CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-243

BIOEQUIVALENCE REVIEW(S)

A.1 Ack
NXP

Lithium Carbonate Capsules, USP
Strength, 300 mg
ANDA 76-243
Reviewer: S. Pradhan

West-Ward Pharmaceutical Corp.
Eatontown, NJ
Submission Date:
September 24, 2001
~~April 23, 2002~~ (KS)

V:\FIRMSNZ\West-Ward\LTRS&REV\76243N0901

REVIEW OF BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

INTRODUCTION

Indication:	Anti-depressant
Type of Submission:	New Application
Contents of Submission:	Single-dose fasting, non-fasting and dissolution studies
RLD:	Eskalith® (Smithkline Beechan) 300 mg, IR capsules
Recommended Dose:	300 mg t.i.d.

BACKGROUND

RLD: **Eskalith®** (lithium carbonate) IR Capsules manufactured by **SmithKline Beecham.**

Protocol No.: 010909, Randomized, 2-Way Crossover, Bioequivalence Study of Lithium Carbonate, 300 mg IR capsules and Eskalith® (Smithkline Beechan) capsules, 300-mg.

The drug **was administered as 2 x 300 mg Capsules in healthy adult males and females under Fasting Conditions**

STUDY INFORMATION

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Medical Director:	[redacted]
Clinical Study Dates:	Period I: 5/15/01 – 5/18/01; Period II: 5/29/01 – 6/01/01
Analytical Facility:	[redacted]
Method:	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	6/05/01 – 6/18/01

Storage Period:	35 Days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	Test	Reference
Product Name:	**Lithium Carbonate, 300 mg IR capsules**	Eskalith® capsules, 300 mg
Manufacturer:	West-Ward Pharnaceutical Corp.	Smithkline Beechan
Manufacture Date:	11/2/00	
Expiration Date:	January, 2003	October 31, 2001
ANDA Batch Size:	——— Capsules	---
Batch/Lot Number:	WWCN 57005, BN02	0002251
Potency:	100.2%	99.4%
Strength:	300 mg	300 mg
Dosage Form:	Capsule	Capsule
Dose Administered:	600mg	600 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:**	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
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	29 events, 11 due to Test drug and 18 due to ref. Drug. None of them are serious in nature (see below).

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.

Blood Sampling Time: 0, 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 36, 48, and 72 hrs. post-drug intake.

Protocol Deviations There were blood sampling time deviations.

DEMOGRAPHIC INFORMATION

Particulars	**Details**			
Study Type	Fasting			
Race	Caucasian=18	Hispanic=0	Black=2	Asian=0
Sex	Males=20	Females=0		
Age, yr.	Ave=32.7	Range=19-45	18-40 yrs=16	41-64 yrs=4
Height, cm	Ave=175.4	Range=164-190		
Weight, kg	Ave=75.5	Range=55.9-95.6		

STUDY RESULTS

1) Clinical

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

Adverse Event	**Test (A)**	**Ref (B)**
Dizziness		2
Frequent urination	1	
Hot and cold flashes		1
Pressure in lower abdominal area when urinating		1
Dehydrated	1	
Feels warmer		1
Headache	1	1
Feels aggressive	1	
Feels warmer than usual		1
Heart palpitation	1	
Body stiffness	1	3

Protocol Deviations: Deviations were minor and was corrected by using the actual time of blood collection in PK calculations.

BIOEQUIVALENCE REVIEW

Redacted 1

Page(s) of trade secret and /or confidential commercial information

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 pharmacokinetic parameters are summarized in Table 2.

TABLE 1. MEAN SERUM LITHIUM LEVELS FOR TEST AND REFERENCE PRODUCTS (SUBJECTS = 20)

Time (hr.)	Mean (A, Test) mcg/mL	CV%	Mean (B, Ref.) Mcg/mL	CV%
0	0.00	--	0.00	---
0.25	0.1475	164.5	0.0332	216.1
0.5	1.3605	77.2	1.1212	65.8
0.75	2.4665	52.2	2.3739	53.9
1	3.1320	43.5	3.1430	50.0
1.25	3.4660	35.8	3.3875	46.1
1.50	3.4781	33.8	3.4582	41.1
1.75	3.3579	29.6	3.3546	37.9
2	3.3091	24.0	3.2565	35.6
2.5	3.3652	21.2	3.1828	32.0
3	3.1862	21.9	3.1093	22.8
3.5	3.1169	21.3	3.0735	24.4
4	2.9840	20.3	3.0064	20.8
5	2.4940	18.8	2.4811	17.3
6	2.1991	16.6	2.1786	16.5
8	1.8212	16.8	1.7903	14.8
12	1.2954	18.6	1.2857	16.1
24	0.8945	17.3	0.8708	19.2
36	0.4847	19.6	0.4614	23.9
48	0.3547	21.3	0.3550	24.8
72	0.1704	44.8	0.1819	60.7

Adjustments Due to Analytical Anomalies:

There were no analytical anomalies for which adjustments to the data set were deemed necessary.

There were no instances of non-zero pre-dose concentrations.

TABLE 2. A Summary of Pharmacokinetic Parameters for Lithium (RSD%)
(Average BE Analysis of Two-way Crossover Study; N=20)

Parameters	TEST	REFERENCE
Arith. Mean		
AUC_{0-T} mcg.hr/mL	58.64 (16)	57.74 (16)
AUC_{inf} mcg.hr/mL	64.96 (16)	64.44 (18)
C_{max} mcg/mL	4.4035 (16)	4.3272 (17)
T_{max} (hours)	2.000 (58)	2.000 (58)
K_{el} (1/hr)	0.0341 (17)	0.0344 (20)
$t_{1/2}$ (hours)	20.77 (15)	20.78 (17)

Geometric	TEST	REFERENCE
AUC_{0-T} mcg.hr/mL	57.931	57.031
AUC_{inf} mcg.hr/mL	64.177	63.460
Cmax mcg/mL	4.3518	4.2694

LSM	TEST	REFERENCE	(T/R)%	90% C.I.
AUC_{0-T} mcg.hr/mL	57.931	57.031	101.6	98.3; 104.9
AUC_{inf} mcg.hr/mL	64.177	63.460	101.1	98.2; 104.3
Cmax mcg/mL	4.3518	4.2694	101.9	95.8; 108.9

Adjustments Due to Pharmacokinetic Anomalies:

There were no pharmacokinetic anomalies for which adjustments to the data set were considered necessary.

Comments

1. 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 calculations on the pharmacokinetic parameters and statistical analysis for the fasting study were spotchecked by the reviewer using SAS and the results were in agreement with what the firm reported.

3. The elimination constants were calculated appropriately.

4. 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}.

Conclusion: The fasting study is acceptable.

Protocol No.: 010912, Randomized, 2-Way Crossover, Bioequivalence Study of Lithium Carbonate, 300 mg Capsule of West-ward and SmithKline Beecham's Eskalith [R] 300 mg Capsule Administered as 2 x 300 mg Capsules in 16 Healthy Adult Males under Non-fasting Conditions

STUDY INFORMATION

STUDY FACILITIES
Same as the fasting study

STUDY DATES
Period I: June 29, 2001
Period II: July 13, 2001
The study samples were analyzed between July 23, 2001 and August 3, 2001. (The maximum storage time was 34 days.)

STUDY DESIGN
A two-way, single-dose, open-label, randomized, two-period, two-treatment, two-sequence crossover study under non-fasting conditions.

TREATMENTS WITH TEST/LOT AND REFERENCE/LOT
Same as fasting 300 mg study.

STUDY SCHEDULES:
Subjects were given the standardized high fat breakfast starting 30 minutes prior to dosing time. The blood sample collection schedule and sample processing were the same as for the fasting studies.

DURING STUDY ANALYTICAL

During Study Analytical For Lithium Carbonate		
Parameter	Q.C. Samples	**Std. Curve Samples**
QC or Std. Curve Conc. (mcg/mL)	0.302, 4.020 and 8.040	0.101, 0.201, 0.503, 1.005, 3.015, 5.025, 9.045, 10.050
Interday Precision (%CV)	4.4 - 11.9	1.6 – 5.3
Interday Accuracy %	94.6-101.1	94.4 – 105.3
Linearity	Correlation Coefficient ≥ 0.9990	
Sensitivity/LOQ (mcg/mL)	0.100	

Conclusion: Methods validation is acceptable.

Study Results:

Sixteen (16) healthy subjects were recruited for this study and all 16 subjects completed the study.

Clinical:

Drop-outs: None

Protocol Deviations: There were some sampling time deviations. Actual times were used in pharmacokinetic calculations.

Pharmacokinetics/Statistics of Fed-study:

TABLE 3. Mean Plasma Concentration of Lithium (N=16)

Time (hr.)	Mean (A, Test) mcg/mL	CV%	Mean (B, Ref.) mcg/mL	CV%
0	0.00	--	0.00	---
0.25	0.00	---	0.00	---
0.5	0.13	204	0.11	238
0.75	0.50	145	0.43	129
1	1.01	87	1.06	69
1.25	1.67	61	1.96	64
1.50	2.20	46	2.52	45
1.75	2.71	32	2.97	31
2	2.95	24	3.07	21
2.5	3.56	14	3.50	13
3	3.46	12	3.47	12
3.5	3.21	13	3.24	12
4	3.05	13	3.12	16
5	2.51	17	2.56	13
6	2.14	15	2.12	14
8	1.73	15	1.68	17
12	1.19	20	1.23	14
24	0.85	16	079	22
36	0.44	24	046	26
48	0.34	27	0.34	26
72	0.13	60	0.13	58

Adjustments Due to Analytical Anomalies:

There were no analytical anomalies for which adjustments to the data set were deemed necessary.

Adjustments Due to Pharmacokinetic Anomalies:

There were no pharmacokinetic anomalies for which adjustments to the data set were considered necessary.

There were no instances of non-zero pre-dose concentrations.

TABLE 4. A Summary of Pharmacokinetic Parameters for Lithium (RSD%)
(Average BE Analysis of Two-way Crossover Study; N=16)

Parameters	**TEST**	**REFERENCE**
Arith. Mean		
AUC_{0-T} mcg.hr/mL	53.83 (14)	53.62 (12)
AUC_{inf} mcg.hr/mL	58.68 (15)	58.77 (13)
C_{max} mcg/mL	3.79 (9)	3.90(9)
T_{max} (hours)	2.67 (29)	2.48 (27)
K_{el} (1/hr)	0.037 (20)	0.036 (19)
$t_{1/2}$ (hours)	19.19 (19)	19.85 (18)
Geometric	**TEST**	**REFERENCE**
AUC_{0-T} mcg.hr/mL	53.30	53.25
AUC_{inf} mcg.hr/mL	58.06	58.35
Cmax mcg/mL	3.78	3.89

LSM	**TEST**	**REFERENCE**	**(T/R)**	**%Intrasubject(CV%)**
AUC_{0-T} mcg.hr/mL	53.30	53.25	100.1	6.0
AUC_{inf} mcg.hr/mL	58.06	58.35	99.5	5.4
Cmax mcg/mL	3.78	3.89	97.3	6.8

3) Statistical Analysis:

1. Plasma concentration data is given in Table 3.

2. The reviewer recalculated the pharmacokinetic parameters and the test/reference ratios for PK parameters (Table 4). The reported values are in good agreement with those obtained by the reviewer.

3. The elimination constants were calculated 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}.

Conclusion: The non-fasting study is acceptable.

FORMULATION (Not to be released under FOI)

Lithium Carbonate, USP	Active Drug Substance	300.0 mg/Cap.
Talc, USP	[redacted]	[redacted]
#1 Grey/ Yellow Hard Gelatin Capsule Printed "West-ward 3189" in Black Inc		[redacted] mg
Total Capsule Fill Weight		382.0 mg

DISSOLUTION (Not to be released under FOI)

The dissolution testing was conducted by West-ward Pharmaceutical Corp. located at 465 Industrial Way West, Eatontown, NJ.

Dissolution Methods/Results:
Dissolution Medium: Detonized Water, 900 mL
Dissolution Apparatus: USP I (Basket) at 100 rpm
Method of Detection: Flame Photometer
Specification: NLT 80% Q in 30 minutes

MEAN DISSOLUTION DATA

	TEST Lot No.: WWCN 57005/BN 02 Strength: 300 mg Batch size: ———— No. of Units: 12			REFERENCE (Eskalith^{R}) Lot No.: 0002251 Strength: 300 mg Exp. Date: 10/31/01 No. of Units: 12		
Time(minutes)	**Mean**	**Range**	**%CV**	**Mean**	**Range**	**%CV**
10	96.8	83.6-103.3	8.7	90.7	79.5-97.3	7.1
20	100.5	96.9-102.5	1.6	94.4	83.2-100.0	5.0
30	100.4	97.7-103.3	1.9	95.9	86.2-100.9	4.3
40	100.1	97.8-102.3	1.4	96.8	89.2-99.9	3.3

The dissolution test meets the tolerance specifications given in USP.

RECOMMENDATIONS

1. The bioequivalence study conducted under fasting conditions by West-Ward Pharmaceutical Corp. on its lithium carbonate, 300 mg capsules, Lot #WWCN 57005/BN 02 comparing it to Eskalith® capsules, 300 mg Lot #0002251 manufactured by Smithkline Beechan, is acceptable.

2. The bioequivalence study conducted under non-fasting conditions by West-Ward Pharmaceutical Corp. on its lithium carbonate 300 mg capsules, Lot #WWCN 57005, BN02 comparing it to Eskalith® capsules, 300 mg Lot #0002251, manufactured by Smithkline Beechan, is acceptable.

3. The dissolution testing conducted by the firm on its lithium carbonate, 300 mg capsules has been found acceptable. The dissolution testing should be incorporated by the firm into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of water at 37 ^{0} C using USP 25 apparatus I (basket) at 100 rpm. The test product should meet the following:

Not less than 80% of the labeled amount of the drug
In the dosage form is dissolved in 30 minutes.

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHUANG
FT INITIALED YCHUANG 4/23/2002

Concur: Date: 5/14/02
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA #76243N0901 (original), HFD-650 (Director), HFD-652 (Huang, Pradhan), Drug File, Division File

Draft: 04/18/10 Final:04 /23/02

BIOEQUIVALENCY COMMENTS

ANDA: 76-243 APPLICANT: West-Ward Pharmaceutical Corp.

DRUG PRODUCT: Lithium Carbonate Capsules 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 25.

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,

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-243 SPONSOR : West-Ward Pharmaceutical Corp.

DRUG AND DOSAGE FORM : Lithium Carbonate Capsules, USP

STRENGTH : 300 mg

TYPES OF STUDIES : Fasting and non-fasting studies and dissolution testing

CLINICAL STUDY SITE(S): [redacted]

ANALYTICAL SITE(S): [redacted]

STUDY SUMMARY : Single-dose fasting, non-fasting studies on 300 mg strength are acceptable.

DISSOLUTION : Dissolution study is acceptable. The dissolution testing was conducted by West-ward Pharmaceutical Corp. located at 465 Industrial Way West, Eatontown, NJ.

DSI INSPECTION STATUS

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

PRIMARY REVIEWER : Sikta Pradhan, Ph.D. BRANCH : I

INITIAL : Sikta Pradhan DATE : 4/23/02

TEAM LEADER : Yih Chain Huang, Ph.D. BRANCH : I

INITIAL : YCH DATE : 4/23/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : DPC DATE : 5/14/02

CC: ANDA 76-243
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Final with Dates)
HFD-652/ S. Pradhan
HFD-650/ Y. Huang 4/23/2002
HFD-617/ K. Scardina 5/15/02
HFD-650/ D. Conner 5/14/02

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BIOEQUIVALENCY - ACCEPTABLE Submission Date: 09/24/2001

1. **FASTING STUDY** (STF) ok Strength: 300 mg
Clinical: [redacted]
Analytical: [redacted] **Outcome: AC**

2. **FOOD STUDY** (STP) ok Strength: 300 mg
Clinical: [redacted]
Analytical: [redacted] **Outcome: AC**

~~3. Study Amendment (STA) Strength: 300 mg~~ (KS)
~~**Outcome: AC**~~

Outcome Decisions: **AC** - Acceptable