

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**75-429**

**BIOEQUIVALENCE**

Sotalol Hydrochloride Tablets  
240 mg, 160 mg, 120 mg, 80 mg  
ANDA # 75-429  
Reviewer: Jahnavi S. Kharidia  
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Teva Pharmaceuticals  
Sellersville, PA  
18960  
Submission Date:  
July 31, 1998

## Review of Two Bioequivalence Studies and Three Waiver Requests

**Class:** Antiarrhythmic Drug, Class III

**RLD:** Betapace® Tablets (80 mg, 120 mg, 160 mg, 240 mg), Berlex Laboratories

**Background:** Sotalol HCl is an antiarrhythmic drug with Class III properties. The drug is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia. The mean pharmacokinetic parameters for sotalol are:

Oral bioavailability	90 - 100%
Tmax	2.5 to 4 hours
Elimination half-life	12 hours

The recommended initial dose is 80 mg twice daily. This may be increased up to 240 mg or 320 mg/day.

**Regulatory History:** [Not to be released under FOI]

### Objective

To compare the relative bioavailability of Teva's sotalol HCL tablets, 160 mg, to the reference drug product, Berlex Laboratories's Betapace® tablets, 160 mg, under fasting and non-fasting conditions following a single oral dose.

**Fasting Study:**

**Study Facility Information:**

Clinical Facility: Phoenix International Life Sciences CRC  
Quebec, Canada, H4R 2N6  
Principal Investigator: Samuel Serfaty, MD  
Clinical Study Date: Period 1: February 7, 1998  
Period 2: February 14, 1998  
Analytical Facility:  
Analytical Study Date: February 19, 1998 - March 18, 1998  
Storage Period: No more than 40 days

**Study Design:**

Protocol No.: 961919: Comparative, Randomized, Single-Dose, 2-Way  
Crossover Bioavailability Study of Teva Pharmaceutical's  
and Berlex (Betapace®) 160 mg Sotalol HCL Tablets in  
Healthy Adult Males Under Fasting Conditions  
Design Type: crossover  
Randomized: Y  
No. of Sequences: 2  
No. of Periods: 2  
No. of Treatments: 2  
Washout Period: 7 days  
Single or Multiple dose: single

**Subjects:**

Normal Healthy Volunteers: Y  
IRB Approval: Y  
Informed Consent: Y  
Obtained:  
No. of Subjects Enrolled: 26 male subjects  
Inclusion/Exclusion criteria: vol. 1.2, pages # 150 - 152  
Housing: Evening prior to each drug administration until 36-hour  
blood draw. Subjects returned for blood draws at 48 and  
60 hours

**Treatment Information:**

Treatment:	A	B
Test or Reference:	Test	Reference
Product Name:	Sotalol HCL Tablets	Betapace® Tablets
Strength:	160 mg	160 mg
Manufacturer:	Teva Pharmaceuticals (mfg: 09/97)	Berlex Laboratories

Batch/Lot No.:	K-22947	W70050
Batch-Size:	tablets	N/A
Expiration Date:	N/A	April 2000
Content Uniformity	100.5 %	97.4 %
Assay	100.3 %	99.7 %
Dose Administered:	1 Tablet	1 Tablet
Length of Fasting:	10 hours	10 hours

**Dosing:**

Each subject randomly received either a test product or a reference product with 240 mL of water. Standard meals were provided at 4 and 9 hours after dosing. Water was not permitted for 1 hour before and 2 hours after dosing in each dosing period.

**Blood Sampling:**

Blood sample volume	10 mL
No. of time points	19
Time points	before dosing (0-hour) and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 60 hours after dosing

The blood samples were centrifuged for 20 minutes at 2500 rpm and plasma samples were separated and stored at -20°C until analyzed.

**Analytical Method**

The plasma samples were assayed for sotalolol by \_\_\_\_\_ method. The details of the analytical method are presented in Table 1:

**Table 1: Validation data for sotalolol**

Parameter		
Method		
Internal Standard		
Sensitivity/LOQ	30.2 ng/mL	
Linearity (Standard curve samples)	30.2 - 2010.5 ng/mL	
Quality Control (QC) Samples	H - 1256.6 ng/mL M - 752.6 ng/mL L - 75.3 ng/mL	
Precision of Standards (%)	2.0 - 5.1 %	
Precision of QC Samples (%)	3.8 - 5.8 %	
Accuracy of Standards (%)	93.5 - 110.0%	
Accuracy of QC Samples (%)	102.2 - 104.9 %	
Stability		
Freeze-thaw	3 cycles	
Processed Sample Stability at RT	31.5 hours	
Long term at -20° C	85 days	
Recovery	Sotalolol (mean) 90%	IS - 27.6 %
Low	80.1 %	
Med	91.4 %	
High	98.5 %	

The assay method and validation data are acceptable.

## Results

Of the 26 healthy, adult subjects enrolled in the study, 24 subjects successfully completed both phases of the study. Two subjects (# 2 and # 3) did not complete the crossover study.

<u>Subject</u>	<u>Reason</u>
# 2	Personal Reasons (period 2)
# 3	Positive urine drug screen (period 2)

### 1. Adverse Events

Both drugs are were well tolerated. During the study, a total of five (Trt A = 4, Trt B = 1) adverse events such as headache, tiredness were reported as possibly or probably related to study drug. Three other events were unrelated to treatment. All events were mild to moderate in nature and resolved spontaneously.

### 2. Pharmacokinetics/Statistical Analysis

Mean sotalol plasma levels of 24 subjects are summarized in Table 2 and Figure 1.

Table 2: Mean levels for test and reference products (N=24)

Time (hour)	Test (ng/mL) (Lot Number: K-22947 )		Reference (ng/mL) (Lot Number: W70050)		Ratio T/R
	Mean	Std	Mean	Std	
0	0.00	0.00	0.00	0.00	-
0.33	118.40	55.96	92.86	74.67	1.27
0.67	501.91	160.31	467.84	305.86	1.07
1.0	678.07	274.77	588.84	402.50	1.15
1.5	914.64	342.01	698.01	353.63	1.31
2.0	946.60	316.95	797.91	312.02	1.19
2.5	1034.29	300.34	976.82	281.14	1.06
3.0	1060.48	242.79	977.40	232.96	1.09
3.5	1017.26	196.57	986.09	238.54	1.03
4.0	972.00	225.42	940.05	237.11	1.03
5.0	902.20	205.34	885.37	197.36	1.02
6.0	773.04	129.08	750.74	164.01	1.03
8.0	638.92	107.22	626.10	131.49	1.02
12.0	447.18	81.61	434.69	81.47	1.03
16.0	303.92	49.17	304.41	48.49	0.99
24.0	175.35	37.67	186.90	77.69	0.94
36.0	71.57	15.72	75.06	15.61	0.95
48.0	32.30	18.49	31.52	18.20	1.02
60.0	0.00	0.00	2.62	8.89	-

## Pharmacokinetic Parameters/Statistical Analysis

Analysis of variance was performed on each pharmacokinetic parameter using SAS GLM procedure. Mean reported pharmacokinetic parameters for sotalol are shown in Table 3. The LS means of pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 4.

Table 3: Test mean/Reference mean ratios of pharmacokinetic parameters

Parameter*	Test Mean	SD	Ref Mean	SD	Ratio
AUCI	14647.5	2233.24	14353.9	2579.21	1.02
AUCT	14040.7	2214.28	13739.6	2605.08	1.02
C <sub>MAX</sub>	1223.0	245.81	1164.6	282.8	1.05
KE	0.0725	0.0116	0.0696	0.0087	1.04
LAUCI	14489.6	2187.9	14137.6	2530.6	1.02
LAUCT	13877.9	2178.8	13504.8	2592.9	1.03
LC <sub>MAX</sub>	1196.8	266.89	1131.0	288.4	1.06
THALF	9.784	1.516	10.12	1.289	0.97
T <sub>MAX</sub>	2.669	0.844	2.695	1.077	0.99

\* AUCT=ng-hr/mL, AUCI= ng-hr/mL, T<sub>MAX</sub>=hr, C<sub>MAX</sub>=ng/ml

Table 4: LSMeans and 90% confidence intervals for Sotalol

Parameter	LS Mean <sub>test</sub>	LS Mean <sub>ref</sub>	Low CI	Upp CI
AUCI	14717.2	14464.6	98.8	104.7
AUCT	14110.2	13850.5	98.7	105.0
C <sub>MAX</sub>	1230.2	1172.5	99.1	110.7
LAUCI	14558.6	14244.5	99.2	105.3
LAUCT	13946.9	13612.6	99.3	105.7
LC <sub>MAX</sub>	1204.2	1139.6	99.5	112.2

### Comment:

The 90% confidence intervals of LAUCT, LAUCI and LC<sub>MAX</sub> for sotalol are all within the acceptable limit of 80 -125% .

### **Non-fasting Study**

#### Study Facility Information:

**Clinical Facility:** Phoenix International Life Sciences CRC  
Que., H4R 2N6

**Principal Investigator:** Samuel Serfaty, MD

**Clinical Study Date:** Period 1: February 6, 1998  
Period 2: February 13, 1998  
Period 3: February 20, 1998

**Analytical Facility:**

**Analytical Study Date:** March 24 1998 - April 6, 1998

**Storage Period:** No more than 59 days

**Study Design:**

**Protocol No.:** 961920: Comparative, Randomized, Single-dose, 3-way Crossover Bioavailability Study of Teva Pharmaceuticals and Berlex (Betapace®) 160 mg Sotalol HCL Tablets in Healthy Adult Males Under Fasting and Fed Conditions

**Design Type:** crossover

**Randomized:** Y

**No. of Sequences:** 6

**No. of Periods:** 3

**No. of Treatments:** 3

**Washout Period:** 7 Days

**Single or Multiple dose:** single

**Subjects:**

**Normal Healthy Volunteers:** Y

**IRB Approval:** Y

**Informed Consent Obtained:** Y

**No. of Subjects Enrolled:** 18 male subjects

**Inclusion/Exclusion criteria:** vol. 1.5, pages 1402-1405

**Housing:** Evening prior to each drug administration until 36-hour blood draw. Subjects returned for blood draws at 48 and 60 hours

**Treatment Information:**

<b>Treatment:</b>	<b>A</b>	<b>B</b>	<b>C</b>
<b>Test or Reference:</b>	Test	Test	Reference
<b>Product Name:</b>	Sotalol HCL Tablets	Sotalol HCL Tablets	Betapace® Tablets
<b>Strength:</b>	160 mg	160 mg	160 mg
<b>Manufacturer:</b>	Teva Pharmaceuticals (mfg: 09/97)	Teva Pharmaceuticals (mfg: 09/97)	Berlex Laboratories
<b>Batch/Lot no.:</b>	K-22947	K-22947	W70050
<b>Expiration Date:</b>	N/A	N/A	April 2000
<b>Dose Administered:</b>	1 Tablet	1 Tablet	1 Tablet
<b>Study Condition:</b>	Fasting	Non-fasting	Non-fasting
<b>Length of Fasting:</b>	10.5 hours	10 hours	-10 hours
<b>Standardized Breakfast:</b>	N	Y	Y

### Breakfast Specifics:

The subjects receiving treatments B and C received the following breakfast.

- 1 egg (fried)
- 1 serving of hash brown,
- 1 buttered english muffin
- 8 fluid oz of whole milk
- 1 slice of american cheese
- 6 fluid oz of orange juice
- 1 slice of canadian bacon

### Dosing:

#### Treatments B & C :

All subjects were required to fast overnight for at least 10 hours. Thirty (30) minutes prior to their scheduled dosing times, subjects were given a standard high-fat breakfast. Each subject then received either a test product or a reference product with 240 mL of water.

#### Treatment A:

Each subject received the test product with 240 mL of water.

During each phase of the study, standardized meals were provided to all subjects at 4 and 9 hours after dosing. Water was provided *ad libitum* until 1 hour before and 1 hour after the drug.

### Blood Sampling:

Blood sample volume	10 mL
No. of time points	19
Time points	before dosing (0-hour) and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36, 48, and 60 hours after dosing

The blood samples were centrifuged for 20 minutes at 2500 rpm and plasma samples were separated and stored at -20°C until analyzed.

### Analytical Method

Plasma samples were analyzed by the same validated method as described above for fasting study.

## Results:

Of the 18 healthy male subjects enrolled, one subject (# 4) did not complete the study due to personal reason. Thus, a total of 17 subjects completed three periods of study:

### 1. Adverse Events

Both drugs are well tolerated. During the study, a total of six (Trt A = 1, Trt B = 3, Trt C = 2) adverse events such as headache, tiredness were reported as possibly or probably related to study drug. Nine other events were unrelated to treatment. All events were mild to moderate in nature and resolved spontaneously.

### 2. Pharmacokinetic/Statistical Analysis

The mean plasma for the test and reference products are shown in Table 5 and Figure 2.

Table 5: Mean levels (ng/mL) for test and reference products (N=17)

Time (hour)	Test <sub>Fasting</sub> - A (Lot Number: K-22947)		Test <sub>Non-fasting</sub> - B (Lot Number: K-22947)		Reference <sub>Non-fasting</sub> - C (Lot Number: W70050)	
	Mean	Std	Mean	Std	Mean	Std
0	0.00	0.00	0.00	0.00	0.00	0.00
0.33	100.92	95.82	30.68	42.15	6.22	17.94
0.67	474.51	215.28	228.39	246.07	74.12	114.66
1.0	672.01	266.73	391.87	366.61	165.61	197.69
1.5	890.88	317.97	610.90	383.46	375.19	275.47
2.0	1009.09	309.46	738.09	312.53	623.65	348.34
2.5	1100.25	248.95	842.55	193.63	788.76	304.03
3.0	1103.08	199.70	926.51	156.94	895.18	251.81
3.5	1081.80	197.82	969.31	154.96	994.26	238.34
4.0	1053.82	207.81	971.18	159.86	1004.49	223.65
5.0	974.47	219.56	926.09	183.73	1015.13	176.03
6.0	837.66	149.95	799.02	157.72	876.62	154.07
8.0	716.19	129.73	641.32	122.95	741.45	126.03
12.0	481.72	83.21	450.24	78.45	491.98	86.73
16.0	340.37	53.83	307.86	55.60	335.81	55.12
24.0	187.29	28.24	179.01	32.36	188.32	36.86
36.0	76.64	13.07	78.62	17.28	76.96	16.39
48.0	26.32	20.54	33.28	21.82	29.46	21.70
60.0	1.84	7.57	3.96	11.23	6.08	13.66

### Pharmacokinetic Parameters

Mean reported pharmacokinetic parameters are shown in Table 6.

Table 6: Mean pharmacokinetic parameters and relative ratio of test

Parameter*	Test (Fasting) E A	Std	Test (Non-fasting) B	Std	Ref (Non-fasting) C	Std	B/C
AUCI	15685.3	2267.5	14281.0	2084.3	14808.2	2111.9	0.96
AUCT	15048.7	2308.9	13639.7	2085.7	14195.1	2169.4	0.96
C <sub>MAX</sub>	1265.7	205.1	1067.8	236.2	1102.8	181.5	0.97
KE	0.0743	0.0105	0.0695	0.0108	0.0727	0.0124	0.96
LAUCI	15514.87	0.16	14138.55	0.15	14667.03	0.14	0.96
LAUCT	14865.65	0.17	13491.13	0.15	14039.80	0.15	0.96
LC <sub>MAX</sub>	1246.79	0.19	1045.52	0.21	1089.02	0.16	0.96
THALF	9.52	1.39	10.21	1.65	9.84	1.89	1.04
T <sub>MAX</sub>	2.85	0.96	3.38	1.17	3.97	1.15	0.85

\*AUCT=ng-hr/mL, AUCI= ng-hr/mL, T<sub>MAX</sub>=hr, C<sub>MAX</sub>=ng/mL

**Comment:**

Values of C<sub>max</sub>, AUCT and AUCI mean ratios for the test product versus the reference product administered under non-fasting conditions (Ratio B/C) are within the acceptable range of 0.8 - 1.2.

**Dissolution Testing:**

The dissolution data and general conditions are described in Table 7:

Table 7- In Vitro Dissolution Testing						
Drug (Generic Name): Sotalol HCL						
Dosage Form: Tablets						
Dose Strength: 240 mg, 160 mg, 120 mg, 80 mg						
I. Conditions for Dissolution Testing:						
Apparatus:	Paddle			Volume:	900 mL	
Speed:	50 rpm			Sampling Time:	10, 20 and 30 minutes	
No. Units	12			Tolerance:	NLT , in 30 minutes	
Medium:	Purified Water, USP at 37°C					
II. Results of In Vitro Dissolution Testing: 240 mg Tablets						
Time	Test Product Lot # K-2287J			Reference Product Lot # W70017		
	Mean %	Range	(CV%)	Mean %	Range	(CV%)
10	88.8		4.3	78.6		9.2
20	101.6		1.0	93.9		2.6
30	102.3		0.7	96.5		1.6
III. Results of In Vitro Dissolution Testing: 160 mg Tablets						
Time	Test Product Lot # K-22947			Reference Product Lot # W70050		
	Mean %	Range	(CV%)	Mean %	Range	(CV%)
10	93.9		2.6	76.5		10.6
20	102.2		0.8	95.8		2.5
30	102.3		1.0	97.8		1.7
IV. Results of In Vitro Dissolution Testing: 120 mg Tablets						
Time	Test Product Lot# K-22946			Reference Product Lot # W50119		
	Mean %	Range	(CV%)	Mean %	Range	(CV%)
10	96.1		2.1	65.9		18.3
20	100.7		1.1	99.2		1.5
30	100.6		1.1	99.1		2.0
V. Results of In Vitro Dissolution Testing: 80 mg Tablets						
Time	Test Product Lot # K-22945			Reference Product Lot # W60187		
	Mean %	Range	(CV%)	Mean %	Range	(CV%)
10	98.4		2.1	65.2		10.3
20	100.7		1.7	100.6		1.6
30	102.0		1.5	101.5		1.3

**Comments:**

1. The dissolution data are acceptable. The dissolution results comply with the firm's specification of "not less than dissolved in 30 minutes".
2. Based on the dissolution data submitted, the reviewer recommends higher specification i.e., "not less than dissolved in 30 minutes".

**Composition**

**(Not To Be Released Under FOI)**

Ingredients	Amount (mg) /Tablet			
	80 mg	120 mg	160 mg	240 mg
Sotalol HCL				
Lactose Monohydrate				
Starch				
FD&C Blue No.				
Povidone				
Magnesium Stearate				
Total				

**Waiver Request**

The firm requests waiver of requirements for in vivo bioequivalence testing on its 80 mg, 120 mg and 240 mg strengths per 21 CFR section 320.22 (d) (2).

**Comments:**

1. Assay method validation: Pre-study and within-study validations are acceptable.
2. Fasting and Non-fasting bioequivalence studies conducted with 160 mg strength are acceptable.
3. The dissolution data of all 4 strengths (240 mg, 160 mg, 120 mg, 80 mg) meet the specification of "not less than dissolved in 30 minutes".
4. The formulations of 80 mg, 120 mg and 240 mg strengths are proportionally similar to the 160 mg strength in their active and inactive ingredients.

**Recommendations:**

1. The *in vivo* bioequivalence study conducted under fasting conditions by Teva Pharmaceuticals on its sotalol HCl tablets, 160 mg, lot # K-22947, comparing it to Berlex Laboratories' Betapace® tablets, 160 mg, lot # W70050, is acceptable.