200.0 ng/mL; N=16
- 3.47% (CV) at 2990.0 ng/mL; N=16

Interday Precision from Control Samples:

- 6.65% (CV) at 15.00 ng/mL; N=32
- 5.38% (CV) at 1000.0 ng/mL; N=32
- 4.26% (CV) at 2000.0 ng/mL; N=32
- 9.20% (CV) at 3.75 mcg/mL; N=30

Stability:

1. Sotalolol was found to be stable in human plasma for 24 hours at room temperature.
2. Processed samples were found to be stable autosampler at room temperature for up to 72 hours.
3. Sotalolol samples in human plasma were found to be stable

through three freeze/thaw cycles at -80°C .

4. The firm has informed the Agency in the recent amendment dated September 9, 1998 that sotalol is stable at -80°C for at least 259 days.

Results:

Twenty-six (26) volunteers were selected for the study and 21 subjects completed both periods of the study (completion date: October 24, 1997). Four (4) additional subjects (group II) were then selected for the study, and all four of them completed the study (completion date: November 9, 1997), giving a total of 25 subjects. In order to keep the design of the study balanced, subject #28 was excluded from the analysis. Thus, the statistical analyses were performed on data obtained from 24 subjects. All subjects were monitored for adverse events during the study. There was no serious adverse event or any event which required terminating any subject from the study. Mean plasma sotalol levels and the pharmacokinetic parameters derived from them are presented in Table 1 (and in Fig.1 attached) and Table 2, respectively, below:

Table 1. Mean Plasma Sotalol Levels (ng/mL)

Time (hour)	Test (A) Sotalol	Reference(B) Betapace ^R
Pre-dose	0.0	0.0
0.5	294.94 (59)*	279.11 (79)
1.0	778.42 (39)	859.96 (40)
1.5	987.04 (30)	1087.48 (41)
2.0	1167.53 (27)	1203.53 (32)
2.5	1342.93 (22)	1261.00 (27)
3.0	1297.69 (24)	1322.97 (21)
3.5	1226.13 (20)	1255.05 (20)
4.0	1185.98 (19)	1239.49 (19)
4.5	1104.35 (18)	1177.53 (20)
5.0	1062.48 (17)	1092.63 (18)
6.0	932.51 (15)	957.88 (16)
8.0	750.93 (17)	755.84 (18)
10.0	634.81 (16)	630.70 (17)
12.0	520.75 (16)	536.85 (17)
14.0	427.59 (17)	430.79 (17)
16.0	350.28 (16)	359.84 (17)
24.0	191.48 (17)	37.34 (19)
36.0	79.58 (25)	22.10 (29)
48.0	36.64 (34)	11.86 (32)
60.0	17.63 (45)	7.42 (43)

* Coefficient of Variation; Number of Subjects 24

Table 2. Mean Pharmacokinetic Parameters for Plasma Sotalol

Parameters (Arith.Mean)	Test (A)	Ref. (B)	A/B	90% C.I.
AUC _{0-T} (ng.hr/mL)	16737.01 (14)	17000.19 (15)		
AUC _{0-inf} (ng.hr/mL)	17007.68 (14)	17259.81 (15)		
C _{MAX} (ng/mL)	1440.73 (19)	1484.59 (20)		
T _{MAX} (hour)	2.65 (22)	2.90 (39)		
t _{1/2} (hour)	10.34 (15)	10.29 (14)		
KE (1/hour)	0.0683 (14)	0.0686 (29)		
LnAUC _{0-T} (Using LSM) Geometric Mean	9.73205 16849.06	9.76127 17348.65	0.97	94; 101
LnAUC _{0-inf} (Using LSM) Geometric Mean	9.74492 17067.31	9.77354 17562.83	0.97	94; 101
LnC _{MAX} (Using LSM) Geometric Mean	7.29024 1465.92	7.31651 1504.94	0.97	91; 104

* Coefficient of Variation

Both test and reference drugs produced sotalol peak concentration between 2.5 to 3.5 hours after their administration. The differences between the test and reference products in LnAUC_{0-T}, LnAUC_{0-inf} and LnC_{MAX} were less than 3%. The 90% confidence intervals for , LnAUC_{0-T} , LnAUC_{0-inf} and LnC_{MAX} for sotalol of the test product remained within the acceptable range of 80 - 125%.

As there were two subgroups (separated by one week) in this study, the analysis of variance (ANOVA) was performed to determine the group effects and the treatment-by-group interaction term. The ANOVA model had treatment, sequence, group, treatment*group, period (group), sequence*group, and subject (sequence*group) as factors/interaction terms. The ANOVA showed that the group effect was not significant for all parameters, indicating that the subjects of both subgroups behaved similarly in regards to the treatment effect.

IV. LIMITED FOOD STUDY:

Protocol #ANA-97-136

The firm has submitted the results of a single oral 1x160 mg dose three-way crossover post-prandial bioequivalence study conducted on the test product, Sotalol Tablets, 160 mg, manufactured by Eon Labs Manufacturing Inc. and the reference product, Betapace^R 160 mg Tablets, manufactured by Berlex. The study was conducted in 18 (plus 6 alternates) normal, healthy, non-smoking male volunteers (31±8 years of age) after completing screening procedures. The subjects were dosed under fed and fasting conditions in order to determine the effect of food on the bioavailability of those products.

The clinical study was conducted at ANAPHARM inc. in Sainte-Foy, Quebec, Canada, beginning on **January 20, 1998 and ending on February 3, 1998.**

Dosing Schedule:

- A. 1x160 mg Sotalol Tablet (test product); Lot #970901, immediately after a high fat breakfast.
- B. 1x160 mg Betapace^R Tablets, manufactured by Berlex (Reference product); Lot #W70049, immediately after a high fat breakfast.
- C. 1x160 mg Sotalol Tablet (test product); Lot #970901, after an overnight fast for at least 10 hours.

Drug Washout Period: One week (as mentioned in fasting study)

Meal and Food Restrictions: Water was given ad lib until one hour pre-drug and after one hour post-drug. A standard meal was served after 4.5 hours post-dose. No alcohol, caffeine and xanthine-containing beverages was served during the study.

Blood Sample Collection: Blood samples were collected in vacutainers tubes containing EDTA at predose (0 hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, 24, 36, 48 and 60 hours post-dose. The plasma samples were separated and kept frozen at -80°C until analysis. Samples were assayed at Anapharm inc. in Sainte-Foy, Quebec, Canada.

Date of First Sample Analysis: February 7, 1998
Date of Last Sample Analysis: February 25, 1998