CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-121

Generic Name: Lithium Carbonate Capsules USP, 300 mg

Sponsor: Able Laboratories, Inc.

Approval Date: September 27, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
76-121

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-121

APPROVAL LETTER

ANDA 76-121

SEP 27 2001

Able Laboratories, Inc.
Attention: Shashikant Shah, R.Ph.
6 Hollywood Court CN 1013
South Plainfield, NJ 07080

Dear Sir:

This is in reference to your abbreviated new drug application dated February 26, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Lithium Carbonate Capsules USP, 300 mg.

Reference is also made to your amendments dated April 30, May 7 and July 13, 2001.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Lithium Carbonate Capsules USP, 300 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Eskalith® Capsules, 300 mg of SmithKline Beecham Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final

printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Gary Buehler 9/27/01
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-121

Final Printed Labeling

LITHIUM CARBONATE CAPSULES, USP 300 mg

Final Insert # 10

SEP 27 2001

APPROVED

PRESCRIBING INFORMATION

Rx Only

WARNING
Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be available before initiating therapy (see **DOSAGE AND ADMINISTRATION**).

DESCRIPTION

Lithium Carbonate Capsules are antipsychotic/antimanics.

Lithium Carbonate Capsules contain lithium carbonate, a white, light alkaline powder with molecular formula Li_2CO_3 and molecular weight 73.89. Lithium is an element of the alkali-metal group with atomic number 3, atomic weight 6.94 and an emission line at 671 nm on the flame photometer.

Each capsule, for oral administration, with opaque pink cap, imprinted with an "A" and opaque pink body imprinted with "270" in black ink, contains 300 mg lithium carbonate. In addition, each capsule contains the following inactive ingredients: lactose monohydrate, povidone, and talc. The gelatin capsules contain: alcohol, black iron oxide, D&C Yellow #10, FD&C Blue #1, FD&C Blue #2, FD&C Red #40, gelatin, pharmaceutical glaze, propylene glycol, red iron oxide, and titanium dioxide.

CLINICAL PHARMACOLOGY

Preclinical studies have shown that lithium alters sodium transport in nerve and muscle cells and effects a shift toward intraneuronal metabolism of catecholamines, but the specific biochemical mechanism of lithium action in mania is unknown.

INDICATIONS AND USAGE

Lithium Carbonate is indicated in the treatment of manic episodes of manic-depressive illness. Maintenance therapy prevents or diminishes the intensity of subsequent episodes in those manic-depressive patients with a history of mania.

Typical symptoms of mania include pressure of speech, motor hyperactivity, reduced need for sleep, flight of ideas, grandiosity, elation, poor judgement, aggressiveness and possibly hostility. When given to a patient experiencing a manic episode, lithium carbonate may produce a normalization of symptomatology within 1 to 3 weeks.

WARNINGS

Lithium should generally not be given to patients with significant renal or cardiovascular disease, severe debilitation or dehydration, or sodium depletion, since the risk of lithium toxicity is very high in such patients. If the psychiatric indication is life-threatening, and if such a patient fails to respond to other measures, lithium treatment may be undertaken with extreme caution, including daily serum lithium determinations and adjustment to the usually low doses ordinarily tolerated by these individuals. In such instances, hospitalization is a necessity.

Chronic lithium therapy may be associated with diminution of renal concentrating ability, occasionally presenting as nephrogenic diabetes insipidus, with polyuria and polydipsia. Such patients should be carefully managed to avoid dehydration with resulting lithium retention and toxicity. This condition is usually reversible when lithium is discontinued.

Morphologic changes with glomerular and interstitial fibrosis and nephron atrophy have been reported in patients on chronic lithium therapy. Morphologic changes have also been seen in manic-depressive patients never exposed to lithium. The relationship between renal functional and morphologic changes and their association with lithium therapy have not been established.

When kidney function is assessed, for baseline data prior to starting lithium therapy or thereafter, routine urinalysis and other tests may be used to evaluate tubular function (e.g., urine specific gravity or osmolality following a period of water deprivation, or 24-hour urine volume) and glomerular function (e.g., serum creatinine or creatinine clearance). During lithium therapy, progressive or sudden changes in renal function, even within the normal range, indicate the need for reevaluation of treatment.

An encephalopathic syndrome (characterized by weakness, lethargy, fever, tremulousness and confusion, extrapyramidal symptoms, leukocytosis, elevated serum enzymes, BUN and FBS) has occurred in a few patients treated with lithium plus a neuroleptic. In some instances, the syndrome was followed by irreversible brain damage. Because of a possible causal relationship between these events and the concomitant administration of lithium and neuroleptics, patients receiving such combined therapy should be monitored closely for early evidence of neurologic toxicity and treatment discontinued promptly if such signs appear. This encephalopathic syndrome may be similar to or the same as neuroleptic malignant syndrome (NMS).

Lithium toxicity is closely related to serum lithium levels, and can occur at doses close to therapeutic levels (see **DOSAGE AND ADMINISTRATION**).

Outpatients and their families should be warned that the patient must discontinue lithium carbonate therapy and contact his physician if such clinical signs of lithium toxicity as diarrhea, vomiting, tremor, mild ataxia, drowsiness or muscular weakness occur.

Lithium carbonate may impair mental and/or physical abilities. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery).

Lithium may prolong the effects of neuromuscular blocking agents. Therefore, neuromuscular blocking agents should be given with caution to patients receiving lithium.

PRECAUTIONS

The ability to tolerate lithium is greater during the acute manic phase and decreases when manic symptoms subside (see **DOSAGE AND ADMINISTRATION**).

Caution should be used when lithium and diuretics are used concomitantly because diuretic-induced sodium loss may reduce the renal clearance of lithium and increase serum lithium levels with risk of lithium toxicity. Patients receiving such combined therapy should have serum lithium levels monitored closely and the lithium dosage adjusted if necessary.

The distribution space of lithium approximates that of total body water. Lithium is primarily excreted in urine with insignificant excretion in feces. Renal excretion of lithium is proportional to its plasma concentration. The half-life of elimination of lithium is approximately 24 hours. Lithium decreases sodium reabsorption by the renal tubules which could lead to sodium depletion. Therefore, it is essential for the patient to maintain a normal diet, including salt, and an adequate fluid intake (2500 to 3000 mL) at least during the initial stabilization period. Decreased tolerance to lithium has been reported to ensue from protracted sweating or diarrhea and, if such occur, supplemental fluid and salt should be administered under careful medical supervision and lithium intake reduced or suspended until the condition is resolved.

In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium [illegible] careful monitoring of thyroid function during lithium stabilization and [illegible] occurs during

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In addition to sweating and diarrhea, concomitant infection with elevated temperatures may also necessitate a temporary reduction or cessation of medication.

Previously existing underlying thyroid disorders do not necessarily constitute a contraindication to lithium treatment; where hypothyroidism exists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters, if any; where hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

Indomethacin and piroxicam have been reported to increase significantly, steady-state plasma lithium levels. In some cases, lithium toxicity has resulted from such interactions. There is also some evidence that other non-steroidal anti-inflammatory agents may have a similar effect. When such combinations are used, increased plasma lithium level monitoring is recommended.

The following drugs can lower serum lithium concentrations by increasing urinary lithium excretion: acetazolamide, urea, xanthine preparations and alkalinizing agents such as sodium bicarbonate.

Pregnancy: Adverse effects on implantation in rats, embryo viability in mice and metabolism *in vitro* of rat testes

and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palates in mice.

In humans, lithium carbonate may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies, especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Nursing Mothers: Lithium is excreted in human milk. Nursing should not be undertaken during lithium therapy except in rare and unusual circumstances where, in the view of the physician, the potential benefits to the mother outweigh possible hazards to the child.

Pediatric Use: Since information regarding the safety and effectiveness of lithium carbonate in children under 12 years of age is not available, its use in such patients is not recommended at this time.

There has been a report of a transient syndrome of acute dystonia and hyperreflexia occurring in a 15 kg child who ingested 300 mg of lithium carbonate.

Geriatric Use: Elderly patients often require lower lithium dosages to achieve therapeutic serum levels. They may also exhibit adverse reactions at serum levels ordinarily tolerated by younger patients.

ADVERSE REACTIONS

The occurrence and severity of adverse reactions are generally directly related to serum lithium concentrations as well as to individual patient sensitivity to lithium, and generally occur more frequently and with greater severity at higher concentrations.

Adverse reactions may be encountered at serum lithium levels below 1.5 mEq/L. Mild to moderate adverse reactions may occur at levels from 1.5 to 2.5 mEq/L, and moderate to severe reactions may be seen at levels of 2 mEq/L and above.

Fine hand tremor, polyuria and mild thirst may occur during initial therapy for the acute manic phase, and may persist throughout treatment. Transient and mild nausea and general discomfort may also appear during the first few days of lithium administration.

These side effects usually subside with continued treatment or a temporary reduction or cessation of dosage. If persistent, cessation of lithium therapy may be required.

Diarrhea, vomiting, drowsiness, muscular weakness and lack of coordination may be early signs of lithium intoxication, and can occur at lithium levels below 2 mEq/L. At higher levels, ataxia, giddiness, tinnitus, blurred vision and a large output of dilute urine may be seen. Serum lithium levels above 3 mEq/L may produce a complex clinical picture, involving multiple organs and organ systems. Serum lithium levels should not be permitted to exceed 2 mEq/L during the acute treatment phase.

The following reactions have been reported and appear to be related to serum lithium levels, including levels within the therapeutic range: **Neuromuscular/Central Nervous System** — tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreo-athetotic movements, hyperactive deep tendon reflex, extrapyramidal symptoms including acute dystonia, cogwheel rigidity, blackout spells, epileptiform seizures, slurred speech, dizziness, vertigo, downbeat nystagmus, incontinence of urine or feces, somnolence, psychomotor retardation, restlessness, confusion, stupor, coma, tongue movements, tics, tinnitus, hallucinations, poor memory, slowed intellectual functioning, startled response, worsening of organic brain syndromes; **Cardiovascular** — cardiac arrhythmia, hypotension, peripheral circulatory collapse, bradycardia, sinus node dysfunction with severe bradycardia (which may result in syncope); **Gastrointestinal** — anorexia, nausea, vomiting, diarrhea, gastritis, salivary gland swelling, abdominal pain, excessive salivation, flatulence, indigestion; **Genitourinary** — glycosuria, decreased creatinine clearance, albuminuria, oliguria, and symptoms of nephrogenic diabetes insipidus including polyuria, thirst and polydipsia; **Dermatologic** — drying and thinning of hair, alopecia, anesthesia of skin, acne, chronic folliculitus, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema; **Autonomic** — blurred vision, dry mouth, impotence/sexual dysfunction; **Thyroid Abnormalities** — euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4. I^{131} uptake may be elevated. (See **PRECAUTIONS**.) Paradoxically, rare cases of hyperthyroidism have been reported; **EEG Changes** — diffuse slowing, widening of the frequency spectrum, potentiation and disorganization of background rhythm; **EKG Changes** — reversible flattening, isoelectricity or inversion of T-waves; **Miscellaneous** — fatigue, lethargy, transient scotomata, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperpara-thyroidism, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, dental caries.

Some reports of nephrogenic diabetes insipidus, hyperparathyroidism and hypothyroidism which persist after lithium discontinuation have been received.

A few reports have been received of the development of painful discoloration of fingers and toes and coldness of the extremities within one day of the starting of treatment with lithium. The mechanism through which these symptoms (resembling Raynaud's syndrome) developed is not known. Recovery followed discontinuance.

Cases of pseudotumor cerebri (increased intracranial pressure and papilledema) have been reported with lithium use. If undetected, this condition may result in enlargement of the blind spot, constriction of visual fields and eventual blindness due to optic atrophy.

Lithium should be discontinued, if clinically possible, if this syndrome occurs.

OVERDOSAGE

The toxic levels for lithium are close to the therapeutic levels. It is therefore important that patients and their families be cautioned to watch for early toxic symptoms and to discontinue the drug and inform the physician should they occur. Toxic symptoms are listed in detail under **ADVERSE REACTIONS**.

Treatment

No specific antidote for lithium poisoning is known. Early symptoms of lithium toxicity can usually be treated by reduction or cessation of dosage of the drug and resumption of the treatment at a lower dose after 24 to 48 hours. In severe cases of lithium poisoning, the first and foremost goal of treatment consists of elimination of this ion from the patient. Treatment is essentially the same as that used in barbiturate poisoning: 1) gastric lavage, 2) correction of fluid and electrolyte imbalance, and 3) regulation of kidney function. Urea, mannitol and aminophylline all produce significant increases in lithium excretion. Hemodialysis is an effective and rapid means of removing the ion from the severely toxic patient. Infection prophylaxis, regular chest x-rays and preservation of adequate respiration are essential.

DOSAGE AND ADMINISTRATION

Immediate release capsules are usually given t.i.d. or q.i.d. When initiating therapy with immediate release or controlled release lithium, dosage must be individualized according to serum levels and clinical response.

Acute Mania — Optimal patient response to lithium carbonate can usually be established and maintained with 1800 mg per day in divided doses. Such doses will normally produce the desired serum lithium level ranging between 1 and 1.5 mEq/L.

Dosage must be individualized according to serum levels and clinical response. Regular monitoring of the patient's clinical state and serum lithium levels is necessary. Serum levels should be determined twice per week during the acute phase, and until the serum level and clinical condition of the patient have been stabilized.

Long-Term Control — The desirable serum lithium levels are 0.6 to 1.2 mEq/L. Dosage will vary from one individual to another, but usually 900 mg to 1200 mg per day in divided doses will maintain this level. Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months.

Patients unusually sensitive to lithium may exhibit toxic signs at serum levels below 1 mEq/L.

N.B.: Blood samples for serum lithium determinations should be drawn immediately prior to the next dose when lithium concentrations are relatively stable (i.e., 8 to 12 hours after the previous dose). Total reliance must not be placed on serum levels alone. Accurate patient evaluation requires both clinical and laboratory analysis.

Elderly patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels ordinarily tolerated by younger patients.

HOW SUPPLIED

Lithium Carbonate [illegible]

Miscellaneous — allergic reactions, transient scotomata, dehydration, weight loss, leukocytosis, headache, transient hyperglycemia, hypercalcemia, hyperpara-thyroidism, excessive weight gain, edematous swelling of ankles or wrists, metallic taste, dysgeusia/taste distortion, salty taste, thirst, swollen lips, tightness in chest, swollen and/or painful joints, fever, polyarthralgia, dental caries.

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Elderly patients often respond to reduced dosage, and may exhibit signs of toxicity at serum levels ordinarily tolerated by younger patients.

HOW SUPPLIED

Lithium Carbonate Capsules USP, 300 mg for oral administration are available as opaque pink capsules imprinted with "A" on the cap and "270" on the body in black ink. They are supplied as follows:

Bottles of 100
Bottles of 1000

Storage: Store at controlled room temperature 15° - 30°C (59° - 86°F). [See USP.] Preserve in well-closed containers.

Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).

Manufactured By:
ABLE LABORATORIES, INC.
6 Hollywood Court, CN1013
South Plainfield, NJ 07080-4295

IN16030/01 07/01 VC 8134 Manufacturer's Code 53265

NDC 53265-270-10

ABLE LABORATORIES INC.

SEP 27 2001

APPROVED

LITHIUM CARBONATE CAPSULES, USP

300 mg

100 PINK CAPSULES

Rx Only

EACH CAPSULE CONTAINS:
Lithium Carbonate, USP ..... 300 mg

USUAL ADULT DOSAGE: See accompanying product literature.

DISPENSE in a tight container as defined in the USP, with a child-resistant closure (as required).

STORE at controlled room temperature 15° - 30°C (59° - 86°F) [see USP].

Mfg. by: ABLE LABORATORIES, INC.
SOUTH PLAINFIELD, NJ 07080

LB10155/01
07/01

Manufacturer's Code
53265

N 53265-270-10 8

LOT NO.:
EXP DATE:

NDC 53265-270-11

ABLE LABORATORIES INC.

LITHIUM CARBONATE CAPSULES, USP

300 mg

1000 PINK CAPSULES

Rx Only

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LB10156/01
07/01

Manufacturer's Code
53265

SEP 27 2001

APPROVED

N 53265-270-11

LOT NO.:
EXP DATE:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-121

CHEMISTRY REVIEW(S)

D.F

1. CHEMIST'S REVIEW NO. 1

2. ANDA **#76-121**

3. NAME AND ADDRESS OF APPLICANT
Able Laboratories, Inc.
6 Hollywood Court
South Plainfield, NJ 07080

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of SmithKline Beecham Pharmaceuticals' ESKALITH® (NDA 16-860). Patent certification and exclusivity statement are provided (Vol. 1.1, pp. 018-028).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Lithium Carbonate Capsules, USP

7. PROPRIETARY NAME
Eskalith® Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		**FDA**	
Orig. submission	2/26/01	Acknowledgment letter	3/ /01
		Bio review (deficient)	5/2/01
		Labeling review	Pending

This review covers submission dated 2/26/01.

10. PHARMACOLOGICAL CATEGORY
Antimanic - Indicated in the treatment of manic episodes of Bipolar Disorder.

11. Rx or OTC
℞

12. RELATED DMF(s)

Other DMFs are found in the Container/closure section.

13. DOSAGE FORM
Capsules (Oral)

14. STRENGTH(S)
300 mg

15. CHEMICAL NAME AND STRUCTURE

Carbonic acid, dilithium salt

Formula: Li_2CO_3 Molecular Weight: 73.89

CAS-554-13-2

Drug substance and drug product are official USP 24 items.

16. RECORDS AND REPORTS None

17. COMMENTS
Application contains minor deficiencies
Labeling: **Pending**
Bio: **Deficient,** 5/2/01.
DMF —— **INADEQUATE** dated 5/16/01
Methods validation: Not required
Establishment Evaluation Report: **Pending**

18. CONCLUSIONS AND RECOMMENDATIONS
NOT APPROVABLE

19. REVIEWER:
Raymond Brown

DATE COMPLETED:
May 21, 2001

Redacted 13

pages of trade secret and/or confidential commercial information

1. CHEMIST'S REVIEW NO. **2**

2. ANDA **#76-121**

3. NAME AND ADDRESS OF APPLICANT
Able Laboratories, Inc.
6 Hollywood Court
South Plainfield, NJ 07080

4. LEGAL BASIS FOR ANDA SUBMISSION
Generic version of SmithKline Beecham Pharmaceuticals' ESKALITH® (NDA 16-860). Patent certification and exclusivity statement are provided (Vol. 1.1, pp. 018-028).

5. SUPPLEMENT(s) N/A

6. ESTABLISHED NAME
Lithium Carbonate Capsules, USP

7. PROPRIETARY NAME
Eskalith® Capsules

8. SUPPLEMENT(s) PROVIDE(s) FOR Original ANDA

9. AMENDMENTS AND OTHER DATES

Firm		**FDA**	
Orig. submission	2/26/01	Acknowledgment letter	3/28/01
		Bio review (deficient)	5/2/01
		Labeling review	8/20/01
		Deficiency FAX	6/28/01
Amendment (MAJOR)	7/13/01		

This review covers submission dated 7/13/01.

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14. STRENGTH(S)
300 mg

15. CHEMICAL NAME AND STRUCTURE

Carbonic acid, dilithium salt

Formula: Li_2CO_3 Molecular Weight: 73.89

CAS-554-13-2

Drug substance and drug product are official USP 24 items.

16. RECORDS AND REPORTS None

17. COMMENTS
Application is satisfactory pending labeling review.
Labeling: **Adequate** dated 8/20/01.
Bio: **Adequate** (Sign-Off, dated 5/23/01).
DMF — **ADEQUATE** dated 8/13/01
Methods validation: Not required
Establishment Evaluation Report: **Pending**

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVE

19. REVIEWER: Raymond Brown
DATE COMPLETED: August 13, 2001

Redacted 13

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confidential

commercial

information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-121

BIOEQUIVALENCE REVIEW

Lithium Carbonate Capsules, USP
300 mg
ANDA #76-121
Reviewer: Mamata Gokhale
v:\firmsam\able\76121SD.201

Able Laboratories Inc.
6 Hollywood Court
South Plainfield
New Jersey 07080
2/26/01

Review of A Bioequivalence Study and Dissolution Data

I. Introduction

Indication: Lithium is a monovalent cation belonging to the group of alkali metals and is commercially available as a carbonate salt. It is an antimanic agent indicated in the treatment of manic episodes of manic-depressive illness.
Type of Submission: original ANDA
Contents of Submission: Single dose fasting bioequivalence study and dissolution data on the 300 mg capsules.
RLD: Eskalith® Capsules, 300 mg, manufactured by SmithKline Beecham Pharmaceuticals.
Recommended dose: Immediate release capsules are usually given t.i.d. or q.i.d. Dosage must be individualized according to serum levels and the clinical response.

Background

Lithium is readily absorbed from the GI tract. Food does not appear to affect the bioavailability of lithium. The PDR 2001 does not contain any information on the pharmacokinetics of lithium following dosing with Eskalith® capsules. Currently, Roxane Laboratories Inc. also has Lithium Carbonate Capsules, 300 mg, approved as NDA 17-812, on the market. The following pharmacokinetic data is from the biopharmaceutics review of a single-dose fasting bioequivalence study submitted to NDA 17-812 comparing Roxane's product with Eskalith® capsules. After an oral dose of 300 mg, peak serum concentrations of 0.5 mEq/L were reported at 1.4 hours. Serum concentrations of lithium appeared to decline in a biphasic manner. In patients with normal renal function, a terminal half-life of 20-27 hours has been observed. Comparable data is reported in the American Society of Health-System Pharmacists, Inc. (AHSP) on-line database.

Although Roxane's product is AB-rated to the RLD, there have been no ANDA submissions for lithium carbonate immediate-release capsules to the Agency to date. Thus, this is a potential first generic ANDA. The DBE earlier reviewed control document #00-213 (6/25/00) by Able Laboratories for lithium carbonate capsules. The DBE recommended that the firm conduct an in vivo fasting bioequivalence study and also recommended methodology for in vitro dissolution testing. The firm has submitted these data to ANDA 76-121.

II. Single-dose Fasting Bioequivalence Study, 300 mg strength

A. Study Information

Study Number [redacted]00-363
Medical Director [redacted]
Scientific Director [redacted]
Clinical Site [redacted]
Study Dates Period 1: October 21-25, 2000, Period 2: November 04-08, 2000
Analytical Site [redacted]
Analytical Director [redacted]
Analysis Dates November 20-December 20, 2000
Sample Storage At –20^{0}C for up to 60 days

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Lithium Carbonate	Eskalith®
Manufacturer	Able Laboratories Inc.	SmithKlein Beecham Pharmaceuticals
Lot No.	TB-073	0000817
Manufacture Date	10/00	N/A
Expiration Date	N/A	7/01
Strength	300 mg	300 mg
Dosage Form	Capsules	Capsules
ANDA Batch Size	[redacted]	N/A
Commercial Batch Size	[redacted]	N/A
Potency (%)	101.3	101.1
Content Uniformity (mean, %cv, range, n)	99.9, 1.1, 97.6-100.9, 10	100.1, 1.2, 98.6-102.0, 10
Formulation	See Table #1	N/A
Dose Administered	300 mg	300 mg
Route of Administration	Oral	Oral
Length of Fasting	10 hours pre-dosing 4.25 hours post-dosing	10 hours pre-dosing 4.25 hours post-dosing

No. of Sequences	2	**Crossover**	Y
No. of Periods	2	**Replicate Design**	N
No. of Treatments	2	**Balanced**	Y
No. of Groups (if appropriate)	0	**Washout Period**	14 days
Randomization Scheme	**AB:** 2, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 22,26 **BA:** 1, 3, 4, 5, 6, 7, 8, 9, 15, 21, 23, 24, 25		
Blood Sampling Times	0 (pre-lithium carbonate dose), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72 and 96 hours		
Blood Volume Collected/Sample	10 mL		
Blood Sample Processing/Storage	Serum samples were stored at –20^{0}C		
IRB Approval	Y		

Informed Consent	Y
No. Dosed	26 (24 + 2 alternates)
No. Completing	26
No. With Plasma Spls Analyzed	First 24 completing the study as stated in the protocol
No. of Dropouts	0
Restrictions	Along with the standard dietary, activity and drug restrictions, the exclusion criteria included hypersensitivity to lithium or related drugs.
Length of Confinement	From 10 hours pre-dosing to 24 hours post-dosing.
Safety Monitoring	Subjects were monitored by the study physician for any adverse events after dosing and throughout the confinement period. Blood pressure and heart rate were measured prior to dosing, at 3, 12 and 24 hours after dosing, and upon completion of the study.
Healthy Subjects Only	Y

B. Study Results

1. Clinical

Dropout Information	There were no dropouts.
Adverse Events	Three adverse events unrelated to study medications in the opinion of the investigators.

Protocol Deviations Minor deviations with respect to blood sampling volume and times; actual sampling times were used for all calculations. See pages 182- 183 of volume 1.2 for details. The reviewer concludes that these sampling deviations do not compromise the integrity of the study.

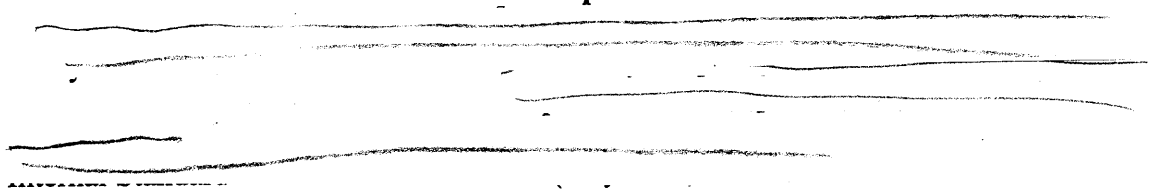
Comments:

None.

2. Analytical

Analytical Method Validation
NOT TO BE RELEASED UNDER FOI

Description



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Conclusion: The analytical method is incomplete. The storage period for study samples (60 days) exceeds the duration of the frozen storage stability study (23 days).

3 Pharmacokinetic/Statistical Analysis

Mean Plasma Concentrations	Table #2, Figure	
Mean Pharmacokinetic Parameters	Table #3	
90% Confidence Intervals	lnAUCt: 98.06-103.46 lnAUCi: 98.15-103.48 lnCmax: 89.52-102.94 Details in Table #4	
AUCt/AUCi ratio	Test	Reference
Mean, %CV, Range	0.95, 1.86, [redacted]	0.95, 1.67, [redacted]

Total SD and within-subject error (root MSE): Values are shown below (for ln-transformed AUCt and Cmax only)

Total standard deviation and root mean square error, ln-transformed PK data		
Drug	Lithium Carbonate	
PK parameter	lnCmax	lnAUCt
Root MSE, test & ref combined	0.1409	0.0540

Comments: (on pharmacokinetic and statistical analyses)

1) During lithium PK analysis, the firm was able to determine the Kel and AUCi values for all the subjects. The reviewer agrees with this decision.

2) In the pharmacokinetic analysis of lithium, subjects with

a) measurable drug concentrations at 0 hour: None
b) first scheduled post-dose sampling time as Tmax: None
c) first measurable concentration as Cmax: None

3) The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with the firm's calculations.

4) No statistically significant period or sequence effects were seen for parameters lnAUCt, lnAUCi and lnCmax during the pharmacokinetic analysis of lithium.

5) The 90% confidence intervals for the log transformed AUCt, AUCi and Cmax are within the acceptable limits of 80-125%.

Conclusion: The single dose fasting study on the 300 mg strength of Lithium Carbonate Capsules, USP is incomplete pending receipt of frozen plasma sample long-term storage stability data.

III. Formulation

Table #1 indicates the formulation of Lithium Carbonate Capsules, USP, 300 mg.

Comments: The formulation of Lithium Carbonate Capsules, USP, 300 mg is acceptable.

IV. Dissolution

Dissolution Method

The firm conducted dissolution testing on Lithium Carbonate Capsules, 300 mg using the compendial method described in USP 24.

Method	FDA
Analyte	[redacted]
No. of Units	12
Medium	Deionized water
Volume	900 mL
Temp.	37^{0}C
Apparatus	Basket
Speed	100 rpm
Sampling Times (minutes)	10, 15, 20, 30, 45
Assay	[redacted]
Specification	NLT [redacted] (Q) in 30 minutes

Results: The dissolution data are presented in Table #5. More than [redacted] of lithium is released within 15 minutes, irrespective of the test or reference formulations. For both strengths, the mean percentage of the labeled amount of lithium released exceeded [redacted] by the second sampling time point (15 minutes). Therefore f2 analysis was not performed for this drug product.

Comments:

1) The lots of Lithium Carbonate Capsules, USP, 300 mg, used in the dissolution testing were same as those used in the *in vivo* bioequivalence study.

2) Due to the rapid dissolution of lithium from Lithium Carbonate Capsules, USP, 300 mg, (Table #5), f2 comparison with the RLD is not relevant for this drug product.

3) The test product meets the USP 24 dissolution specification listed above.

Deficiency

The firm did not submit stability data showing that lithium is stable in plasma stored frozen under the same conditions for the same time duration as the bioequivalence study samples.

Recommendations

1) The single-dose fasting bioequivalence study, protocol #R00-363 conducted by Able Laboratories Inc. on its Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073, comparing them to Eskalith® Capsules, 300 mg, Lot #0000187, manufactured by SmithKlein Beecham Pharmaceuticals has been found incomplete by the Division of Bioequivalence because of the deficiency noted above.

2) The in vitro dissolution testing conducted by Able Laboratories Inc. on its Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073 is acceptable. The formulation of the test product which underwent bioequivalency testing is acceptable.

3) Dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of deionized, water using apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

> Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations

Mamata S. Gokhale, Ph.D. /S/ 4/18/01
Division of Bioequivalence

RD INITIALED BDAVIT 4/16/01
FT INITIALED BDAVIT /S/ Date 4/18/01

Concur: /S/ Date 4/27/2001
Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-121 (original, duplicate), Davit, HFD-658, Gokhale, Davit, HFD-658, Drug File, Div. File

Table #1
Formulation

Able's Lithium Carbonate Capsules, USP, 300 mg		
[1]Ingredient	mg/capsule	%w/w
[2]Lithium Carbonate, USP	300.00	—
Povidone, USP	—	—
Lactose Monohydrate, NF	—	—
Talc, USP	—	—
Talc, USP	—	—
Total	400.00	—
[3,4]Capsule Shell		
#1 Capsules, Opague Pink Cap imprinted "A" and Opague Pink Body imprinted "270" in Black Ink.	-	

[1]To be scaled up to ANDA batch size of — capsules and commercial batch size of — capsules.
[2]Active ingredient.
All inactive ingredients are within acceptable limits (FDA Inactive Ingredient Guide, January 1996).
[3]Consisting of Red Iron Oxide, Titanium Dioxide and Gelatin.
[4]The black ink consisting of — Pharmaceutical Glaze (Modified) in —. Black Iron Oxide, —, Propylene Glycol, FD&C Blue #2, FD&C Red #40, FD&C Blue #1 and D&C Yellow #10; — consisting of Pharmaceutical Glaze (Modified) in — Synthetic Black Iron Oxide. — FD&C Blue #2, FD&C Red #40, FD&C Blue #1 and D&C Yellow #10.

APPEARS THIS WAY
ON ORIGINAL

Table #2
Mean Plasma Concentrations of Lithium
Following an Oral Dose of 300 mg (Fasting Study)
Treatment A: Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073
Treatment B: Eskalith® Capsules, 300 mg, Lot #0000187

Time (hours)	Mean (± SD) Plasma Concentrations (ng/mL)				
	Treatment A		Treatment B		Ratio A/B
0.00	0.00	0.00	0.00	0.00	0.00
0.33	577.70	452.78	560.71	506.90	1.03
0.67	1674.19	701.15	1688.54	833.59	0.99
1.00	1956.08	691.58	1897.33	827.22	1.03
1.50	1883.75	567.33	1885.42	620.72	1.00
2.00	1688.54	345.21	1770.54	479.91	0.95
2.50	1635.83	313.23	1645.83	234.91	0.99
3.00	1573.75	268.57	1517.17	253.77	1.04
4.00	1339.83	239.27	1302.42	252.70	1.03
5.00	1103.42	138.41	1108.75	146.34	1.00
6.00	983.13	118.95	997.38	164.37	0.99
8.00	789.54	109.92	780.50	126.04	1.01
10.00	671.63	81.92	658.38	99.83	1.02
12.00	582.79	95.87	572.08	84.37	1.02
16.00	455.38	72.95	451.21	80.78	1.01
24.00	373.50	65.39	374.54	67.78	1.00
48.00	168.42	39.26	166.79	37.10	1.01
72.00	85.63	22.81	85.66	24.03	1.00
96.00	43.98	17.42	43.16	15.80	1.02

Table #3
Lithium Pharmacokinetic Parameters
Single Dose Fasting Study, 300 mg Dose
Treatment A: Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073
Treatment B: Eskalith® Capsules, 300 mg, Lot #0000187

Plasma Parameters	Cmax (ng/mL)		Tmax (hours)		Kel (1/hours)	
Treatment	A	B	A	B	A	B
MEAN	2290.42	2367.08	1.48	1.49	0.03	0.03
CV%	19.42	16.26	48.93	56.56	13.91	14.76

Plasma Parameters	T1/2 (hours)		AUCt (ng/mL-hours)		AUCi (ng/mL-hours)	
Treatment	A	B	A	B	A	B
MEAN	23.76	23.76	29245.71	29088.38	30873.92	30679.83
CV%	14.38	14.54	14.13	15.27	15.06	15.87

Table #4
Summary Statistics for Lithium
Single Dose Fasting Study, 300 mg Dose
Treatment A: Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073
Treatment B: Eskalith® Capsules, 300 mg, Lot #0000187

PK Parameter	Geometric Mean		Ratio	90% C.I.
(Treatment)	A	B	A/B	
LnAUCt (ng·hr/mL)	28978.20	28769.53	1.01	98.06-103.46
LnAUCi (ng·hr/mL)	30557.73	30320.82	1.01	98.15-103.48
LnCmax (ng·hr/mL)	2242.69	2336.14	0.96	89.52-102.94

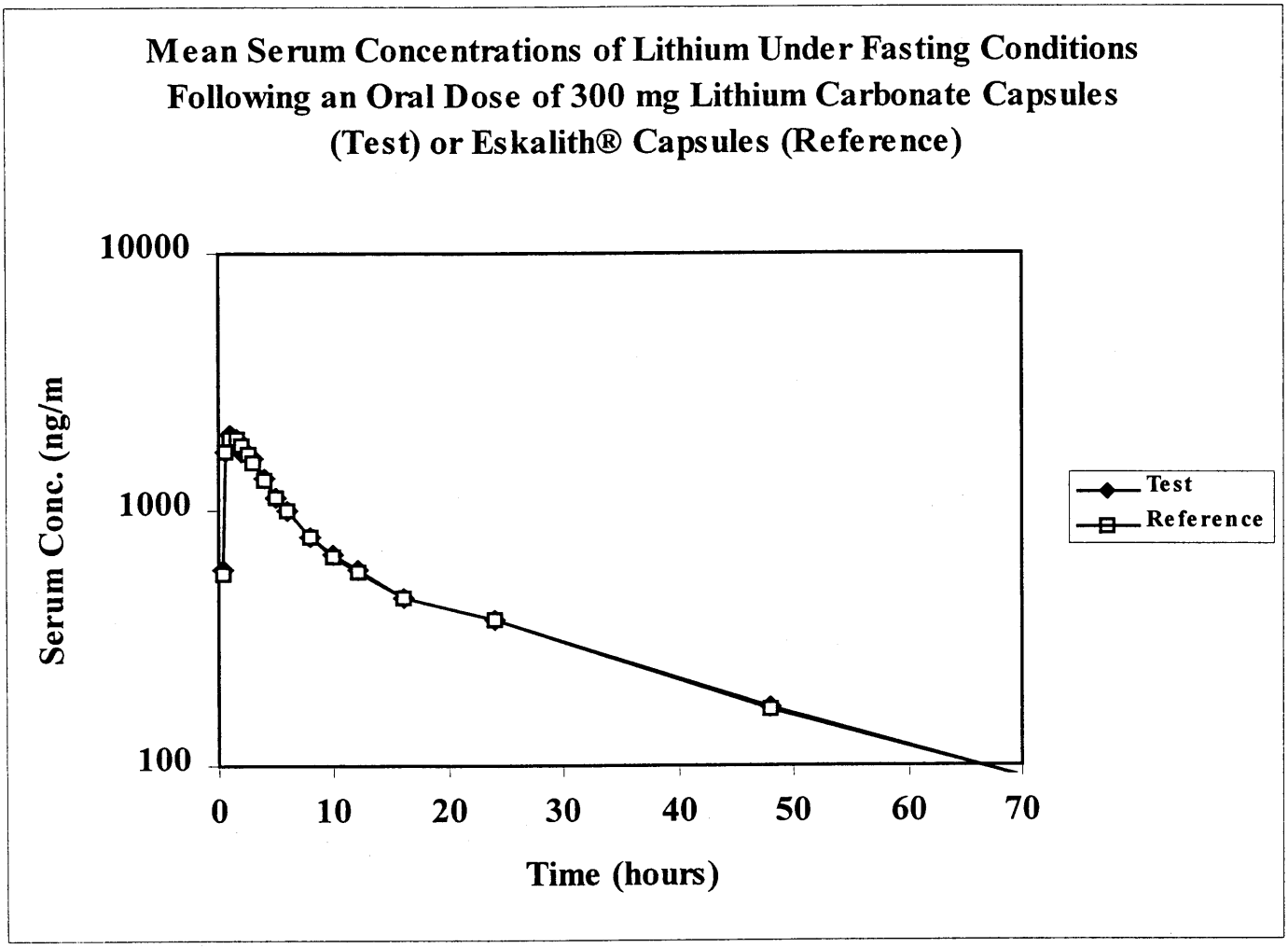
APPEARS THIS WAY
ON ORIGINAL

Table #5
Results of In Vitro Dissolution Testing
Test Product: Lithium Carbonate Capsules by Able Laboratories Inc.
Reference Product: Eskalith® Capsules by SmithKlein Beecham Pharmaceuticals

RESULTS OF *IN VITRO* DISSOLUTION TESTING						
USP 24 Method: 900mL Deionized water, Basket, 100 rpm						
300 mg Strength						
Sampling Times (min.)	Test Product Lot #TB-073			Reference Product Lot #0000187		
	Mean %	Range	% CV	Mean %	Range	% CV
10	84.6		16.6	89.3		12.5
15	94.2		9.3	98.5		2.4
20	99.1		6.1	99.8		1.6
30	102.6		1.1	100.6		1.7
45	103.4		1.3	99.9		1.2

APPEARS THIS WAY
ON ORIGINAL

Figure



APPEARS THIS WAY
ON ORIGINAL

CC: ANDA # 76-121
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: B. Davit

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Printed in final on 4/18/2001

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale /S/ 4/18/01
HFD-658/ B. Davit 4/18/01
HFD-650/ D. Conner for 4/27/2001
HFD-617/ S. Mazzella

Bioequivalency- Incomplete Submission Date: 2/26/01

OK 1) Fasting Study (STF) Strength: 300 mg
Clinical:
Analytical: Outcome: IC

Outcome Decisions: IC- Incomplete

Winbio comments: STF – Incomplete

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY AMENDMENT

ANDA 76-121

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY - 2 2001

TO: APPLICANT: Able Laboratories, Inc. TEL: 908-754-2253

ATTN: Shashikant Shah FAX: 908-753-9383

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on February 26, 2001, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lithium Carbonate Capsules USP, 300 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

MAY - 2 2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-121 APPLICANT: Able Laboratories Inc.
DRUG PRODUCT: Lithium Carbonate Capsules, USP
300 mg

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

Please submit stability data showing that lithium is stable in plasma stored frozen under the same conditions for the same time duration as the bioequivalence study samples.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : ~~76-104~~ 76-121 SPONSOR : Able Laboratories Inc.

DRUG AND DOSAGE FORM : Lithium Carbonate Capsules, USP

STRENGTH(S) : 300 mg

TYPES OF STUDIES : [SD] [SDF] MULT [OTHER]

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : In the single dose fasting bioequivalence study, Lithium Carbonate Capsules, 300 mg were shown to be bioequivalent to Eskalith® Capsules, 300 mg.

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: YES / [NO]	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : /S/ DATE : 5/18/01

TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : /S/ DATE : 5/18/01

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

INITIAL : /S/ DATE : 5/23/2001

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-121 APPLICANT: Able Laboratories Inc.
DRUG PRODUCT: Lithium Carbonate Capsules, USP
300 mg

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

We acknowledge that the dissolution testing will be incorporated in your stability and quality control programs as specified in USP 24.

The dissolution testing should be conducted in 900 mL of deionized, water using apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than ~ (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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/

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

Lithium Carbonate Capsules, USP
300 mg
ANDA #76-121
Reviewer: Mamata Gokhale
v:\firmsam\able\76121STA.501

Able Laboratories Inc.
6 Hollywood Court
South Plainfield
New Jersey 07080
~~5/1/01~~, ~~5/8/01~~
4/30/01 5/7/01

Review Of Amendments

Objective

The firm has submitted two bioequivalence amendments in response to deficiencies communicated by the letters dated 3/28/01 and 5/2/01.

Background

In the original ANDA 76-121 dated 2/26/01, the firm submitted fasting *in vivo* bioequivalence study and *in vitro* dissolution data on Lithium Carbonate Capsules, USP, 300 mg. The bioequivalence study and dissolution data were found incomplete by the DBE due to deficiencies.

Deficiency 1a

Please submit the Procedure SOP for the bioequivalence study results.

Response

The firm provided Procedure SOP-MOP_HX027. The method operating procedure (MOP) includes:

[redacted]

Comment

The firm's response is acceptable.

Deficiency 1b

Please submit [redacted] for the bioequivalence study results.

Response

[redacted]

Comment

The firm's response is acceptable.

Deficiency 2

Please submit stability data showing that lithium is stable in serum stored frozen under the same conditions for the same time duration as the bioequivalence study samples.

Response

The firm conducted long term stability assessment of lithium in human serum stored for 872 days at -20 ± 5^0C. Lithium concentrations were determined using the same validated [redacted] method used to determine lithium in the fasting bioequivalence study samples.

Results: QC samples stored at -20 ± 5^0C for 872 days

*QC concentration (ng/mL)	75	750	7500
Precision (%CV)	3.15	1.21	1.28
Accuracy (% of initial)	96.58	95.91	99.38

*Four Replicates were analyzed for each QC concentration.

Conclusion

Based on the above results, lithium is stable in serum at 20 ± 5^0C for a period of 872 days. This exceeds the period for which the *in vivo* bioequivalence study samples were stored.

Comment

The firm's response is acceptable.

Recommendations

1) The single-dose fasting bioequivalence study, protocol #R00-363 conducted by Able Laboratories Inc. on its Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073, comparing them to Eskalith® Capsules, 300 mg, Lot #0000187, manufactured by SmithKlein Beecham Pharmaceuticals has been found acceptable by the Division of Bioequivalence. This study demonstrates that Lithium Carbonate Capsules, USP, 300 mg manufactured by Able Laboratories Inc. are bioequivalent Eskalith® Capsules, 300 mg, manufactured by SmithKlein Beecham Pharmaceuticals.

2) The in vitro dissolution testing conducted by Able Laboratories Inc. on its Lithium Carbonate Capsules, USP, 300 mg, Lot #TB-073 is acceptable. The formulation of the test product which underwent bioequivalency testing is acceptable.

3) Dissolution testing should be incorporated into the firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of deionized water using apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

> Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

The firm should be informed of the above recommendations

Mamata S. Gokhale, Ph.D. /S/ 5/18/01
Division of Bioequivalence

RD INITIALED BDAVIT /S/ 5/18/01
FT INITIALED BDAVIT /S/ Date 5/18/01

Concur: /S/ Date 5/23/2001
for Dale P. Conner, Pharm.D. Director
Division of Bioequivalence

cc: ANDA# 76-121 (original, duplicate), Davit, HFD-658, Gokhale, Davit, HFD-658, Drug File, Div. File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-121 APPLICANT: Able Laboratories Inc.
DRUG PRODUCT: Lithium Carbonate Capsules, USP
300 mg

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

We acknowledge that the dissolution testing will be incorporated in your stability and quality control programs as specified in USP 24.

The dissolution testing should be conducted in 900 mL of deionized, water using apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

Not less than — (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

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

CC: ANDA # 76-121
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ Reviewer: M. Gokhale
HFD-658/ TL: B. Davit

V:\FIRMSAM\ABLE\LTRS&REV\76121SD.201.DOC
Printed in final on 5/18/2001

Endorsements: (Final with Dates)
HFD-658/ M. Gokhale /S/ 5/18/01
HFD-658/ B. Davit /S/ 5/18/01
HFD-650/ D. Conner /S/ 5/23/2001
HFD-617/ S. Mazzella

Bioequivalency- Acceptable

Submission Dates: 5/1/01, 5/8/01

1) Study Amendment dated 5/1/01 (STA)

Strength: 300 mg
Outcome: AC

2) New Correspondence dated 5/8/01

Strength: 300 mg
Outcome: AC

Outcome Decisions: AC- Acceptable

Winbio comments: STA – Acceptable

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : ~~76-121~~ 76-121 SPONSOR : Able Laboratories Inc.

DRUG AND DOSAGE FORM : Lithium Carbonate Capsules, USP

STRENGTH(S) : 300 mg

TYPES OF STUDIES : [SD] [SDF] MULT [OTHER]

CLINICAL STUDY SITE(S) : ———————

ANALYTICAL SITE(S) : ———————

STUDY SUMMARY : In the single dose fasting bioequivalence study, Lithium Carbonate Capsules, 300 mg were shown to be bioequivalent to Eskalith® Capsules, 300 mg.

DISSOLUTION : Acceptable

DSI INSPECTION STATUS

Inspection needed: YES / [NO]	Inspection status:	Inspection results:
First Generic ____ New facility ____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : MAMATA S. GOKHALE, Ph.D. BRANCH : III

INITIAL : /S/ _____ DATE : 5/18/01

TEAM LEADER : BARBARA M. DAVIT, Ph.D. BRANCH : III

INITIAL : ___ /S/ _____ DATE : 5/18/01

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

INITIAL : _____ /S/ _____ DATE : 5/23/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-121

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-121 Date of Submission: July 13, 2001

Applicant: Able Laboratories Established Name: Lithium Carbonate Capsules USP, 300 mg

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

- Do you have 12 Final Printed Labels and Labeling? YES
- Container Labels: (100 & 1,000) 7/13/01 submission is satisfactory for approval.
- Professional Package Insert Labeling: FPL submitted 7/13/01 is satisfactory for approval.
- Revisions needed post-approval: None

BASIS OF APPROVAL:

- Was this approval based upon a petition? NO
- What is the RLD on the 356(h) form: Eskalith
- NDA Number: 16-860
- NDA Drug Name: Eskalith (Lithium Carbonate) Capsule
- NDA Firm: Smith Kline & French Laboratories
- Date of Approval of NDA Insert and supplement #: October 30, 1986; S-063
- Has this been verified by the MIS system for the NDA? YES
- Was this approval based upon an OGD labeling guidance? NO
- Basis of Approval for the Container Labels: Side By Side
- Basis of Approval for the Carton Labeling: N/A

FOR THE RECORD

1. MODEL LABELING: NDA 16-860/S063, Eskalith Capsules, "permitted" October 30, 1986. Team Leader, John Grace, states that "permitted" is an old term used by HFD-120 that we have accepted for use as model labeling.
2. INACTIVE INGREDIENTS: Consistent with the inactive ingredients listed on page 1102, vol. 1.2.
3. PATENTS/EXCLUSIVITIES: No unexpired patents or exclusivities.
4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in well-closed containers
   - NDA: Store at controlled room temperature
   - ANDA: Store at controlled room temperature 150-300C (590-860F). [See USP.]
5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight container
   - ANDA: Dispense in a tight container as defined in the USP, with a child-resistant closure (as required).
6. PACKAGE CONFIGURATION
   - NDA: 100 & 500
   - ANDA: 100 & 1000
7. CONTAINER/CLOSURE (page 1400, Vol. 1.3)
   - Container:
   - Closure:CRC for the 100 and non-CRC for the 1000
8. FINISHED DOSAGE FORM
   - NDA: Capsule
   - ANDA: White to Off-White powder filled in # 1 capsules. Pink opaque cap imprinted "A" in black ink & pink opaque body imprinted "270" in black ink.

Date of Review: August 20, 2001 Date of Submission: July 13, 2001
Primary Reviewer: Koung Lee /S/ Date: 8/21/01
Team Leader: Charlie Hoppes /S/ Date: 8/21/01

cc: ANDA: 76-121
DUP/DIVISION FILE
HFD-613/KLee/CHoppes (no cc)
V:\FIRMSAM\ABLE\LTRS&REV\76121.NA.LABELING Review

DIVISION REVIEW SUMMARY

ANDA 76-121 **DRUG PRODUCT:** Lithium Carbonate

FIRM: Able Laboratories, Inc. **DOSAGE FORM:** Capsules

STRENGTH: 300 mg

CGMP STATEMENT/EIR UPDATE STATUS: Pending -

BIO INFORMATION: Adequate -
See Bio sign-off dated 5/23/01.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Not required, both items are compendia.

STABILITY: Adequate -
Accelerated (40 ± 2°C/75 ± 5% RH) stability data are provided for packaged lot no. TB-073A tested initial, 1, 2, and 3-month test intervals upright positions. The data appear to be adequate and within the specified limits. The container/closure system used in stability studies is the same as the one container section. An expiration dating of 24 month has been granted.

LABELING: Pending -
See Review of Professional Labeling dated 8/20/01.

STERILIZATION VALIDATION: N/A -

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -
Lot no. TB-073A [redacted] Lot no. 9908-9 used. DMF [redacted] found **ADEQUATE** dated 8/7/01.

SIZE OF STABILITY BATCHES - Satisfactory -
Lot no. TB-073A (yielded = [redacted] capsules) is provided. Waste accounted for [redacted] capsules [redacted]. Q.C. samples accounted for [redacted] capsules. Total packaged = [redacted] capsules. Total available capsules = [redacted]. Total accountability = [redacted].
The batch was manufactured using production scale equipment under production conditions.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

The proposed production batch size is ——— capsules. The manufacturing process is the same as for the exhibit batch.

RECOMMENDATION:

APPROVED

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-121

CORRESPONDENCE

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

July 13, 2001

N/Am
ORIG AMENDMENT

FACSIMILE
Dr. Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

MINOR AMENDMENT TO
ABBREVIATED NEW DRUG APPLICATION
ANDA # 76-121
LITHIUM CARBONATE CAPSULES, USP 300 mg

Dear Dr. Buehler:

Pursuant to Facsimile communication from Ms. Kassandra Sherrod on June 28, 2001, ABLE LABORATORIES, INC., herewith submits a MINOR AMENDMENT to our original Abbreviated New Drug Application, dated February 26, 2001, for Lithium Carbonate Capsules, USP 300 mg. as described in 21CFR 314.120.

We have fully addressed each of the observations referenced in the facsimile transmission, and have included final labeling, inserts and other exhibits as applicable.

We trust that this Amendment to the Abbreviated New Drug Application for Lithium Carbonate Capsules, USP 300 mg meets all requirements.

We have submitted a true copy of this amendment to the Field.
If you should require additional information or have any questions regarding this Amendment please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 16 2001
OGD

Thank you.

Sincerely,

Mr. Shashikant Shah, R.Ph.
V.P. of Quality / Regulatory Affairs

6 Hollywood Court ◢ South Plainfield ◢ New Jersey 07080
Telephone: 908-754-2253 ◢ Fax: 908-754-2476

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

May 7, 2001

N/AB

ORIG AMENDMENT

FACSIMILE
Dr. Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

BIOEQUIVALENCE AMENDMENT TO
ABBREVIATED NEW DRUG APPLICATION
ANDA # 76-121
LITHIUM CARBONATE CAPSULES, USP 300 mg

Dear Dr. Buehler:

Pursuant to Facsimile communication from Mr. Steven Mazzella on May 2, 2001, ABLE LABORATORIES, INC., herewith submits an amendment to complete the bioequivalence portion of our original Abbreviated New Drug Application, dated February 26, 2001, for Lithium Carbonate Capsules, USP 300 mg.

Enclosed please find:
(1) Supplement 01 to the Validation Report for Determination of Lithium in Human Serum Samples by —— , - Longterm Stability.

We trust that this Amendment to the Abbreviated New Drug Application for Lithium Carbonate Capsules, USP 300 mg meets all requirements.

If you should require additional information or have any questions regarding this Amendment please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

CENTER FOR DRUG
MAY 0 8 2001
OGD
EVALUATION AND RESEARCH

Thank you.

Sincerely,

Mr. Shashikant Shah, R.Ph.
V.P. of Quality / Regulatory Affairs

6 Hollywood Court ◢ South Plainfield ◢ New Jersey 07080
Telephone: 908-754-2253 ◢ Fax: 908-754-2476

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

April 30, 2001

FACSIMILE

Dr. Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ORIG AMENDMENT
N/AB

BIOEQUIVALENCE AMENDMENT TO
ABBREVIATED NEW DRUG APPLICATION
ANDA # 76-121
LITHIUM CARBONATE CAPSULES, USP 300 mg

Dear Dr. Buehler:

Pursuant to written communication from Ms. Saundra Middleton on March 28, 2001, ABLE LABORATORIES, INC., herewith submits an amendment to complete the bioequivalence portion of our original Abbreviated New Drug Application, dated February 26, 2001, for Lithium Carbonate Capsules, USP 300 mg.

Enclosed please find:

(1) Procedure SOP - MOP _HX027 in original German and English traslation.

(2) ~~~~~

We trust that this Amendment to the Abbreviated New Drug Application for Lithium Carbonate Capsules, USP 300 mg meets all requirements.

6 Hollywood Court ◢ South Plainfield ◢ New Jersey 07080
Telephone: 908-754-2253 ◢ Fax: 908-754-2476

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

Ref: ANDA# 76-121
Lithium Carbonate Capsules, USP 300 mg.

If you should require additional information or have any questions regarding this Amendment please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

Thank you.

Sincerely,

Mr. Shashikant Shah, R.Ph.
V.P. of Quality / Regulatory Affairs
/enclosure

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-121

Able Laboratories, Inc.
Attention: Shashikant Shah, R.Ph.
6 Hollywood Court CN 1013
South Plainfield, NJ 07080

MAR 28 2001

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated March 21, 2001 and your correspondence dated March 21, 2001.

NAME OF DRUG: Lithium Carbonate Capsules USP, 300 mg

DATE OF APPLICATION: February 26, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 28, 2001

In the interim, please submit the following for the bioequivalence study results:

- Procedure SOP
- ~~~~~~~~~~

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

February 27, 2001

FEDERAL EXPRESS
Dr. Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

NEW CORRESP
NC

AMENDMENT TO
ABBREVIATED NEW DRUG APPLICATION
LITHIUM CARBONATE CAPSULES, USP
300 mg

Dear Dr. Buehler:

ABLE LABORATORIES, INC., herewith submits an amendment to complete our original Abbreviated New Drug Application, dated February 26, 2001, for Lithium Carbonate Capsules, USP 300 mg.

Enclosed is the electronic submission for the Fasting Bio Study and Correspondence from the Agency dated August 8, 2000 which specifies the dissolution and Bioequivalence requirements for Lithium Carbonate Capsules, USP 300 mg.

We trust that this Amendment to the Abbreviated New Drug Application for Lithium Carbonate Capsules, USP 300 mg meets all requirements.

If you should require additional information or have any questions regarding this Amendment please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 753-9383.

Thank you.

Sincerely,

Mr. Shashikant Shah, R.Ph.
V.P. of Quality / Regulatory Affairs

6 Hollywood Court ◢ South Plainfield ◢ New Jersey 07080
Telephone: 908-754-2253 ◢ Fax: 908-754-2476

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

ACK for filing 3/28/01
187
505(j)(2)(A)(i)

February 26, 2001

FEDERAL EXPRESS
Dr. Gary Buehler
Acting Director
Office of Generic Drugs (HFD-600)
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

ABBREVIATED NEW DRUG APPLICATION
LITHIUM CARBONATE CAPSULES, USP
300 mg

Dear Dr. Buehler:

Pursuant to Section 505(j)(1) of the Federal Food, Drug and Cosmetic Act, ABLE LABORATORIES, INC., herewith submits an original Abbreviated New Drug Application (ANDA) for Lithium Carbonate Capsules, USP 300 mg.

The Lithium Carbonate Capsules, USP 300 mg drug product for which this ANDA is submitted is identical to SmithKline Beecham's Eskalith Capsules, 300 mg, previously approved by the Food and Drug Administration under New Drug Application 016860.

It is the opinion of ABLE LABORATORIES, INC., and to the best of our knowledge, with respect to each patent which claims the listed drug or which claims a use for such listed drug for which we are seeking approval that such patent(s), if filed, has expired and therefore will not be infringed by the manufacture, use, or sale of the drug for which this Abbreviated New Drug Application is being submitted.

In vivo bioavailability studies have been conducted on ABLE Laboratories, Inc.'s Lithium Carbonate Capsules, USP 300 mg and compared to the Reference Listed Drug, SmithKline Beecham's Eskalith Capsules, 300 mg. Electronic copies of the analytical section of the bioequivalence study from ——— .. have been included in Volume I..

Dissolution testing was also performed on the product. The comparative dissolution for the drug product is included in Section VI.3.

6 Hollywood Court ◢ South Plainfield ◢ New Jersey 07080
Telephone: 908-754-2253 ◢ Fax: 908-754-2476

ABLE
LABORATORIES
INC. Subsidiary of DynaGen, Inc.

We are requesting a two (2) year expiration dating period for this product based on accelerated stability data provided herein. We trust that this Abbreviated New Drug Application for Lithium Carbonate Capsules, USP 300 mg meets all requirements.

If you should require additional information or have any questions regarding this Abbreviated New Drug Application, please do not hesitate to contact me directly by phone at (908) 754-2253, ext. 505 or by facsimile at (908) 754-2476.

We have submitted a true copy of the chemistry section to the field .

Thank you.

Sincerely,

ABLE LABORATORIES, INC.

/S/

Mr. Shashikant Shah, R. Ph.
V.P. Quality

Volumes Submitted:

Archival - 7 (2 sets of 7 each)
Field Copy - 7
Chemistry - 4
Bioequivalence - 4