CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76170

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-170 SPONSOR : Barr Labs.

DRUG AND DOSAGE FORM: Lithium Carbonate ER Tablets

STRENGTH(S) : 300 mg

TYPES OF STUDIES : Fasting, Non-fasting, Dissolution

CLINICAL STUDY SITE(S):

ANALYTICAL SITE(S) :

STUDY SUMMARY : Fasting and non-fasting studies are acceptable.

DISSOLUTION : Dissolution study is acceptable

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __Yes__ New facility __No_ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : S. P. Shrivastava, Ph.D. BRANCH : II

INITIAL: _____ DATE: 2/7/02

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH :

INITIAL : __ /S/ DATE : 2/7/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

for INITIAL : __ /S/ DATE : 2/20/2002

3.1

LITHIUM CARBONATE ER TABLETS
Strength, 300 mg
ANDA 76-170
Reviewer: S. P. Shrivastava
V:\firmsam\barr\76170a0102.doc

Barr Laboratories, Inc.
Pomona, NY

Amendment: January 22, 2002

REVIEW OF AN AMENDMENT

INTRODUCTION

Indication:	**Anti-depressant**
Type of Submission:	**Amendment**
Contents of Submission:	**Comparative dissolution in 5 media**
RLD:	**Lithobid® (Solvay))**

BACKGROUND: The firm submitted biostudies and dissolution testing on May 11, 2001. However, the dissolution data were incomplete. In this amendment, the firm has responded to the deficiency (see review, SShrivastava 11/15/01).

Deficiency: *You have provided dissolution data for the products in USP recommended media. However, you have not provided in vitro dissolution data in other media. For appropriate evaluation and setting up dissolution specifications, comparative dissolution profiles for products should be generated in water and in aqueous media at following pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5.*

Response: The firm has provided dissolution in 5 media. The results are summarized below.

DISSOLUTION (Not to be released under FOI)

Dissolution Methods/Results

1. Dissolution Medium	**Dilute Hydrochloric Acid, pH 1.2**
Volume	800 mL
Dissolution Apparatus	USP I (Basket) at 100 rpm
Test	**REFERENCE**
Lot No.: 403450002R	Lot No.: 91108 (new lot, biolot expired)
Strength: 300 mg	Strength: 300 mg
No. of Units: 12	No. of Units: 12

Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
15	4		23.0	5		15.9
30	16		15.6	17		10.5
45	30		10.9	31		8.8
90	70		6.4	70		6.8
120	89		4.0	99		3.4
150	102		3.4	101		3.5
F2	**66.64**					

2. Dissolution Medium **Sodium Acetate, pH 4.5**
Volume 800 mL
Dissolution Apparatus USP I (Basket) at 100 rpm

Test **REFERENCE**
Lot No.: 403450002R Lot No.: 91982, Exp. Date 3/4/03
Strength: 300 mg Strength: 300 mg
No. of Units: 12 No. of Units: 12

Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
30	17		4.7	18		5.0
60	39		3.8	41		7.2
120	75		3.3	101		1.3
180	99		2.6	101		1.7
300	106		1.8	102		1.5
F2	**41.05**					

3. Dissolution Medium **Phosphate Buffer, pH 6.5**
Volume 800 mL
Dissolution Apparatus USP I (Basket) at 100 rpm

Test **REFERENCE**
Lot No.: 403450002R Lot No.: 91982
Strength: 300 mg Strength: 300 mg
No. of Units: 12 No. of Units: 12

Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
30	5		9.5	7		8.2
60	12		9.3	14		8.9
120	26		6.1	32		23.8
180	39		5.2	61		13.7
300	59		4.4	87		8.9

420	76	70-81	4.2	99	88-106	4.9
F2	**37.79**					

4. Dissolution Medium **Phosphate Buffer, pH 7.5**
Volume 800 mL
Dissolution Apparatus USP I (Basket) at 100 rpm

Test **REFERENCE**
Lot No.: 403450002R Lot No.: 91982
Strength: 300 mg Strength: 300 mg
No. of Units: 12 No. of Units: 12

Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
30	4		7.4	6		4.8
60	10		8.0	11		5.5
120	22		7.0	23		13.0
180	30		5.6	40		13.4
300	45		5.4	59		11.2
420	53		4.9	69		9.9
F2	**44.64**					

5. Dissolution Medium **Water**
Volume 800 mL
Dissolution Apparatus USP I (Basket) at 100 rpm

Test **REFERENCE**
Lot No.: 403450002R Lot No.: 91982
Strength: 300 mg Strength: 300 mg
No. of Units: 12 No. of Units: 12

Time(minutes)	Mean	Range	%CV	Mean	Range	%CV
30	17		6.2	17		10.8
60	40		5.9	40		11.1
120	78		3.6	102		2.6
180	102		4.0	104		2.4
300	104		2.0	104		1.4
F2	**42.86**					

COMMENTS

1. Dilute hydrochloric acid appears to be the best dissolution medium, because the dissolution profile matches better with the reference, it gradually dissolves over % of the products in 120 minutes, and it does not cause any dose-dumping.

2. USP 24 also recommends this method (see Test 1).

3. The USP tolerance limit is applicable for this product as well

RECOMMENDATIONS

1. The dissolution testing conducted by the firm on its lithium carbonate ER, 300 mg tablets, Lot #403450002R comparing it to Lithobid® Slow Release tablets, 300 mg Lot #91108 and 91982 manufactured by Solvay, is acceptable.

   The dissolution testing should be conducted in dilute HCl (7 mL in 1000 mL water), 800 mL using Apparatus I (Basket) at 100 rpm. The product should meet the following specifications:

   15 minutes %
   45 minutes %
   90 minutes %
   120 minutes NLT %

2. The firm has conducted an acceptable bioequivalence study under fasting conditions on its lithium carbonate ER, 300 mg tablets, Lot #403450002R comparing it to Lithobid® Slow Release tablets, 300 mg Lot #91108 manufactured by Solvay.

3. The firm has also conducted an acceptable bioequivalence study under non-fasting conditions on its lithium carbonate ER, 300 mg tablets, Lot #403450002R comparing it to Lithobid® Slow Release tablets, 300 mg Lot #91108 manufactured by Solvay.

4. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalence and *in vitro* dissolution studies, and the application is complete.

The firm should be informed of the recommendations.

/S/

S.P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 2/7/2002

/S/ 2/20/2002

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-170 APPLICANT: Barr Labs.

DRUG PRODUCT: Lithium Carbonate ER Tablets USP: 300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

NOV 20 2001

ANDA: 76-170 APPLICANT: Barr Labs.

DRUG PRODUCT: Lithium Carbonate ER tablets: 300 mg

The Division of Bioequivalence has completed its review of your submission(s) **acknowledged on the cover sheet. The following deficiencies have been identified:**

1. You have provided dissolution data for the products in USP recommended media. However, you have not provided *in vitro* dissolution data in other media. For appropriate evaluation and setting up dissolution specifications, comparative dissolution profiles for products should be generated in water, and in aqueous media at following pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

LITHIUM CARBONATE ER TABLETS
Strength, 300 mg
ANDA 76-170
Reviewer: S. P. Shrivastava

Barr Laboratories, Inc.
Pomona, NY

Submission Date: May 11, 2001
Amendment: July 26, 2001

REVIEW OF BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA (ELECTRONIC SUBMISSION)

INTRODUCTION

Indication:	**Anti-depressant**
Type of Submission:	**New Application**
Contents of Submission:	**Single-dose fasting, non-fasting and dissolution studies**
RLD:	**Lithobid® (Solvay) 300 mg, ER tablets**
Recommended Dose:	**300 mg t.i.d.**

BACKGROUND

RLD: LITHOBID® (lithium carbonate) ER Tablets. Lithium carbonate Extended release tablets are available in 300 mg (Solvay) and 450 mg (SmithKline Beecham) strengths, IR tablets in 300 mg (Pfizer), and as IR capsules in 150 mg (Roxane) and 300 mg (SmithKline Beecham) strengths.

Financial Disclosure:

The sponsor has certified that the investigator(s), has/have not entered into any financial arrangement with the sponsor, has/have no proprietary interest in the product(s), or was/were recipient(s) of significant payments of other sorts.

Protocol No.: 2427, Randomized, 2-Way Crossover, Bioequivalence Study of Lithium Carbonate, USP 300 mg ER tablets and Lithobid® 300 mg Slow-Release Tablet Administered as 1 x 300 mg Tablet in Healthy Adult Males and Females under Fasting Conditions

STUDY INFORMATION

STUDY FACILITY INFORMATION

Clinical Facility:	
Medical Director:	
Clinical Study Dates:	11/28/00 – 1/30/01
Analytical Facility	
Principal Investigator:	
Study Dates	11/28/00 – 2/3/01

Analytical Study Dates:	2/12/01 – 3/16/01
Storage Period:	108 Days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	Test	Reference
Product Name:	Lithium carbonate ER tablets	Lithobid® (lithium carbonate) ER tablets
Manufacturer:	Barr Labs.	Solvay
Manufacture Date:	11/2/00	
Expiration Date:		2/2/01 (very close to 1/30/01, the end of the study)
ANDA Batch Size:		
Full Batch Size:		
Batch/Lot Number:	403450002R	91108
Potency:	100.7%	98.7%
Content Uniformity (wt.):	100% (0.8% CV)	98.8 % (1.2% CV)
Strength:	300 mg	300 mg
Dosage Form:	tablet	tablet
Dose Administered:	300 mg	300 mg
Study Condition:	fasting	fasting
Length of Fasting:	at least 10 hours	at least 10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Trt Design:**	Y
No. of Periods:	4	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	21 days

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	24
Route of Administration:	oral	**No. of Subjects Completing:**	20
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	20
Number of Doses:	N/A	**No. of Dropouts:**	#5 and 19 due to adverse events, and #12 and 18 due to noncompliance
Loading Dose:	N/A	**Sex(es) Included:**	Male and Female
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	14 in 9 subjects

Dietary Restrictions: Subjects were instructed to abstain from alcohol, grapefruit products,

caffeine and xanthine-containing foods and fluids 48 hours prior to dosing until after the last sample collection of each period.

Activity Restrictions: For their personal safety, subjects were required to remain in a seated or semi-seated position for at least 4 hours after dosing avoiding complete rest.

Drug Restrictions: No OTC drugs 7 days prior to the study, and no prescription drugs 14 days prior to the study and during the study.

Randomization Scheme Sequence: ABAB –1, 2, 7, 8, 9, 10, 12, 14, 15, 19, 21, 22.
Sequence: BABA – 3, 4, 5, 6, 11, 13, 16, 17, 18, 20, 23, 24

Blood Sampling Time: 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hrs. post-drug intake.

Protocol Deviations 91; 86 were blood sampling time deviations; 1 for water intake; 4 for early centrifugation of blood samples. None were serious.

DEMOGRAPHIC INFORMATION

Particulars	Details			
ANDA	76-170	Lithium carbonate ER tablets	300 mg	
CRO	Biovail Contract Research			
Study Type	Fasting			
Race	Caucasian=17	Hispanic=3	Black=3	Asian=1
Sex	Males=12	Females=12		
Age, yrs.	Ave=32	Range=21-46	18-40 yrs=19	41-64 yrs=5
Height, inches	Ave=68	Range=60-74		
Weight, lbs.	Ave=154	Range=117-204		

STUDY RESULTS

1) Clinical

Adverse Events: Adverse events related to drug appear to be isolated and are listed below:

Adverse Event	Test	Reference
Diarrhea	1	0
Vomiting	2	0
Headache	1	1
Stomach upset	0	1

Protocol Deviations: Deviations were minor and most of them were in blood sampling. Blood sampling deviations were included in PK calculations.

Dropouts: #5 and 19 due to adverse events, and #12 and 18 due to noncompliance.

2) Analytical
Pre-Study Assay Validation:

ANALYTE: LITHIUM CARBONATE
ASSAY METHOD:

WITHIN STUDY ASSAY VALIDATION FOR FASTING STUDY #01138

3) Statistical Analysis

The mean plasma concentrations of lithium carbonate for 20 subjects at each time point after test and reference products are shown in Table 1. The plasma concentration-time profiles of lithium carbonate for the two products are plotted in Figure P-1. The pharmacokinetic parameters are summarized in Tables 2 and 3. BE assessment was performed using PROC MIXED program in SAS suggested by Don Schuirmann (CDER, FDA) for replicate design studies.

Comments

1. As indicated above, the reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.

2. The elimination constants were calculated appropriately for all.

3. None of the subjects showed 0-hour drug level, first scheduled post-dose time point as T_{max}, or first measurable drug concentration as C_{max}.

4. The test/reference ratios for AUC_{0-t} ranged from 0.82 to 1.28 (mean = 1.00), AUC_{0-Inf} ranged from 0.81 to 1.26 (mean = 1.00), and for C_{max} ranged from 0.73 to 1.58 (mean = 1.15).

5. The AUC_{0-t}/AUC_{0-Inf} ratios ranged between 0.92 and 0.98 for the test and reference products.

6. ANOVA coefficient of variation for AUC_{0-t}, AUC_{0-Inf}, and C_{max}, respectively, were: 7.50, 7.39 and 11.79%.

7. Root Mean Square Error for log transformed parameters were: AUC_{0-t} - 0.072990, AUC_{0-Inf} - 0.071103, and C_{max} – 0.111889.

Conclusion: The fasting study is acceptable

FIG P—1. PLASMA LITHIUM CARBONATE LEVELS (N=20)

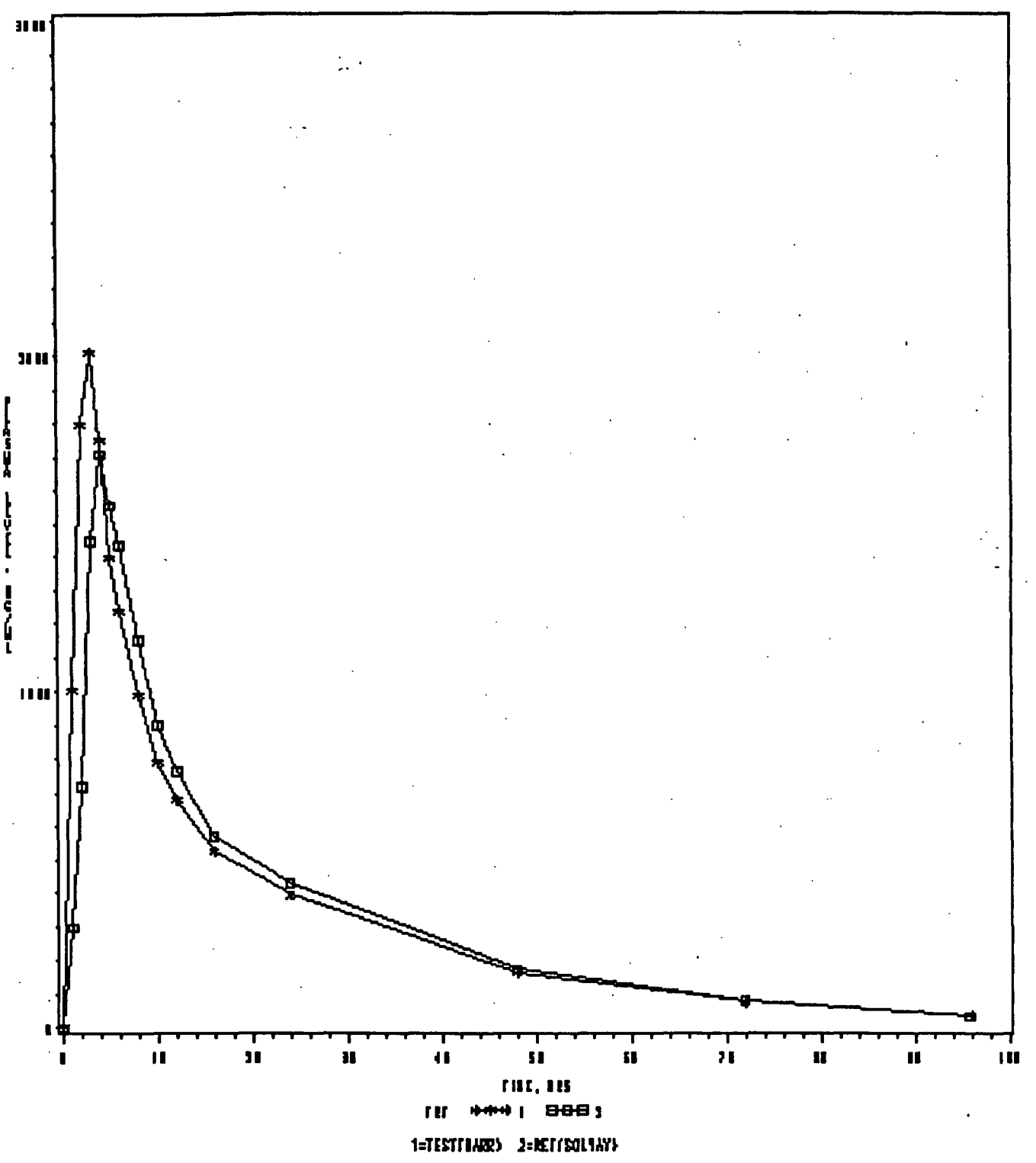

TABLE 1. MEAN PLASMA LITHIUM CARBONATE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	1002.88	534.77	297.00	86.22	3.38
2	1795.78	511.97	718.28	272.70	2.50
3	2008.03	472.25	1447.20	498.20	1.39
4	1753.25	348.21	1710.50	405.02	1.02
5	1394.70	294.96	1554.70	278.12	0.90
6	1234.55	239.58	1434.50	273.79	0.86
8	988.35	189.02	1151.35	265.17	0.86
10	787.08	153.30	900.93	187.54	0.87
12	681.73	134.23	763.83	143.04	0.89
16	523.68	104.11	569.73	105.91	0.92
24	392.78	82.95	428.55	80.05	0.92
48	162.56	46.04	173.85	45.73	0.94
72	74.95	25.18	78.81	27.07	0.95
96	32.59	23.12	31.39	22.57	1.04

MEAN1=TEST MEAN2=REFERENCE UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 2. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	32138.76	6357.46	32302.36	5524.95	0.99
AUCT	30783.87	5968.13	30939.77	5331.09	0.99
CMAX	2118.00	416.15	1865.00	364.28	1.14
KE	0.03	0.00	0.04	0.01	0.97
LAUCI	31594.30	0.18	31865.68	0.17	0.99
LAUCT	30275.49	0.18	30514.58	0.17	0.99
LCMAX	2078.20	0.20	1830.14	0.20	1.14
THALF	20.64	2.75	20.07	2.93	1.03
TMAX	2.75	0.63	4.43	1.03	0.62

MEAN1=TEST MEAN2=REFERENCE UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 3. LSMEANS AND 90% CONFIDENCE INTERVALS (Regular 2-Way X-over Analysis)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	32138.76	32302.36	0.99	96.74	102.25
AUCT	30783.87	30939.77	0.99	96.70	102.29
CMAX	2118.00	1865.00	1.14	108.86	118.27
LAUCI	31594.30	31865.68	0.99	96.50	101.87
LAUCT	30275.49	30514.58	0.99	96.52	101.98
LCMAX	2078.20	1830.14	1.14	108.86	118.46

Protocol No.: 2428, Randomized, 2-Way Crossover, Bioequivalence Study of Lithium Carbonate, USP 300 mg ER tablets and Lithobid 300 mg Slow-Release Tablet Administered as 1 x 300 mg Tablet in Healthy Adult Males and Females under Nonfasting Conditions

STUDY INFORMATION

STUDY FACILITY INFORMATION

Clinical Facility:	
Medical Director:	
Clinical Study Dates:	11/28/00 – 1/30/01
Analytical Facility	
Principal Investigator:	
Study Dates	12/12/00 – 12/20/00
Analytical Study Dates:	
Storage Period:	Days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	Test	Reference
Product Name:	Lithium carbonate ER tablets	Lithobid® (lithium carbonate) ER tablets
Manufacturer:	Barr Labs.	Solvay
Manufacture Date:	11/2/00	
Expiration Date:		2/2/01 (very close to 1/30/01, the end of the study)
ANDA Batch Size:		
Full Batch Size:		
Batch/Lot Number:	403450002R	91108
Potency:	100.7%	98.7%
Content Uniformity (wt.):	100% (0.8% CV)	98.8 % (1.2% CV)
Strength:	300 mg	300 mg
Dosage Form:	tablet	tablet
Dose Administered:	300 mg	300 mg
Study Condition:	Non-fasting	Non-fasting
Length of Fasting:	at least 10 hours	at least 10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	crossover
No. of Sequences:	2	**Replicated Trt Design:**	N
No. of Periods:	2	**Balanced:**	Y
No. of Treatments:	2	**Washout Period:**	2 Weeks

DOSING		SUBJECTS	
Single or Multiple Dose:	single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	20
Route of Administration:	oral	**No. of Subjects Completing:**	20
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	20
Number of Doses:	N/A	**No. of Dropouts:**	None
Loading Dose:	N/A	**Sex(es) Included:**	Male and Female
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	5 in 4 subjects

Dietary Restrictions: Subjects were been instructed to abstain from alcohol, grapefruit products, caffeine and xanthine-containing foods and fluids 48 hours prior to dosing until after the last sample collection of each period.

Activity Restrictions: For their personal safety, subjects were required to remain in a seated or semi-seated position for at least 4 hours after dosing avoiding complete rest.

Drug Restrictions: No OTC drugs 7 days prior to the study, and no prescription drugs 14 days prior to the study and during the study.

Randomization Scheme **AB:** 6, 7, 10, 11, 13, 14, 15, 16, 17, 18
BA: 1, 2, 3, 4, 5, 8, 9, 12, 19, 20

Blood Sampling Time: 0, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hrs. post-drug intake.

Protocol Deviations 95; 91 were blood sampling time deviations; 1 for attending physician arriving late; 1 for attending physician leaving during dosing, 1 for lack of hematological data, and 1 for lack of urine microscopy data.

DEMOGRAPHIC INFORMATION

Particulars	Details			
ANDA	76-170	Lithium carbonate ER tablets	300 mg	
CRO	Biovail Contract Research			
Study Type	Fasting			
Race	Caucasian=13	Hispanic=0	Black=7	Asian=0
Sex	Males=10	Females=10		
Age, yrs.	Ave=31	Range=20-47	18-40 yrs=17	41-64 yrs=3
Height, inches	Ave=68	Range=62-72		
Weight, lbs.	Ave=158	Range=107-198		

STUDY RESULTS

1) Clinical
Adverse Events: Adverse events related to drug appear to be isolated and are listed below:

Adverse Event	Test	Reference
Headache	2	0
Stomach upset	1	0
Dizziness	0	1

Protocol Deviations: Deviations were minor and most of them were in blood sampling. Blood sampling deviations were included in PK calculations.

Dropouts: None

2) Analytical
Pre-Study Assay Validation:

ANALYTE: LITHIUM CARBONATE
ASSAY METHOD:

3) Statistical Analysis:

1. Plasma concentration data is given in Table 4 and Figure P-2.

2. The reviewer recalculated the pharmacokinetic parameters and the test/reference ratios for PK parameters (Tables 5-6). The reported values are in good agreement with those obtained by the reviewer.

3. The elimination constants were calculated for all subjects appropriately.

4. There were no subjects with 0 hour drug level, no subjects with first scheduled post-dose time point as T_{max}/subjects with first measurable drug concentration as C_{max}.

5. The test/reference ratios for AUC_{0-t} ranged from 0.80 to 1.18 (mean = 0.98), AUC_{0-inf} ranged from 0.81 to 1.19 (mean = 0.98), and for C_{max} ranged from 0.81 to 1.26 (mean = 1.00).

6. The AUC_{0-t}/AUC_{0-inf} ratios ranged between 0.91 and 0.98 for the test and reference products.

7. ANOVA coefficient of variation for AUC_{0-t}, AUC_{0-inf}, and C_{max}, respectively, were: 4.71, 4.67 and 8.87%.

8. Root Mean Square Error for log transformed parameters were: AUC_{0-t} - 0.049008, AUC_{0-inf} - 0.046800, and C_{max} – 0.092820.

Conclusion: The non-fasting study is acceptable.

FIG P—2. PLASMA LITHIUM CARBONATE LEVELS (N=20)

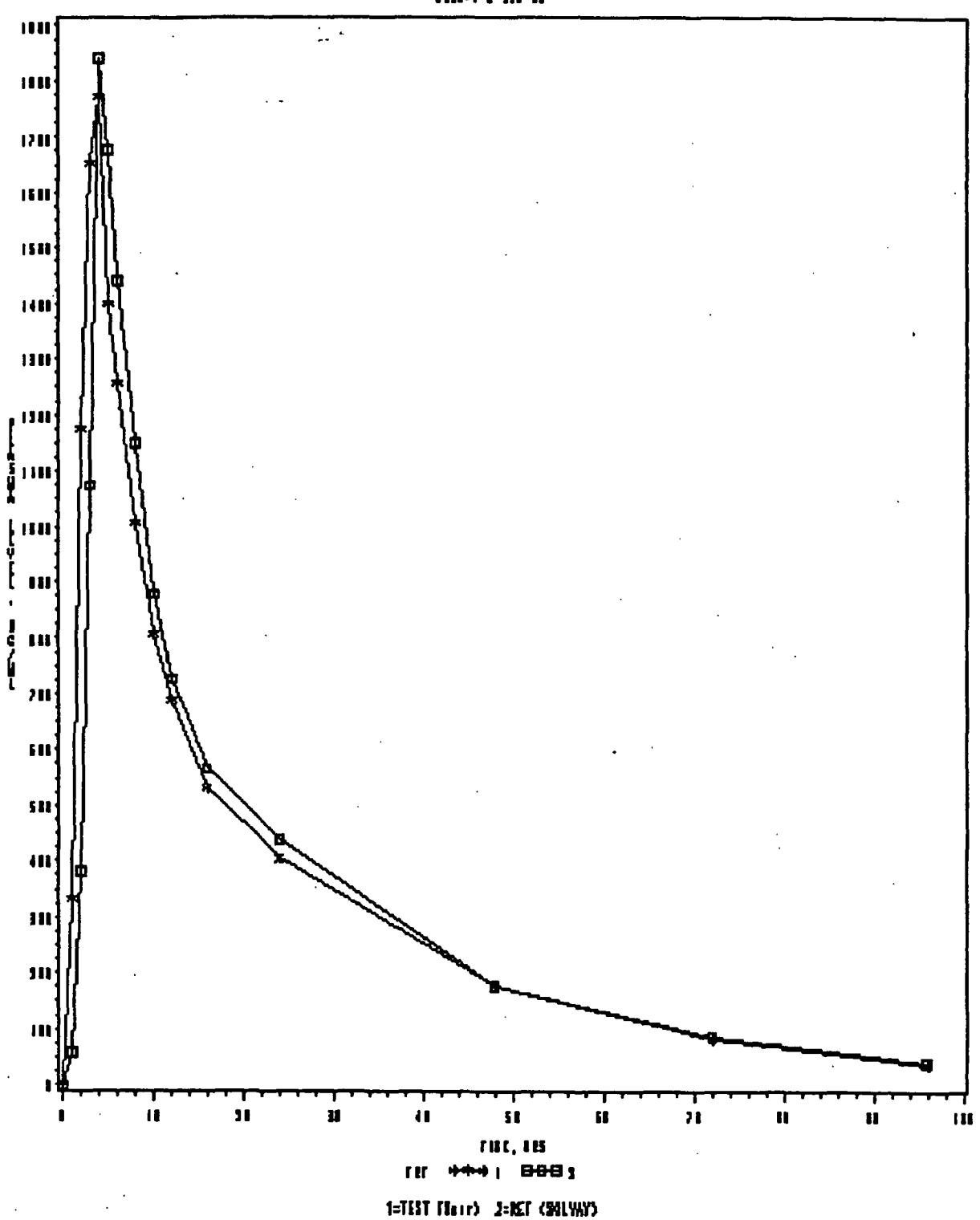

TABLE 4. MEAN PLASMA LITHIUM CARBONATE LEVELS FOR TEST AND REFERENCE PRODUCTS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	331.06	367.77	57.37	61.05	5.77
2	1174.95	824.65	380.88	311.79	3.08
3	1654.80	524.68	1075.10	667.41	1.54
4	1771.25	410.96	1842.30	691.07	0.96
5	1398.20	349.41	1676.95	457.76	0.83
6	1256.90	243.40	1441.95	288.67	0.87
8	1006.32	195.34	1149.85	246.58	0.88
10	806.05	154.12	878.40	151.14	0.92
12	689.21	126.76	727.85	111.07	0.95
16	531.40	84.24	568.20	70.40	0.94
24	404.25	60.55	439.50	57.92	0.92
48	176.70	43.43	176.89	45.26	1.00
72	83.92	26.46	87.48	30.00	0.96
96	38.42	21.37	42.22	22.30	0.91

MEAN1=TEST, MEAN2=REF UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TABLE 5. ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	31661.01	4283.19	32549.89	4299.44	0.97
AUCT	30180.07	3953.09	31014.01	3732.51	0.97
CMAX	2134.50	403.28	2138.00	369.08	1.00
KE	0.03	0.00	0.03	0.00	1.00
LAUCI	31360.14	0.15	32285.99	0.13	0.97
LAUCT	29908.59	0.14	30803.25	0.12	0.97
LCMAX	2098.88	0.19	2106.17	0.18	1.00
THALF	21.41	3.13	21.43	3.26	1.00
TMAX	3.36	1.03	4.46	1.05	0.75

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

TABLE 6. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	31661.01	32549.89	0.97	94.74	99.80
AUCT	30180.07	31014.01	0.97	94.77	99.86
CMAX	2134.50	2138.00	1.00	94.98	104.70
LAUCI	31360.14	32285.99	0.97	94.67	99.66
LAUCT	29908.59	30803.25	0.97	94.52	99.74
LCMAX	2098.88	2106.17	1.00	94.71	104.86

WAIVER REQUEST: Not applicable

Formulation (Not to be released under FOI)

INGREDIENT	AMOUNT, MG/TABLET
Core Tablet	
Lithium carbonate, USP	
Sodium starch glycolate, NF	
Carnuba wax	
Povidone, USP	
Sorbitol, NF	
Calcium stearate, NF	
Purified water, USP	
Core Tablet Wt.	**435.0**
Film Coating	
Methyl cellulose, USP	
Purified water, USP	
TOTAL WT. (COATED TABLET)	**446.0**

* Not retained in the finished product.
** Coating dispersion is sprayed onto the core until a target wt. of 11 mg (7-15 mg) is reached.

How Supplied

Test: Round, off white, film coated, biconvex, unscored, debossed "b" on one side and"345" on the other.
Ref: Peach colored with "Solvay 4492" debossed on the tablet.

Formulation Comments: The inactive ingredients are within the IIG limits.

DISSOLUTION (Not to be released under FOI)

Dissolution Methods/Results: The firm has used USP dissolution method in the study.
Dissolution Medium: Dilute Hydrochloric Acid, (7:1000)
Volume: 800 mL
Dissolution Apparatus: USP I (Basket) at 100 rpm

Mean Dissolution Data

	TEST Lot No.: 403450002R Strength: 300 mg No. of Units: 12			REFERENCE Lot No.: 91108 Strength: 300 mg No. of Units: 12		
Time(minutes)	**Mean**	**Range**	**%CV**	**Mean**	**Range**	**%CV**
15	4		23.0	5		15.9
30	16		15.6	17		10.5
45	30		10.9	31		8.8
90	70		6.4	70		6.8
120	89		4.0	99		3.4
150	102		3.4	101		3.5
Similarity Factor	**F2**					

Dissolution Comments: The dissolution test meets the tolerance specifications given below for USP Drug Release Test 1. Two out of 12 test ER tablets show less than % dissolution at 120 minutes, but the differences are within the USP criteria in Acceptance Table 1 – "the average value of 12 units ...is not less than the stated amount at the final test time; ....; and none is more than % of the labeled content below the stated amount at the final test time".

15 minutes	%
45 minutes	%
90 minutes	%
120 minutes	NLT %

COMMENTS

1. The firm has provided dissolution data for the products in USP recommended media. However, it has not provided *in vitro* dissolution data in other media that is necessary to test the robustness of the test formulation. For appropriate evaluation for the test formulation (no dose dumping) and setting up dissolution specifications, comparative dissolution profiles for products should be generated in water, and in aqueous media at following pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5 .

RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by Barr Labs.on its lithium carbonate ER, 300 mg ER tablets, Lot #403450002R comparing it to Lithobid® Slow Release ER tablets, 300 mg Lot #91108 manufactured by Solvay, is acceptable.

2. The bioequivalence study conducted under non-fasting conditions by Barr Labs.on its lithium carbonate ER, 300 mg ER tablets, Lot #403450002R comparing it to Lithobid® Slow Release ER tablets, 300 mg Lot #91108 manufactured by Solvay, is acceptable.

3. The dissolution testing conducted by the firm on its lithium carbonate ER, 300 mg ER tablets, Lot #403450002R comparing it to Lithobid® Slow Release ER tablets, 300 mg Lot #91108 manufactured by Solvay, is acceptable. However, it has not provided *in vitro* dissolution data for products in other media. For setting up appropriate dissolution specifications, comparative dissolution profiles for products should be generated in water, and in aqueous media at following pH ranges: 1-1.5, 4-4.5, 6-6.5 and 7-7.5.

4. From bioequivalence point of view, the firm has not met the requirements of *in vitro* dissolution studies, and the application is incomplete due to comment #1.

The firm should be informed of the recommendations.

/S/

S.P. Shrivastava, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR /S/
FT INITIALED S.NERURKAR Date 11/6/2001

Concur: /S/ Date 11/15/01

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

SPS/sps/11-01-01/76170SD.501

cc: ANDA #76-170 (Original, Duplicate), HFD-655 (SNerurkar, SShrivastava), Drug File, Division File.