CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076832

Name: Lithium Carbonate Extended-Release Tablets USP 300 mg

Sponsor: Roxane Laboratories, Inc.

Approval Date: October 28, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

CONTENTS

Reviews / Information Included in this Review	
Approval Letter	X
Tentative Approval Letter	
Labeling	X
Labeling Review(s)	X
Medical Review(s)	
Chemistry Review(s)	X
Bioequivalence Review(s)	X
Statistical Review(s)	
Microbiology Review(s)	
Administrative & Correspondence Documents	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

APPROVAL LETTER

ANDA 76-832

OCT 28 2004

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated August 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Lithium Carbonate Extended-Release Tablets USP, 300 mg.

Reference is also made to your amendments dated May 7, May 26, June 11, and August 20, 2004.

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 Extended-Release Tablets USP, 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Lithobid® Slow-release Tablets, 300 mg, of Solvay Pharmaceuticals).

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> 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 "interim" specifications:

Time (minutes)	Percent Dissolved
30	10% - 30%
90	55% - 75%
150	NLT 85%

The "interim" dissolution tests and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" when there are no revisions to be made to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

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.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Robert Lumpkin for 10/28/2004

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-832
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/D.Maldonado/ 10/14/04.
HFD-643/B.Arnwine/10/12/04 10/25/04
HFD-617/Y.Kong/
HFD-613/K.Lee/ 10/21/04
HFD-613/L.Golson 10/21/04

10/27/04

10/28/2004

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F/T by rad10/13/04

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

LABELING

APPROVED

OCT 28 2004

10002523/01

LITHIUM CARBONATE
Extended Release Tablets USP, 300 mg

10002523/01

ROXANE LABORATORIES, INC.
Columbus, Ohio 43216

LITHIUM CARBONATE
Extended Release Tablets USP, 300 mg

R_x 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 Extended Release Tablets USP contain lithium carbonate, a white, odorless 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 beige-colored, extended release tablet contains 300 mg of lithium carbonate. This slowly dissolving, film-coated tablet is designed to give lower serum lithium peak concentrations than obtained with conventional oral lithium dosage forms. Inactive ingredients consist of calcium stearate, Opadry II (Flesh), povidone, sodium chloride, sodium lauryl sulfate, and sorbitol. Opadry II (Flesh) contains hypromellose, iron oxide red, iron oxide yellow, polyethylene glycol, polydextrose, titanium dioxide, and triacetin.

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 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 judgment, aggressiveness, and possibly hostility. When given to a patient experiencing a manic episode, lithium 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, dehydration, sodium depletion, and to patients receiving diuretics, or angiotensin converting enzyme (ACE) inhibitors, 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 function and morphologic changes and their association with lithium therapy have not been established.

Kidney function should be assessed prior to and during lithium therapy. 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 re-evaluation 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, most notably haloperidol. In some instances, the syndrome was followed by irreversible brain damage. Because of possible causal relationship between these events and the concomitant administration of lithium and neuroleptic drugs, patients receiving such combined therapy or patients with organic brain syndrome or other CNS impairment 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 concentrations and can occur at doses close to the therapeutic concentrations (see **DOSAGE AND ADMINISTRATION**).

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

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

Usage in Pregnancy

Adverse effects on nidation in rats, embryo viability in mice, and metabolism *in vitro* of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium 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 by their physician of the potential hazard to the fetus.

Usage in 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 hazard to the infant or neonate. Signs and symptoms of lithium toxicity such as hypertonia, hypothermia, cyanosis and ECG changes have been reported in some infants and neonates.

Pediatric Use

Safety and effectiveness in pediatric patients under 12 years of age have not been determined; its use in these patients is not recommended.

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

PRECAUTIONS

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

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 elimination half-life 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 3500 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 thyroid disorders do not necessarily constitute a contraindication to lithium treatment. Where hypothyroidism preexists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters and/or adjustment of lithium doses, if any. If hypothyroidism occurs during lithium stabilization and maintenance, supplemental thyroid treatment may be used.

In general, the concomitant use of diuretics or angiotensin converting enzyme (ACE) inhibitors with lithium carbonate should be avoided. In those cases where concomitant use is necessary extreme caution is advised since sodium loss from these drugs may reduce the renal clearance of lithium resulting in increased serum lithium concentrations with the risk of lithium toxicity. When such combinations are used, the lithium dosage may need to be decreased, and more frequent monitoring of lithium serum concentrations is recommended. See **WARNINGS** for additional caution information.

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

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

Concomitant extended use of iodide preparations, especially potassium iodide, with lithium may produce hypothyroidism.

Concurrent use of calcium channel blocking agents with lithium may increase the risk of neurotoxicity in the form of ataxia, tremors, nausea, vomiting, diarrhea and/or tinnitus.

Concurrent use of metronidazole with lithium may provoke lithium toxicity due to reduced renal clearance. Patients receiving such combined therapy should be monitored closely.

Concurrent use of fluoxetine with lithium has resulted in both increased and decreased serum lithium concentrations. Patients receiving such combined therapy should be monitored closely.

Nonsteroidal anti-inflammatory drugs (NSAIDS): Lithium levels should be closely monitored when patients initiate or discontinue NSAID use. In some cases, lithium toxicity has resulted from interactions between an NSAID and lithium. Indomethacin and piroxicam have been reported to increase significantly steady-state plasma lithium concentrations. There is also evidence that other nonsteroidal anti-inflammatory agents, including the selective cyclooxygenase-2 (COX2) inhibitors, have the same effect. In a study conducted in healthy subjects, mean steady-state lithium plasma levels increased approximately 17% in subjects receiving lithium 450 mg BID with celecoxib 200 mg BID as compared to subjects receiving lithium alone.

Lithium may impair mental and/or physical abilities. Patients should be cautioned about activities requiring alertness (e.g., operating vehicles or machinery).

Pregnancy

Pregnancy Category D. (see **WARNINGS**).

Nursing Mothers

Because of the potential for serious adverse reactions in nursing infants and neonates from lithium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see **WARNINGS**).

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 have not been established (see **WARNINGS**).

Geriatric Use

Clinical studies of lithium carbonate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other therapy.

ADVERSE REACTIONS

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

Adverse reactions may be encountered at serum lithium concentrations below 1.5 mEq/L. Mild to moderate adverse reactions may occur at concentrations from 1.5 to 2.5 mEq/L, and moderate to severe reactions may be seen at concentrations from 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 with a temporary reduction or cessation of dosage. If persistent, a 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 concentrations below 2 mEq/L. At higher concentrations, giddiness, ataxia, blurred vision, tinnitus and a large output of dilute urine may be seen. Serum lithium concentrations above 3 mEq/L may produce a complex clinical picture involving multiple organs and organ systems. Serum lithium concentrations 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 concentrations, including concentrations within the therapeutic range:

Central Nervous System: tremor, muscle hyperirritability (fasciculations, twitching, clonic movements of whole limbs), hypertonicity, ataxia, choreoathetotic 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. 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.

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 folliculitis, xerosis cutis, psoriasis or its exacerbation, generalized pruritus with or without rash, cutaneous ulcers, angioedema;

Autonomic Nervous System: blurred vision, dry mouth, impotence/sexual dysfunction;

Thyroid Abnormalities: euthyroid goiter and/or hypothyroidism (including myxedema) accompanied by lower T_3 and T_4. ^{131}Iodine uptake may be elevated (see **PRECAUTIONS**). Paradoxically, rare cases of hyperthyroidism have been reported.

EEG Changes: diffuse slowing, widening of frequency spectrum, potentiation and disorganization of background rhythm.

EKG Changes: reversible flattening, isoelectricity or inversion of T-waves.

Miscellaneous: Fatigue, lethargy, transient scotomata, exophthalmos, dehydration, weight loss, leucocytosis, headache, transient hyperglycemia, hypercalcemia, hyperparathyroidism, albuminuria, 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, and 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 starting lithium treatment. The mechanism through which these symptoms (resembling Raynaud's Syndrome) developed is not known. Recovery followed discontinuance.

OVERDOSAGE

The toxic concentrations for lithium (≥1.5 mEq/L) are close to the therapeutic concentrations (0.6 to 1.2 mEq/L). 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. Treatment is supportive. 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 functioning. 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. However, patient recovery may be slow.

Infection prophylaxis, regular chest X-rays, and preservation of adequate respiration are essential.

DOSAGE AND ADMINISTRATION

Acute Mania

Optimal patient response can usually be established with 1800 mg/day in the following dosages:

ACUTE MANIA			
	Morning	**Afternoon**	**Nighttime**
Lithium Carbonate Extended Release Tablets[1]	3 tabs (900 mg)		3 tabs (900 mg)

[1]Can also be administered on 600 mg t.i.d. recommended dosing interval.

Such doses will normally produce an effective serum lithium concentration ranging between 1 and 1.5 mEq/L. Dosage must be individualized according to serum concentrations and clinical response. Regular monitoring of the patient's clinical state and of serum lithium concentrations is necessary. Serum concentrations should be determined twice per week during the acute phase, and until the serum concentrations and clinical condition of the patient have been stabilized.

Long-Term Control

Desirable serum lithium concentrations are 0.6 to 1.2 mEq/L which can usually be achieved with 900 to 1200 mg/day. Dosage will vary from one individual to another, but generally the following dosages will maintain this concentration.

LONG-TERM CONTROL			
	Morning	**Afternoon**	**Nighttime**
Lithium Carbonate Extended Release Tablets[1]	2 tabs (600 mg)		2 tabs (600 mg)

[1]Can be administered on t.i.d. recommended dosing interval up to 1200 mg/day.

Serum lithium concentrations in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months. Patients abnormally sensitive to lithium may exhibit toxic signs at serum concentrations of 1 to 1.5 mEq/L. Geriatric patients often respond to reduced dosage, and may exhibit signs of toxicity at serum concentrations ordinarily tolerated by other patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Important Considerations

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 previous dose). Total reliance must not be placed on serum concentrations alone. Accurate patient evaluation requires both clinical and laboratory analysis.

Lithium Carbonate Extended Release Tablets USP must be swallowed whole and never chewed or crushed.

HOW SUPPLIED

Lithium Carbonate Extended Release Tablets USP, 300 mg are supplied as beige-colored, biconvex, film-coated tablets with "54 107" debossed on one side and plain on the other side.

0054-0021-25	300 mg beige tablet, bottle of 100
0054-0021-29	300 mg beige tablet, bottle of 500

Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Protect from moisture. Dispense in tight, child-resistant container (USP).

10002523/01 Revised January 2004

Boehringer Ingelheim
Roxane Laboratories

ORIG.


DOSAGE AND ADMINISTRATION: See accompanying insert for complete directions for use.
WARNINGS: See package insert.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Roxane Laboratories, Inc.
Columbus, Ohio 43216
NDC 0054-0021-25 100 Tablets
LITHIUM CARBONATE
Extended Release
Tablets USP
300 mg
Each tablet contains 300 mg of Lithium Carbonate USP.
℞ only
Boehringer Ingelheim
Roxane Laboratories
EXP. LOT
APPROVED
10002521/01
© RLI, 2004


DOSAGE AND ADMINISTRATION: See accompanying insert for complete directions for use.
WARNINGS: See package insert.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Roxane Laboratories, Inc.
Columbus, Ohio 43216
NDC 0054-0021-25 100 Tablets
LITHIUM CARBONATE
Extended Release
Tablets USP
300 mg
Each tablet contains 300 mg of Lithium Carbonate USP.
℞ only
Boehringer Ingelheim
Roxane Laboratories
EXP. LOT
APPROVED
10002521/01
© RLI, 2004

NDC 0054-0021-29 500 Tablets

LITHIUM CARBONATE
Extended Release Tablets USP
300 mg

Each tablet contains 300 mg of Lithium Carbonate USP.

℞ only

Boehringer Ingelheim
Roxane Laboratories

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LOT
EXP.

DOSAGE AND ADMINISTRATION:
See accompanying insert for complete directions for use.

WARNINGS: See package insert.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0021-29 500 Tablets

LITHIUM CARBONATE
Extended Release Tablets USP
300 mg

Each tablet contains 300 mg of Lithium Carbonate USP.

℞ only

Boehringer Ingelheim
Roxane Laboratories

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LOT
EXP.

DOSAGE AND ADMINISTRATION:
See accompanying insert for complete directions for use.

WARNINGS: See package insert.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Roxane Laboratories, Inc.
Columbus, Ohio 43216

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

LABELING REVIEWS

1.1

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

ANDA Number: 76-832 Date of Submission: August 26, 2003

Applicant's Name: Roxane Laboratories, Inc.

Established Name: Lithium Carbonate Extended-release Tablets USP, 300 mg

Labeling Deficiencies:

1. CONTAINER (100 and 500)

   a. Please include the USP drug release test with which your product complies.

   b. Revise the storage temperature statement to read "Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature)"

2. INSERT

   a. DESCRIPTION

      Please include the USP drug release test with which your product complies.

   b. Replace the section heading "ACTIONS" with "CLINICAL PHARMACOLOGY".

   c. Revise the section heading "INDICATIONS" to read "INDICATIONS AND USAGE"

   d. PRECAUTIONS

      i. Revise the subsection headings "Usage in Pregnancy" and "Usage in Nursing Mothers" with "Pregnancy" and "Nursing Mothers", respectively.

      ii. Geriatric Use

         Delete the last paragraph.

   e. OVERDOSAGE

      Switch the position of the OVERDOSAGE section with the DOSAGE AND ADMINISTRATION section.

   f. HOW SUPPLIED

      See CONTAINER comment b.

Please revise your labeling as instructed above and submit 12 final printed copies of labels and labeling for a full approval of this application.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

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

- Do you have 12 Final Printed Labels and Labeling?

	Date Submitted	Vol. #	Revised	Recommendation

- Professional Package Insert Labeling:
- Revisions needed post-approval:

BASIS OF APPROVAL:

- Was this approval based upon a petition?
- What is the RLD on the 356(h) form:
- NDA Number:
- NDA Drug Name:
- NDA Firm:
- Date of Approval of NDA Insert and supplement #:
- Has this been verified by the MIS system for the NDA?
- Was this approval based upon an OGD labeling guidance?
- Basis of Approval for the Container Labels:
- Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, Does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging		X	

configuration?			
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
		X	

Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING: Lithobid Slow Release Tablets, 300 mg under NDA 18-027/S-049, approved October 7, 2002.
2. INACTIVE INGREDIENTS: Consistent with the COMPONENTS AND COMPOSITION section. See pages 1559 and 1592, volume 1.2.
3. PATENTS/EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
		None		

Exclusivity Data -

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in well closed container.
   - NDA: Store at Controlled Room Temperature, 15° to 30° C(59° to 86°F)

   ANDA: Store between [redacted] (b) (4). Stability conducted at 25°C/60%RH and 40°C/75%RH (P 2069 Vol. 1.3). Firm is asked to revise the storage temperature statement to read "Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature)"
5. DISPENSING STATEMENT COMPARISON
   - NDA: Dispense in a tight, child resistant container (USP).
   - ANDA: Dispense in a tight, child-resistant container (USP).
6. PACKAGE CONFIGURATION
   - NDA: Bottles of 100 and 1000.
   - ANDA: Bottles of 100 and 500
7. CONTAINER/CLOSURE - HDPE/non-CRC for both sizes (Page 1861, vol. 1.3).
8. FINISHED DOSAGE FORM
   - NDA: Peach colored imprinted "SOLVAY 4492"
   - ANDA: Beige coated, 3/8 inch biconvex tablets with "54 107" debossed on one side and plain on the other side. Consistent with application. (page 1942, Vol. 1.3)
9. The manufacturer is Roxane Laboratories, Inc., 1809 Wilson Road, Columbus, Ohio 43228.

Date of Review: December 30, 2003 — Date of Submission: August 26, 2003

Primary Reviewer: Koung Lee — Date: 1/9/04

Team Leader: Lillie Golson — Date: 1/5/04

cc: ANDA: 76-832
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSNZ\ROXANE\LTRS&REV\76832.NA1.Labeling Review

This Approval Summary is SUPERSEDED by the Approval summary for the 2/18/04 submission

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

ANDA Number: 76-832 Date of Submission: January 22, 2004

Applicant's Name: Roxane Laboratories, Inc.

Established Name: Lithium Carbonate Extended-release Tablets 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?

	Date Submitted	Code	Revised	Recommendation
Bottle of 100	1/22/04	10002521/01	RLI,2004	Acceptable for Approval
Bottle of 500	1/22/04	10002522/01	RLI,2004	Acceptable for Approval
INSERT	1/22/04	10002523/01	Revised January 2004 RLI,2004	Acceptable for Approval

- Revisions needed post-approval:

INSERT

Add the USP drug release test with which your product complies to in the DESCRIPTION section.

BASIS OF APPROVAL:

- Was this approval based upon a petition? no
- What is the RLD on the 356(h) form: Lithobid Slow Release Tablets, 300 mg
- NDA Number: 18-027
- NDA Drug Name: Lithobid
- NDA Firm: Solvay Pharmaceuticals, Inc.
- Date of Approval of NDA Insert and supplement #: October 7, 2002
- 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: NA

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X

Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used.		X	

However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING: Lithobid Slow Release Tablets, 300 mg under NDA 18-027/S-049, approved October 7, 2002.
2. INACTIVE INGREDIENTS: Consistent with the COMPONENTS AND COMPOSITION section. See pages 1559 and 1592, volume 1.2.
3. PATENTS/EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
		None		

Exclusivity Data -

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in well closed container.
   - NDA: Store at Controlled Room Temperature, 15^0 to 30^0 C(59^0 to 86^0F)

   ANDA: Store between [redacted] (b) (4). Stability conducted at 25^0C/60%RH and 40^0C/75%RH (P 2069 Vol. 1.3). Firm is asked to revise the storage temperature statement to read "Store at 20^0 - 25^0C (68^0 - 77^0F) (See USP Controlled Room Temperature)"
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7. CONTAINER/CLOSURE - HDPE/non-CRC for both sizes (Page 1861, vol. 1.3).
8. FINISHED DOSAGE FORM
   - NDA: Peach colored imprinted "SOLVAY 4492"
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9. The manufacturer is Roxane Laboratories, Inc., 1809 Wilson Road, Columbus, Ohio 43228.
10. In the firm's January 22, 2004 amendment, Elizabeth Ernst of Roxane, states "we have not received the comments from the Division of Bioequivalence whether our proposed dissolution method, submitted in the ANDA, acceptable". Firm may add the USP drug release test statement post approval.

Date of Review: January 27, 2004 — Date of Submission: January 22, 2004
Primary Reviewer: Koung Lee — Date: 2/2/04
Team Leader: Lillie Golson — Date: 2/3/04

cc: ANDA: 76-832
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)
V:\FIRMSNZ\ROXANE\LTRS&REV\76832.AP.Labeling Review

APPROVAL SUMMARY
(This APPROVAL SUMMARY SUPERSEDES the APPROVAL SUMMARY for the January 22, 2004 submission)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-832 Date of Submission: February 18, 2004

Applicant's Name: Roxane Laboratories, Inc.

Established Name: Lithium Carbonate Extended-release Tablets 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?

	Date Submitted	Code	Revised	Recommendation
Bottle of 100	2/18/04	10002521/01	RLI,2004	Acceptable for Approval
Bottle of 500	2/18/04	10002522/01	RLI,2004	Acceptable for Approval
INSERT	1/22/04	10002523/01	Revised January 2004 RLI,2004	Acceptable for Approval

- Revisions needed post-approval:

INSERT

Add the USP drug release test with which your product complies to in the DESCRIPTION section.

BASIS OF APPROVAL:

- Was this approval based upon a petition? no
- What is the RLD on the 356(h) form: Lithobid Slow Release Tablets, 300 mg
- NDA Number: 18-027
- NDA Drug Name: Lithobid
- NDA Firm: Solvay Pharmaceuticals, Inc.
- Date of Approval of NDA Insert and supplement #: October 7, 2002
- 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: NA

Other Comments:

Telephoned Ms. Earnest and asked that she send a letter of commitment to edit the USP DR test # on the labels, whichever reading is the case 10/21/04

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26	X		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the			X

recommendations? If the name was unacceptable, has the firm been notified?			
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
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Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
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Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
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Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
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Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
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Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. MODEL LABELING: Lithobid Slow Release Tablets, 300 mg under NDA 18-027/S-049, approved October 7, 2002.
2. INACTIVE INGREDIENTS: Consistent with the COMPONENTS AND COMPOSITION section. See pages 1559 and 1592, volume 1.2.
3. PATENTS/EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
		None		

Exclusivity Data -

Code/sup	Expiration	Use Code	Description		Labeling Impact
			There is no unexpired exclusivity for this product		

4. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   - USP: Preserve in well closed container.
   - NDA: Store at Controlled Room Temperature, 15° to 30° C(59° to 86°F)

   ANDA: Store between [redacted] (b) (4). Stability conducted at 25°C/60%RH and 40°C/75%RH (P 2069 Vol. 1.3). Firm is asked to revise the storage temperature statement to read "Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature)"
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9. The manufacturer is Roxane Laboratories, Inc., 1809 Wilson Road, Columbus, Ohio 43228.
10. In the firm's January 22, 2004 amendment, Elizabeth Ernst of Roxane, states "we have not received the comments from the Division of Bioequivalence whether our proposed dissolution method, submitted in the ANDA, acceptable". Firm may add the USP drug release test statement post approval.

Date of Review: February 24, 2004 — Date of Submission: February 18, 2004

Primary Reviewer: Koung Lee 3/3/04 — Date:

Team Leader: Lillie Golson — Date: 3/3/04

cc: ANDA: 76-832
DUP/DIVISION FILE
HFD-613/KLee/LGolson (no cc)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

CHEMISTRY REVIEWS

ANDA #76-832

Lithium Carbonate Extended Release Tablets USP, 300 mg

Roxane Laboratories, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-832

2. REVIEW #: 1

3. REVIEW DATE: January 19, 2004

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	August 26, 2003
labeling amendment	January 22, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lithium Carbonate ER Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The RLD is submitted as Lithobid® Slow-release Tablets, 300 mg) manufactured by Solvay Pharmaceuticals, Inc. the subject of NDA # 18-027. To the best of the applicant's knowledge there are no patents existing (Paragraph I statement) and no marketing exclusivity either (p. 7).

10. PHARMACOL. CATEGORY: Anti-manic

11. DOSAGE FORM: Extended-release Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

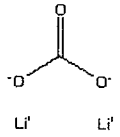
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

_____SPOTS product – Form Completed

_____X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



Lithium Carbonate, Li_2CO_3 with a molecular weight of 73.89.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3			By RRajagopalan
	III			4	N/A		Packaging Component
	III			4	N/A		Packaging Component
	III			4	N/A		Packaging Component
	III			4	N/A		Packaging Component
	III			4	N/A		Packaging Component
	III			4	N/A		Packaging Component
	III			4	N/A		Packaging Component

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

N/A

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Pending		
Methods Validation	NA		
Labeling	Acceptable	2/3/04	KLee
Bioequivalence	Pending		
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA # 76-832

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug product is Lithium Carbonate Extended Release tablets manufactured as (b) (4) (b) (4) (b) (4) The finished tablets will be marketed in bottles of 100's and 500's. (b) (4) (b) (4) The inactive ingredients used in the proposed formulation are calcium stearate, povidone, sodium chloride, sodium lauryl sulfate, sorbitol and Opadry II Flesh. All the stated ingredients are common pharmaceutical tableting excipients

The tablets contain the active ingredient lithium carbonate, a white, odorless, light alkaline powder. Lithium is an element of the alkali-metal group with an atomic number of 3, atomic weight of 6.94 and an emission line at 671 nm on the flame photometer. Based upon available data, lithium carbonate is a simple molecule in its lowest chemical form. It does not degrade or form synthetic intermediates.

The solubility of lithium carbonate in water at 0°C is 1.5 g/100 mL. The solubility decreases significantly with increase in temperature (water at 37°C:1.0 g/100 mL; Water at 100°C: 0.7 g/100 mL). Lithium forms insoluble salts with several common anions including phosphate, fluoride, and the carboxylate anion of the $C_{14} - C_{18}$ fatty acids. Lithium carbonate, as an inorganic salt is inherently thermodynamically stable and is not prone to degradation like the more complex organic molecules and also, is less hygroscopic than several of the lithium salts.

Lithium Carbonate is an antimanic indicated for the treatment of manic-depressive illness.

B. Description of How the Drug Product is Intended to be Used
See Labeling

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645 /DMaldonado
HFD-645 BArnwine/
HFD-617/ NPark/

C. CC Block

ANDA 76-832

Following this page, 10 pages withheld in full (b)(4)-CCI/TS

(b) (4)

[redacted]

30. MICROBIOLOGY
Not Applicable.

31. SAMPLES/METHODS VALIDATION
N/A

32. LABELING
Pending.

33. ESTABLISHMENT INSPECTION
Acceptable 8/20/03.

34. BIOEQUIVALENCE
Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A Categorical exclusion statement is included for the environmental impact analysis statement (p 2087). In addition, the applicant's facility is in compliance with all applicable Federal, State and Local environmental laws and regulations. The Generic Drug Enforcement Act is fully enforced (p 2088).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-832 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lithium Carbonate Extended-release Tablets, 300mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. (b) (4)

10.

11.

12.

13. Your stability report forms should be revised to specify the product manufacturing date, product expiration and packaging dates.

Sincerely yours,

Brenda J. Gannine for 2/18/04

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-832

Endorsements (Draft and Final with Dates):

HFD-647/DMaldonado/1/21/04 DMC 2/12/04.
HFD-647/BArnwine/2/11/04 BA 2/12/04
HFD-617/NPark/2/11/04 NLP 2/18/04

V:\FIRMSNZ\Roxane\LTRS&REV\76832r1

TYPE OF LETTER: Not Approvable

Chemistry Review Data Sheet

ANDA #76-832

Lithium Carbonate Extended Release Tablets USP, 300 mg

Roxane Laboratories, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-832

2. REVIEW #: 2

3. REVIEW DATE: June 2, 2004

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 26, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Minor Amendment	March 16, 2004
Amendment	June 11, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lithium Carbonate ER Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The RLD is submitted as Lithobid® Slow-release Tablets, 300 mg) manufactured by Solvay Pharmaceuticals, Inc. the subject of NDA # 18-027. To the best of the applicant's knowledge there are no patents existing (Paragraph I statement) and no marketing exclusivity either (p. 7).

10. PHARMACOL. CATEGORY: Anti-manic

11. DOSAGE FORM: Extended-release Tablet

12. STRENGTH/POTENCY: 300 mg

13. ROUTE OF ADMINISTRATION: Oral

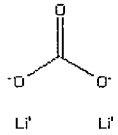
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note22]:

_____SPOTS product – Form Completed

_____X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



Lithium Carbonate, Li_2CO_3 with a molecular weight of 73.89.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	Adequate	3/5/02	By RRajagopalan (b) (4)
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

N/A

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Microbiology	NA		
EES	Acceptable	5/17/04	
Methods Validation	NA		
Labeling	Acceptable	2/3/04	KLee
Bioequivalence	Reviewed	5/20/04	Z.Whaba
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA # 76-832

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Not Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug product is Lithium Carbonate Extended Release tablets manufactured as (b) (4) (b) (4) (b) (4) The finished tablets will be marketed in bottles of 100's and 500's. (b) (4) (b) (4) The inactive ingredients used in the proposed formulation are calcium stearate, povidone, sodium chloride, sodium lauryl sulfate, sorbitol and Opadry II Flesh. All the stated ingredients are common pharmaceutical tableting excipients

The tablets contain the active ingredient lithium carbonate, a white, odorless, light alkaline powder. Lithium is an element of the alkali-metal group with an atomic number of 3, atomic weight of 6.94 and an emission line at 671 nm on the flame photometer. Based upon available data, lithium carbonate is a simple molecule in its lowest chemical form. It does not degrade or form synthetic intermediates.

The solubility of lithium carbonate in water at 0°C is 1.5 g/100 mL. The solubility decreases significantly with increase in temperature (water at 37°C:1.0 g/100 mL; Water at 100°C: 0.7 g/100 mL). Lithium forms insoluble salts with several common anions including phosphate, fluoride, and the carboxylate anion of the $C_{14} - C_{18}$ fatty acids. Lithium carbonate, as an inorganic salt is inherently thermodynamically stable and is not prone to degradation like the more complex organic molecules and also, is less hygroscopic than several of the lithium salts.

Lithium Carbonate is an antimanic indicated for the treatment of manic-depressive illness.

B. Description of How the Drug Product is Intended to be Used
See Labeling

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645 /DMaldonado/6/3/04; 7/20/04
HFD-645 BArnwine/7/20/04
HFD-617/ NPark/6/25/04

C. CC Block

ANDA 76-832

Following this page, 13 pages withheld in full (b)(4)-CCI/TS

(b) (4)

30. MICROBIOLOGY
Not Applicable.

31. SAMPLES/METHODS VALIDATION
N/A

32. LABELING
Pending.

33. ESTABLISHMENT INSPECTION
Acceptable 8/20/03.

34. BIOEQUIVALENCE
Pending

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A Categorical exclusion statement is included for the environmental impact analysis statement (p 2087). In addition, the applicant's facility is in compliance with all applicable Federal, State and Local environmental laws and regulations. The Generic Drug Enforcement Act is fully enforced (p 2088).

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-832 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lithium Carbonate Extended-release Tablets, 300 mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.

6. (b) (4)

Sincerely yours,

Brenda L Gannine /for 7/21/04

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-832

Endorsements (Draft and Final with Dates):

HFD-647/DMaldonado/6/3/04; ~~7/20~~/04 DMR 7/20/04.
HFD-647/BArnwine/7/20/04 BJ 7/21/04
HFD-617/NPark/6/25/04 NPK for NLee 7/22/04

V:\FIRMSNZ\Roxane\LTRS&REV\76832r2

TYPE OF LETTER: Not Approvable

Chemistry Review Data Sheet

ANDA #76-832

Lithium Carbonate Extended Release Tablets USP, 300 mg

Roxane Laboratories, Inc.

Damaris Maldonado
Office of Generic Drugs, Division of Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA # 76-832

2. REVIEW #: 3

3. REVIEW DATE: September 30, 2004.

4. REVIEWER: Damaris Maldonado

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	August 26, 2003
Minor Amendment	March 16, 2004
Amendment	June 11, 2004
Labeling Amendment	1/22/04
Labeling Amendment	2/18/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	August 20, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	614-272-4785

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: NA
b) Non-Proprietary Name (USAN): Lithium Carbonate ER Tablets, USP

9. LEGAL BASIS FOR SUBMISSION: The RLD is submitted as Lithobid® Slow-release Tablets, 300 mg, manufactured by Solvay Pharmaceuticals, Inc. the subject of NDA # 18-027. To the best of the applicant's knowledge there are no patents existing (Paragraph I statement) and no marketing exclusivity either (p. 7).

10. PHARMACOL. CATEGORY: Anti-manic

11. DOSAGE FORM: Extended-release Tablet

12. STRENGTH/POTENCY: 300 mg

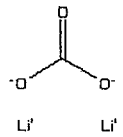
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

_____X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:



Lithium Carbonate, Li_2CO_3 with a molecular weight of 73.89.

17. RELATED/SUPPORTING DOCUMENTS:

Chemistry Review Data Sheet

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
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	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
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4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:
N/A

18. STATUS:

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	NA		
EES	Acceptable	5/17/04	

Methods Validation	NA		
Labeling	Acceptable	3/3/04	KLee
Bioequivalence	Acceptable	9/3/04	Z.Whaba
EA	NA		
Radiopharmaceutical	NA		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA # 76-832

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
Approve

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
The drug product is Lithium Carbonate Extended Release tablets manufactured as (b) (4) (b) (4) (b) (4) The finished tablets will be marketed in bottles of 100's and 500's. (b) (4) (b) (4). The inactive ingredients used in the proposed formulation are calcium stearate, povidone, sodium chloride, sodium lauryl sulfate, sorbitol and Opadry II Flesh. All the stated ingredients are common pharmaceutical tableting excipients

The tablets contain the active ingredient lithium carbonate, a white, odorless, light alkaline powder. Lithium is an element of the alkali-metal group with an atomic number of 3, atomic weight of 6.94 and an emission line at 671 nm on the flame photometer.

The solubility of lithium carbonate in water at 0°C is 1.5 g/100 mL. The solubility decreases significantly with increase in temperature (water at 37°C:1.0 g/100 mL; Water at 100°C: 0.7 g/100 mL). Lithium forms insoluble salts with several common anions including phosphate, fluoride, and the carboxylate anion of the $C_{14} - C_{18}$ fatty acids. Lithium carbonate, as an inorganic salt is inherently thermodynamically stable and is not prone to degradation like the more complex organic molecules and also, is less hygroscopic than several of the lithium salts.

Lithium Carbonate is an antimanic indicated for the treatment of manic-depressive illness.

B. Description of How the Drug Product is Intended to be Used
See Labeling

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

HFD-645 /DMaldonado/9/30/04
HFD-645 BArnwine/10/12/04
HFD-617/ YKong/10/5/04

C. CC Block

ANDA 76-832

Following this page, 14 pages withheld in full (b)(4)-CCI/TS

(b) (4)

30. MICROBIOLOGY
Not Applicable.

31. SAMPLES/METHODS VALIDATION
N/A

32. LABELING
Acceptable 3/3/04

33. ESTABLISHMENT INSPECTION
Acceptable 5/17/04

34. BIOEQUIVALENCE
Acceptable 9/3/04

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

A Categorical exclusion statement is included for the environmental impact analysis statement (p 2087). In addition, the applicant's facility is in compliance with all applicable Federal, State and Local environmental laws and regulations. The Generic Drug Enforcement Act is fully enforced (p 2088).

cc: ANDA 76-832

Endorsements (Draft and Final with Dates):

HFD-647/DMaldonado/9/30/04 10/14/04
HFD-647/BArnwine/10/12/04 10/25/04
HFD-617/YKong/10/5/04 10/19/04

V:\FIRMSNZ\Roxane\LTRS&REV\76832r3
F/t by rad10/13/04

TYPE OF LETTER: Approve

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-832
Drug Product Name	Lithium Carbonate Extended Release Tablets, USP
Strength	300 mg
Applicant Name	Roxane Laboratories, Inc.
Address	Columbus, OH
Submission Date(s)	08/26/03
Amendment Date(s)	~~04/08/04~~ 5/7/04 5/26/04
Reviewer	Zakaria Z. Wahba
First Generic	No
File Location	V:\firmsnz\ Roxane\ltrs&rev\76832n0803.doc

I. Executive Summary

This submission consisted of two (fasting and non-fasting) bioequivalence (BE) studies and dissolution data on the 300 mg strength. Both BE studies are single dose two-way crossover studies in normal males and females (fasting, n=27; non-fasting n=29). The reference listed drug is Solvay's Lithobid® Extended Release Tablets, 300 mg.

Statistical analyses of the plasma concentration data for lithium for both studies demonstrate bioequivalence. For the fasting BE study, lithium results are (point estimate, 90% CI): $LAUC_t$ of 0.99, 94.69-103.15%; $LAUC_i$ of 0.99, 95.05-103.44% and LCmax of 0.95, 84.67-105.63%. For the non-fasting BE study, lithium results are (point estimate, 90% CI): $LAUC_t$ of 1.00, 97.43-101.79%; $LAUC_i$ of 0.98, 96.26-100.59% and LCmax of 1.00, 94.27-106.83%.

In addition, the firm submitted a third BE study, a pilot study under fasting conditions (#LITH-11). This study is a failed BE study. The firm submitted the results of this study only for information purpose, as requested by the Division of Bioequivalence. It was a single dose three-treatment (Test Formulation A, Test Formulation B, and reference product), three period crossover design in normal male subjects (n=12). Statistical analyses of the plasma concentration data for Formulation-A demonstrated bioequivalence. Lithium results (point estimate, 90% CI) are: (b) (4) (b) (4). For the Formulation-B, statistical analyses of the plasma concentration data didn't demonstrate bioequivalence. Lithium results (point estimate, 90% CI) are: (b) (4) (b) (4).

The firm also conducted dissolution testing according to the Agency BA/BA guidance, using the dissolution media of water; 0.1 N HCl, pH 1.2; acetate buffer pH 4.5; tris buffer pH 6.8. The firm's proposed method (900 mL water, basket at 100 rpm) is acceptable. However, the firm's proposed dissolution specifications are unacceptable. Based on the data submitted, the DBE recommends the following interim specifications:

Time (minutes)	Amount dissolved
30	between 10 - 30%
90	between 55% - 75%
150	NLT 85%

The application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Roxane's Lithium Carbonate Extended Release Tablets, 300 mg.
Reference Product	Solvay's Lithobid® Extended Release Tablets, 300 mg.
RLD Manufacturer	Solvay
NDA No.	18-027
RLD Approval Date	Based on COMIS database: 04/27/79 (Electronic Orange Book: prior to 01/01/82)
Indication	in the treatment of manic episodes of manic-depressive illness.

B. PK/PD Information

Bioavailability	Lithium is readily absorbed from GI tract.
Food Effect	Food does not appear to affect the bioavailability of lithium
Tmax	0.5 - 3 hours
Metabolism	-
Excretion	Lithium is nearly completely excreted via the kidneys.
Half-life	20-27 hours (in patient with normal renal function)
Relevant OGD or DBE History	The relevant DBE drug file includes the following: • An acceptable ANDA #76-170 by Barr on the 300 mg strength (DBE review date: 11/21/2002), only fasted and fed studies were submitted. • Two acceptable ANDAs #76-170 by Barr and 76-691 by Roxane on the 450 mg strength (DBE review date: 11/21/2002 and 10/21/2003, respectively), only fasted and fed studies were submitted. • Two protocols (#01-011 by Roxane for the 450 mg strength and 01-016 by Roxane) for the 300 mg strength, DBE recommended two BE studies under fasting and fed conditions.
Agency Guidance	There is no specific guidance on Lithium Carbonate ER Tablets.
Drug Specific Issues (if any)	None

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	Yes	1
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

(information on pp 355-376, vol. C1.2)	**Parent (Lithium)**
Analyte name	Lithium
Internal Standard	N/A
Method description	Atomic Absorption Spectrophotometry
QC range	High Conc.: 0.100 to 8.008 (mcg/mL) Low Conc.: 50.3 to 2572.8 ng/mL
Standard curve range	High Conc.: 0.100 to 10.010 (mcg/mL) Low Conc.: 50.3 to 3015.0 (ng/mL)
Limit of quantitation	50.3 ng/mL
Average recovery of Drug (%)	Not required since no extraction is involved in this method.
Average Recovery of Int. Std (%)	N/A
QC Intraday precision range (%CV)	High Conc.: 3.1 to 7.3 Low Conc.: 3.3 to 17.3
QC Intraday accuracy range (%)	High Conc.: 97.3 to 113.8 Low Conc.: 85.8 to 102.4
QC Interday precision range (%CV)	High Conc.:4.6 to 6.1 Low Conc.: 2.4 to 14.2
QC Interday accuracy range (%)	High Conc.: 98.2 to 105.2 Low Conc.: 96.4 to 101.8
Bench-top stability (hrs)	18
Stock stability (hrs)	24
Processed stability (hrs)	135.5
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	358 days (p 371, vol. C1.2)
Dilution integrity	108.4% @1:10 for 20.040 mcg/mL concentration (p 370, vol. C1.2)
Specificity	Yes
SOPs submitted	Yes
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	N/A (The firm provided the Atomic Absorbance Spectra printouts, see p 448, vol. C1.2)
Random or Serial Selection of Chrom	N/A

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	LITH-11
Study Design	Randomized, 2-way crossover, bioequivalence study under fasting conditions.
No. of subjects enrolled	29 enrolled (30 subjects were required by the protocol)
No. of subjects completing	27
No. of subjects analyzed	27 (#1, 3-10, 12-19, 21-30)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 17 Female: 10
Test product	Roxane's Lithium Carbonate Extended Release Tablets, 300 mg.
Reference product	Solvay's Lithobid® Extended Release Tablets, 300 mg.
Strength tested	300 mg tablet
Dose	1 X 300 mg

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	0.99	94.69-103.15
AUC_{∞}	0.99	95.05-103.44
C_{max}	0.95	84.67-105.63

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
No repeats were reported								

Did use of recalculated plasma concentration data change study outcome? N/A

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	LITH-12
Study Design	Randomized, 2-way crossover, bioequivalence study under fed conditions.
No. of subjects enrolled	30
No. of subjects completing	29
No. of subjects analyzed	29 subjects (#1-22, and 24-30)
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 18 Female 11
Test product	Roxane's Lithium Carbonate Extended Release Tablets, 300 mg.
Reference product	Solvay's Lithobid® Extended Release Tablets, 300 mg.
Strength tested	300 mg tablet
Dose	1 X 300 mg

Summary of Statistical Analysis, Fed Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.00	97.43-101.79
AUC_{∞}	0.98	96.26-100.59
C_{max}	1.00	94.27-106.83

Reanalysis of Study Samples, Fed Bioequivalence Study Additional information in Appendix, Table 17								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
No repeats were reported								

Did use of recalculated plasma concentration data change study outcome? N/A

3. Single-dose Fasted Pilot Bioequivalence Study (Failed Study)

- This is a failed pilot BE study. The firm provided this information as requested by the DBE.
- In this pilot study, the firm tested two different formulations (A and B) vs. the RLD(C).
- The firm provided only a hard copy of the statistical analysis. A diskette with the raw data was not included in the submission.
- The information on the failed study is reported on pages 168-173, C1.1.

Study No.	Protocol Study LITH-10
Study Design	Randomized, 3-way crossover, bioequivalence study under fasting conditions.
No. of subjects enrolled	12
No. of subjects completing	12
No. of subjects analyzed	12
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Not given
Test product	Roxane's Lithium Carbonate Extended Release Tablets, 300 mg.
Reference product	Solvay's Lithobid® Extended Release Tablets, 300 mg.
Strength tested	300 mg tablet
Dose	1 X 300 mg

Summary of Statistical Analysis (%CI) (As reported by the firm)		
Parameter	**Point Estimate**	**90% Confidence Interval**
	[redacted] (b) (4)	
AUC0-t		
AUC∞		
Cmax		

A: Roxane's Formulation A; B: Roxane's Formulation B; C: RLD's Lithobid

F. Formulation

Location in appendix	SectionIV.B, Page 27
Are inactive ingredients within IIG limits?	Yes
If No, list ingredients outside of limits	-
If a tablet, is the product scored?	No
If yes, which strengths are scored?	-
Is scoring of RLD the same as test?	RLD not scored
Is the formulation acceptable?	Yes
If not acceptable, why?	-

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	USP Drug Release Test 2 {Pharmacopeial Forum Vol. 30(2)[Mar.-Apr. 2004]}
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	Apparatus 1 (Basket)
Rotation (rpm)	100 rpm
Firm's proposed specifications	Apparatus 1, 100 rpm Water, 900 mL Time (min.) Amount dissolved 30 between (b) (4) 90 between 150 NLT (b) (4) (information on pages 56, vol. C1.1)
FDA-recommended specifications	See dissolution comments
F2 metric calculated?	Yes
If no, reason why F2 not calculated	-
Is method acceptable?	Yes
If not then why?	-

F2 metric, lower strengths compared to highest strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A			

F2 metric, test compared to reference	
Strength	F2 metric
Test vs Reference (water)	55.30
Test vs Reference (pH 1.2)	50.74
Test vs Reference (pH 4.2)	43.84
Test vs Reference (pH 6.8)	48.09

Dissolution Comments:
The firm's proposed specifications were discussed with Dr.Tran (DBE Dissolution expert) and the following specifications were recommended (see the attached e-mail):
30 min: 10-30%
90 min: 55-75%
150 min: NLT 85%.

H. Waiver Request(s)

Strengths for which waivers are requested	N/A
Regulation cited	N/A
Proportional to strength tested in vivo?	N/A
Is dissolution acceptable?	N/A
Waivers granted?	N/A
If not then why?	N/A

I. Deficiency Comments

The firm's proposed specifications are not acceptable.

J. Recommendations

1. The two single-dose bioequivalence studies, under fasting and fed conditions (projects # LITH-11 and LITH-12, respectively) conducted by Roxane Laboratories, Inc. on its Lithium Carbonate Extended Release Tablets, 300 mg, comparing it to the RLD Solvay's Lithobid® Extended Release Tablets, 300 mg, have been found acceptable.

2. The dissolution testing conducted by the firm on its Lithium Carbonate Extended Release Tablets, 300 mg, is incomplete. The firm's proposed specifications are not acceptable. Based on the submitted data, DBE recommends the following interim specifications:

Time (minutes)	Amount dissolved
30	between 10 - 30%
90	between 55% - 75%
150	NLT 85%

The firm should be informed of the deficiency.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D. Date: 5/27/04
Review Branch III

RD INITIALED YCHuang
FT INITIALED YCHuang Date: 5/27/2004

Concur: Barbara M Davit Date: 5/27/04
for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information (pp175, 196; vol. C1.1)	
Study Number	LITH-11
Study Title	Randomized, 2-way crossover, bioequivalence study under fasting conditions.
Clinical Site	Novum Pharmaceutical Research Services 5900 Penn Avenue Pittsburgh, PA 15206
Principal Investigator	Shirley Ann Kennedy, M.D.
Study/Dosing Dates	Period 1: 04/26/03; Period 2: 05/10/03 (p 271, vol. C1.1)
Analytical Site	(b) (4)
Analytical Director	(b) (6) (p 326)
Analysis Dates	06/03/03 to 06/20/03 (p 329)
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	54 days

Treatment ID	**Test**	**Reference**
Test or Reference	T	R
Product Name	Lithium Carbonate Extended Release Tablets, 300 mg.	Lithobid® Extended Release Tablets, 300 mg.
Manufacturer	Roxane	Solvay
Batch/Lot No.	029080	91996
Manufacture Date	12/04/02 (p 53)	N/A
Expiration Date	N/A	05/27/03 (p 53)
Strength	300 mg	300 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	101.6% (p 112)	98.3% (p110)
Content Uniformity (mean, %CV)	101.5% (%CV=1.00)	97.9% (%CV=1.2)
Formulation	See Appendix Section B	
Dose Administered	1 X 300 mg	1 X 300
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	None
Washout Period	14 days
Randomization Scheme	Yes (p 271, vol. C1.1)
Blood Sampling Times	Predose, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, and 96 hours
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -20°C
IRB Approval	Yes, approved date: 04/01/03 (p 208 vol. C1.1)
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours predose until 4 hours postdose
Length of Confinement	10 hours predose until 24 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 1 Demographics of Study Subjects (N=27)

(information on enrolled subjects, reported on pages 189 & 270, vol. C1.1)

Age		**Weight (lb)**		**Age Groups**		**Gender**		**Race**	
				Range	**%**	**Sex**	**%**	**Category**	**%**
				<18	0			Caucasian	58
Mean	26	Mean	159	18-40	100	Male	66	Afr. Amer.	31
SD	6.8	SD	25.6	41-64	0	Female	34	Hispanic	0
Range	18-39	Range	115-204	65-75	0			Asian	3
				>75	0			Others	8

Table 2 Dropout Information

(information on pages 211, 291, vol.C1.1)

Subject No	Reason	Period	Replaced?
2	Positive drug screening	At Period-2 check-in	no
11	Due to high blood pressure	Prior to Period-1 check-in	no
20	Heavy alcohol use during the wash-out period	Prior to Period-2	no

Table 3 Study Adverse Events

(information on page 273, vol. C1.1)

Adverse Event Description	# in Test Group	# in Ref. Group
Headache	1	1
Elevated bilirubin	0	1
Dizzy	0	1
Protein in urine	1	0
Hemoglobin in urine	1	0
Elevated RBC/HPF in urine	2	0
Elevated glucose	1	0
*Emesis	1	0
Total:	7	2

* Subject #28: occurred 12.5 hours after dosing the subject with the test treatment.

Table 4 Protocol Deviations

(information on page 190, vol. C1.1)

Type	Subject #s (Test)	Subject #s (Ref.)
Subject #30 had caffeinated beverages 44 hrs prior to Period-1	0	1
Some of the 7-hr plasma samples in Period-2 became contaminated. It was not possible to confirm the accuracy of their collection and the samples were discarded. Note: It should be noted that these samples (at the 7-hr) passed Tmax (2-3 hours). The loss of these samples was considered unlikely to influence the outcome of the study.	13	14

Comments on Dropouts/Adverse Events/Protocol Deviations: The test and reference products adverse events were comparable to each other. No serious adverse events were reported. The PK analysis was based on actual sampling times. The reported adverse events and protocol deviations are not likely to compromise the integrity of study.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

(Info on pp 334, 336, 337, vol. C1.1)	Parent (Lithium)
QC Conc. (ng /mL)	125.1, 1001.0, and 2562.6
Inter day Precision (%CV)	4.6 to 5.3
Inter day Accuracy (%)	99.5 to 101.4
Cal. Standards Conc. (ng /mL)	52.1 to 3003.0
Inter day Precision (%CV)	1.8 to 7.7
Inter day Accuracy (%)	98.4 to 100.9
Linearity Range (range of R^2 values)	0.9918 to 0.9998

Comments on Study Assay Quality Control: The QC data are acceptable.

Any interfering peaks in chromatograms?	N/A
Were 20% of chromatograms included?	N/A
Were chromatograms serially or randomly selected?	N/A

Comments on Chromatograms: N/A

Table 6 SOP's dealing with analytical repeats of study samples

(The information was provided in the 05/07/04 Amendment)

SOP No.	**Date of SOP**	**SOP Title**
AL-G-1520-11	04/19/02	Reporting of Data Generated from the Analysis of Biological Matrices

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	N/A (No repeat samples were reported)
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	-

Summary/Conclusions, Study Assays: The study assay is acceptable.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	34140.02	18.18	34642.14	22.83	0.99
AUCT	31428.46	18.38	32026.26	22.80	0.98
CMAX	1657.44	26.02	1751.42	24.35	0.95
KE	0.03	17.73	0.03	18.69	1.01
THALF	22.18	16.35	22.56	19.18	0.98
TMAX	4.44	29.82	4.35	22.94	1.02

MEAN1=Test, MEAN2=Reference

UNIT: AUC=ng hr/mL, CMAX=ng/mL, KE=hrs^{-1}, THALF=hrs, TMAX=hrs

Table 9 Least Squares Geometric Means and 90% Confidence Intervals (N=27)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	33672.53	33959.04	0.99	95.05	103.44
LAUCT	30982.04	31349.83	0.99	94.69	103.15
LCMAX	1601.52	1693.42	0.95	84.67	105.63

Table 10 Additional Study Information

Root mean square error, AUC_{0-t}	0.091985
Root mean square error, AUC_{∞}	0.090889
Root mean square error, C_{max}	0.237759
K_{el} and AUC_{∞} determined for how many subjects?	All 27 subjects
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	-
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

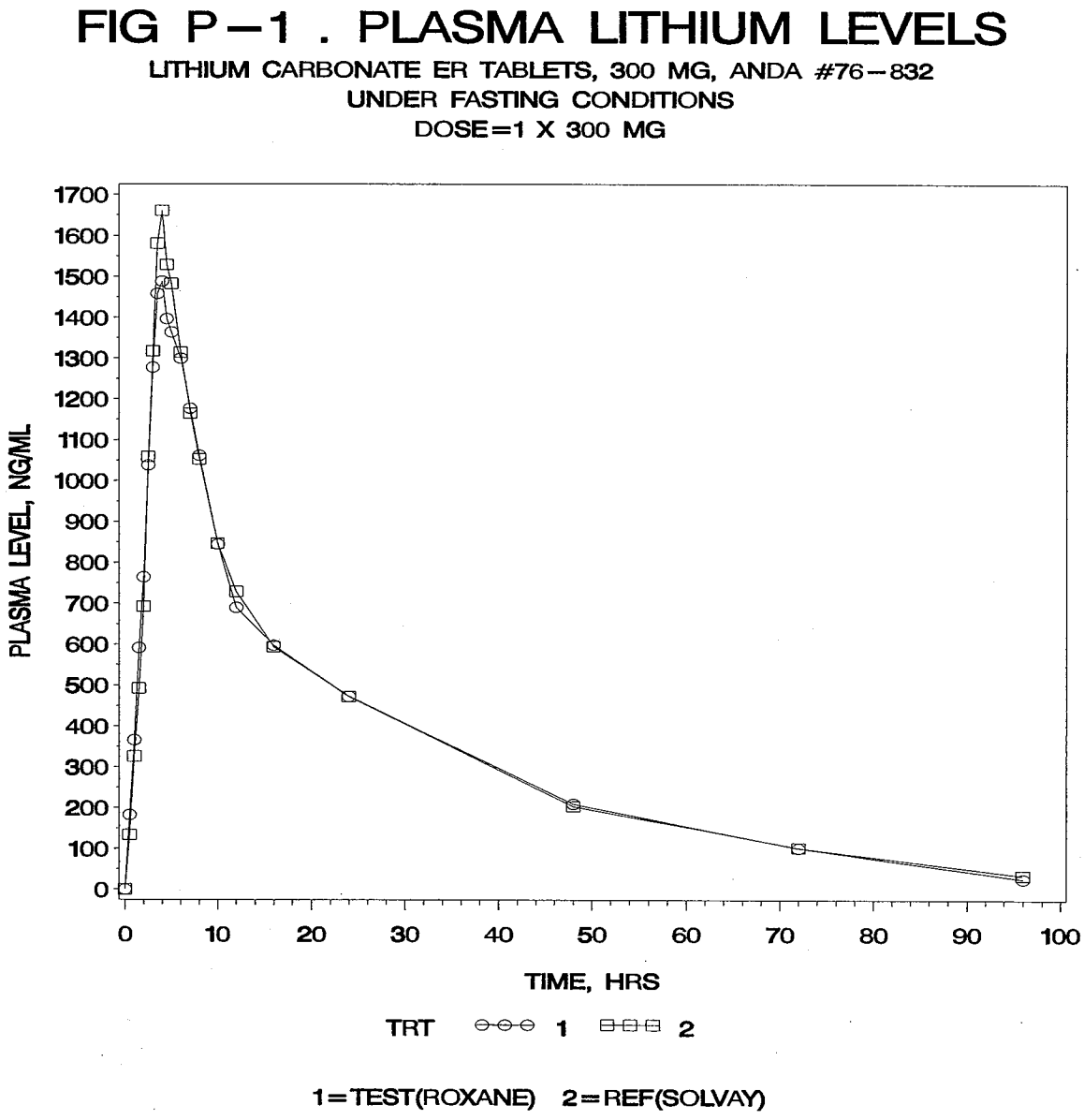
Comments on Pharmacokinetic and Statistical Analysis: Acceptable.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The 90% confidence intervals for AUCt, AUCi, and Cmax were within the acceptable range limits of 80-125%. The BE study is acceptable.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.5	182.77	60.27	134.04	67.52	1.36
1	366.21	29.60	325.84	39.82	1.12
1.5	591.43	42.12	492.38	30.92	1.20
2	764.57	45.08	692.25	36.01	1.10
2.5	1038.39	55.28	1059.24	36.41	0.98
3	1277.99	44.76	1317.66	35.31	0.97
3.5	1458.48	37.78	1580.90	29.56	0.92
4	1488.90	32.61	1661.01	28.12	0.90
4.5	1396.74	24.87	1528.84	25.07	0.91
5	1364.07	21.48	1482.93	23.43	0.92
6	1299.80	17.52	1314.80	20.96	0.99
7	1177.46	20.16	1165.20	18.91	1.01
8	1062.19	18.19	1052.91	17.30	1.01
10	845.01	18.65	846.78	21.17	1.00
12	690.19	26.27	728.87	20.85	0.95
16	597.50	20.72	593.34	21.16	1.01
24	472.72	19.16	472.04	21.57	1.00
48	209.81	28.63	203.80	36.26	1.03
72	101.42	38.20	102.67	48.36	0.99
96	26.50	151.78	34.71	121.38	0.76

Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information (p 857, vol. C1.3)	
Study Number	LITH-12
Study Title	Randomized, 2-way crossover, bioequivalence study under fed conditions.
Clinical Site	Novum Pharmaceutical Research Services 5900 Penn Avenue Pittsburgh, PA 15206
Principal Investigator	Shirley Ann Kennedy, M.D.
Study/Dosing Dates	Period 1: 05/07/03; Period 2: 05/21/03 (p 971, vol. C1.3)
Analytical Site	(b) (4)
Analytical Director	(b) (6) (p 1053, vol. C1.3)
Analysis Dates	06/19/03 to 07/11/03 (p1031, vol. C1.3)
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	62 days

Treatment ID	**Test Product**	**Reference Product**
Test or Reference	T	R
Product Name	Lithium Carbonate Extended Release Tablets, 300 mg.	Lithobid® Extended Release Tablets, 300 mg.
Manufacturer	Roxane	Solvay
Batch/Lot No.	029080	91996
Manufacture Date	12/04/02 (p 53)	N/A
Expiration Date	N/A	05/27/03 (p 53)
Strength	300 mg	300 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	101.6% (p 112)	98.3% (p110)
Content Uniformity	101.5% (%CV=1.00)	97.9% (%CV=1.2)
Formulation	See Appendix Section B	
Dose Administered	1 X 300 mg	1 X 300 mg
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	None
Washout Period	14 days
Randomization Scheme	Yes (p 271, vol. C1.1)
Blood Sampling Times	Predose, 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 48, 72, and 96 hours
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -20°C
IRB Approval	Yes (approved date: 04/29/03)
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	10 hours predose until 30 minutes before dosing
Length of Confinement	10 hours predose until 24 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.
Standard FDA Meal Used?	Yes (pp 989, 907, vol. C1.13)
If no, then meal is listed in table below	N/A

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	N/A (FDA standard meal)	
Carbohydrate		
Protein		
Total		

Comments on Study Design: The study design is acceptable.

b) Clinical Results

Table 12 Demographics of Study Subjects (N=29?)

(information on enrolled subjects, reported on pages 871 & 970, vol. C1.3)

Age		Weight (lb)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	23
Mean	26	Mean	151	18-40	100	Male	63	Afr. Amer.	54
SD	6.1	SD	21.7	41-64	0	Female	37	Hispanic	20
Range	18-38	Range	109-199	65-75	0			Asian	3
				>75	0			Others	0

Table 13 Dropout Information

(information on p 893, vol. C1.3)

Subject No	Reason	Period	Replaced?
23	Personal reasons	Period-2, check-in	No

Table 14 Study Adverse Events

(information on p 974, vol. C1.3)

Adverse Event Description	# in Test Group	# in Ref. Group
Itch, right shoulder or calf	1	2
Decreased temperature	1	0
Abnormal urine analysis: elevated WBC estrase, WBC/HPF, epithelial cells, bacteria, occult blood, trace ketones, or bilirubin.	4	3
Headache	1	3
Red spots, right or left calf	0	2
Tangle sensation, right or left foot	0	2
Elevated SGPT	0	1
Tired	0	1
Hot flashes, intermittent	0	1
Elevated total bilirubin	0	1
Total:	7	16

Table 15 Protocol Deviations

(information on p 872, vol. C1.3)

Type	Subject #s (Test)	Subject #s (Ref.)
There were no significant deviations reported.		

Comments on Adverse Events/Protocol Deviations: The test and reference products adverse events were comparable to each other. No serious adverse events were reported. The PK analysis was based on actual sampling times. The reported adverse events and protocol deviations are not likely to compromise the integrity of study.

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

(Info on pp 1036, 1038, vol. C1.3)	Parent (Lithium)
QC Conc. (ng /mL)	125.1, 1001.0, and 2562.6
Inter day Precision (%CV)	3.3 to 4.6
Inter day Accuracy (%)	99.4 to 100.6
Cal. Standards Conc. (ng /mL)	52.1 to 3003.0
Inter day Precision (%CV)	1.9 to 7.2
Inter day Accuracy (%)	98.8 to 102.9
Linearity Range (range of R^2 values)	0.9965 to 0.9998

Comments on Study Assay Quality Control: Acceptable

Any interfering peaks in chromatograms?	N/A
Were 20% of chromatograms included?	N/A
Were chromatograms serially or randomly selected?	N/A

Comments on Chromatograms: N/A

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
AL-G-1520-11	04/19/02	Reporting of Data Generated from the Analysis of Biological Matrices

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	N/A (No repeat samples were reported)
Does the reviewer agree with the outcome of the repeat assays?	N/A
If no, reason for disagreement	-

Summary/Conclusions, Study Assays: The study assay is acceptable.

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22 and Figure 2

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	33543.84	14.32	34080.68	14.21	0.98
AUCT	30998.30	13.78	31162.10	14.41	0.99
CMAX	2204.19	22.42	2185.02	18.62	1.01
KE	0.03	20.22	0.03	16.84	1.00
THALF	23.00	22.46	22.71	19.74	1.01
TMAX	3.86	34.93	4.19	42.84	0.92

MEAN1=Test, MEAN2=Reference

UNIT: AUC=ng hr/mL, CMAX=ng/mL, KE=hrs^{-1}, THALF=hrs, TMAX=hrs

Table 20 Least Squares Geometric Means and 90% Confidence Intervals (N=29)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	33257.11	33798.38	0.98	96.26	100.59
LAUCT	30744.29	30871.05	1.00	97.43	101.79
LCMAX	2153.35	2145.72	1.00	94.27	106.83

Table 21 Additional Study Information

Root mean square error, AUC_{0-t}	0.048887
Root mean square error, AUC_{∞}	0.049189
Root mean square error, C_{max}	0.139764
K_{el} and AUC_{∞} determined for how many subjects?	All 29 subjects
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	-
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

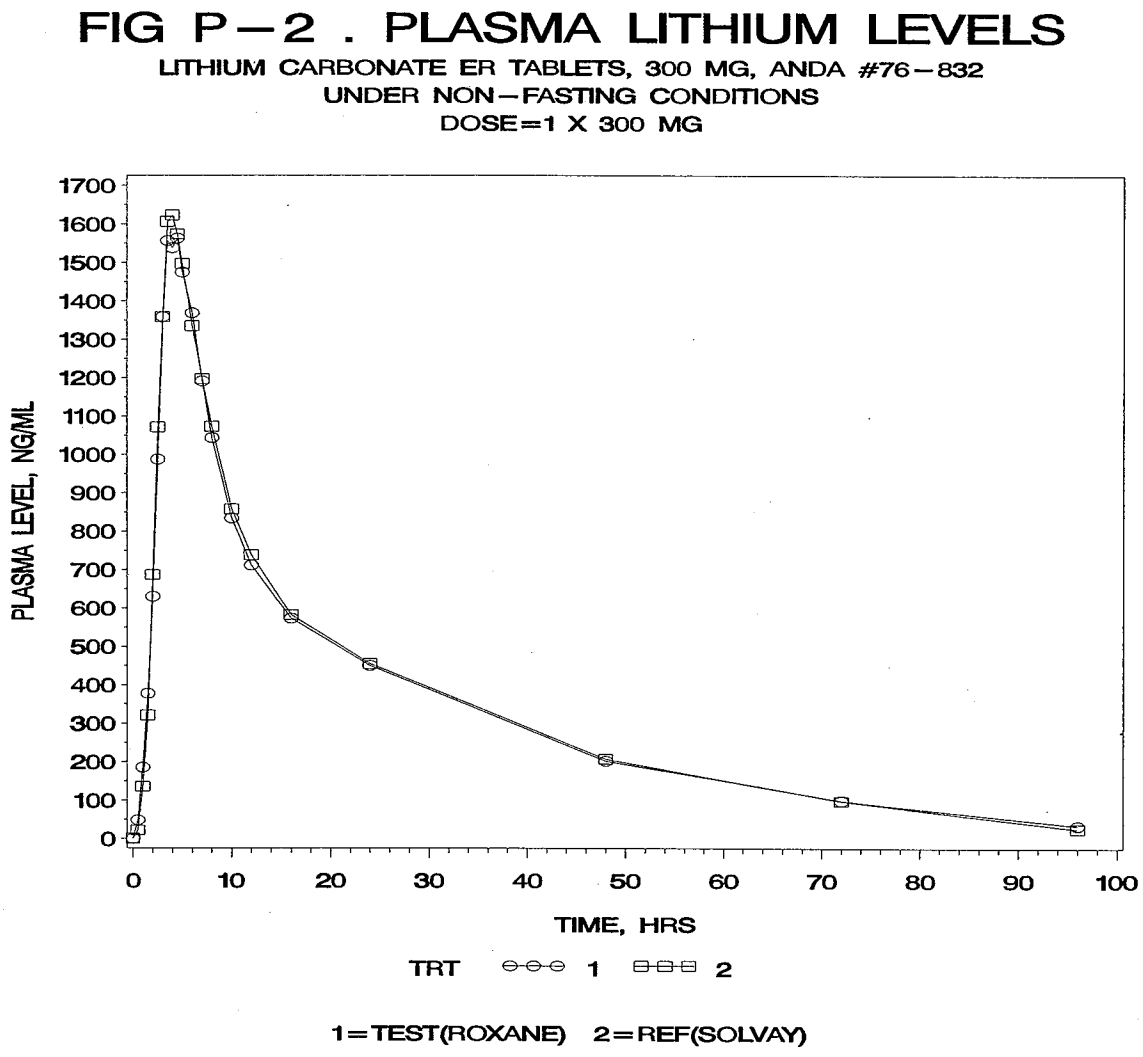
Comments on Pharmacokinetic and Statistical Analysis: Acceptable

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The 90% confidence intervals for AUCt, AUCi, and Cmax were within the acceptable range limits of 80-125%. The BE study is acceptable.

Table 22 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.5	48.31	216.79	21.89	319.30	2.21
1	185.50	186.76	135.76	131.86	1.37
1.5	377.71	130.79	320.89	102.15	1.18
2	630.16	103.13	686.28	83.88	0.92
2.5	987.53	85.98	1071.32	73.62	0.92
3	1358.83	61.58	1358.40	59.26	1.00
3.5	1556.58	52.00	1606.21	47.38	0.97
4	1538.20	41.59	1622.66	42.21	0.95
4.5	1563.12	29.14	1574.04	33.38	0.99
5	1474.92	24.00	1497.13	30.74	0.99
6	1368.91	28.43	1334.76	29.16	1.03
7	1191.37	25.57	1196.97	32.44	1.00
8	1043.63	24.15	1072.87	27.64	0.97
10	834.17	19.47	857.72	24.10	0.97
12	711.71	18.60	738.45	21.85	0.96
16	573.23	16.18	582.31	16.95	0.98
24	450.22	13.52	454.78	13.66	0.99
48	202.37	21.56	207.07	23.55	0.98
72	99.54	39.51	98.14	44.53	1.01
96	34.80	112.24	26.16	155.88	1.33

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



3. Single-dose Fasted Pilot Bioequivalence Study (Failed Study)

- This is a failed pilot BE study. The firm provided this information as requested by the DBE.
- In this pilot study, the firm tested two different formulations (A and B) vs. the RLD(C).
- The firm provided only a hard copy of the statistical analysis. A diskette with the raw data was not included in the submission.
- The information on the failed study is reported on pages 168-173, C1.1.

Study No.	Protocol Study LITH-10
Study Design	Randomized, 3-way crossover, bioequivalence study under fasting conditions.
No. of subjects enrolled	12
No. of subjects completing	12
No. of subjects analyzed	12
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Not given
Test product	Roxane's Lithium Carbonate Extended Release Tablets, 300 mg.
Reference product	Solvay's Lithobid® Extended Release Tablets, 300 mg.
Strength tested	300 mg tablet
Dose	1 X 300 mg

Note: The following PK values were obtained from the submission (see page 172, volume C1.1). The firm submitted this information for the failed BE study for information only as requested by the DBE.

Parameter	**Units**	**Test**		**Reference**
		Formulation A	**Formulation B**	**C**
		Mean (SD)	**Mean (SD)**	**Mean (SD)**
AUC0-t		(b) (4)		
AUC∞				
Cmax				
Tmax				
T1/2				

A: Roxane's Formulation A

B: Roxane's Formulation B
C: RLD's Lithobid

Summary of Statistical Analysis (%CI)		
Parameter	**Point Estimate**	**90% Confidence Interval**
	[redacted]	(b) (4)
AUC0-t		
AUC∞		
Cmax		

Comment on the Pilot BE Study (#LITH-10):

The firm indicated in the May 25, 2004, Amendment, that Roxane's Formulation A was selected for the pivotal fasted (Protocol #LITH-11) and fed (Protocol #LITH-12) studies.

B. Formulation Data

(information on pages 60, vol. C1.1 and p. 1559)

Ingredients	mg/tablet
Lithium carbonate USP	300 mg
Povidone USP	(b) (4)
Sodium chloride USP	
Sodium Lauryl Sulfate, NF	
Sorbitol,NF (b) (4)	
Calcium Stearate, NF	
(b) (4)	
Theoretical Uncoated Tablet Weight	
Opadry II, (b) (4) (Flesh)	
(b) (4)	
Total Theoretical Weight	430.0 mg

(b) (4)

Composition of Opadry II Flesh (b) (4)

Ingredients	%w/w
Titanium Dioxide	(b) (4)
Polydextrose	
(b) (4) Hypromellose (b) (4)	
(b) (4)	
Triacetin	
(b) (4)	
(b) (4) PEG (b) (4)	
Iron Oxide Yellow	
Iron Oxide Red	

Comment:

- The inactive ingredients are within the acceptable range according to the IIG.

C. Dissolution Data

(information on pages 111, 113, vol. C1.1)

Sampling Time (hr)	Medium: **Water** Volume: 900 mL USP Apparatus: I Rotation: 100 rpm					
	Test Product, Roxane's Lithium Carbonate ER Tablets Strength: 300 mg Lot No. 029080			Reference Product, Solvay's Lithobid® ER Tablets Strength: 300 mg Lot No. 91996		
	Mean	%CV	Range	Mean	%CV	Range
0.5	21	3.9	(b) (4)	15	6.2	(b) (4)
1	46	3.9		36	6.3	
1.5	67	3.8		60	9.3	
2	86	4.4		95	4.1	
2.5	96	1.7		102	1.3	

(information on pages 115, 118, vol. C1.1)

Sampling Time (hr)	Medium: **pH 1.2 HCl** Volume: 900 mL USP Apparatus: I Rotation: 100 rpm					
	Test Product, Roxane's Lithium Carbonate ER Tablets Strength: 300 mg Lot No. 029080			Reference Product, Solvay's Lithobid® ER Tablets Strength: 300 mg Lot No. 91996		
	Mean	%CV	Range	Mean	%CV	Range
0.5	29	12.3	(b) (4)	18	16.7	(b) (4)
1	61	2.6		47	7.8	
1.5	86	1.6		74	8.1	
2	100	1.7		100	1.7	
2.5	102	2.1		101	1.5	

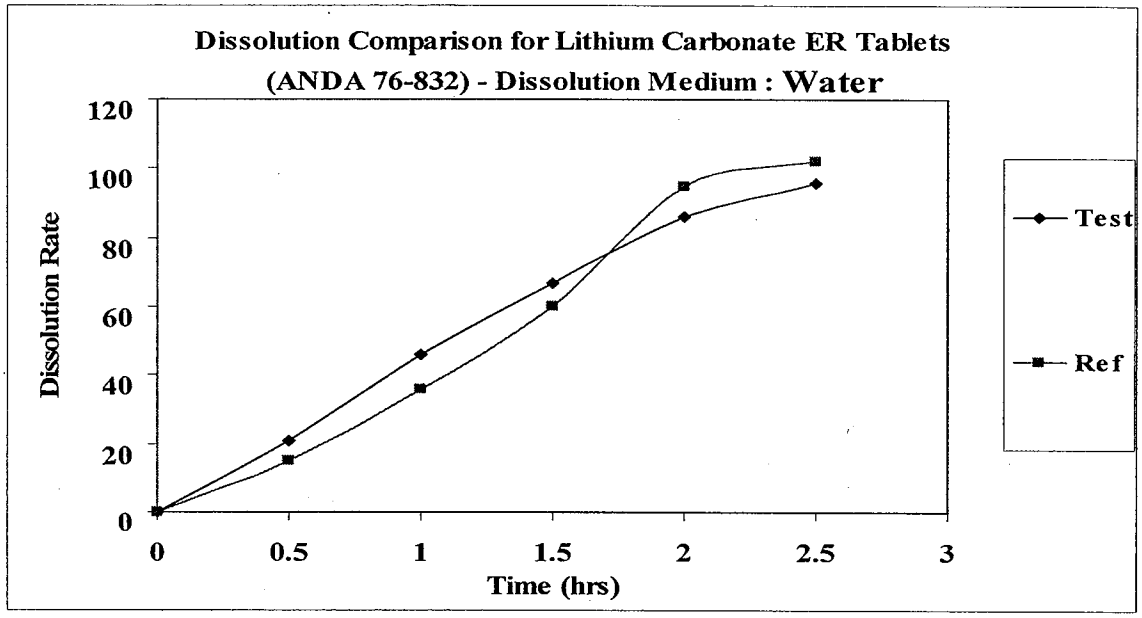
(information on pages 116, 119, vol. C1.1)

Sampling Time (hr)	Medium: **pH 4.5 Acetate Buffer** Volume: 900 mL USP Apparatus: I Rotation: 100 rpm					
	Test Product, Roxane's Lithium Carbonate ER Tablets Strength: 300 mg Lot No. 029080			Reference Product, Solvay's Lithobid® ER Tablets Strength: 300 mg Lot No. 91996		
	Mean	%CV	Range	Mean	%CV	Range
0.5	14	4.8	(b) (4)	24	5.6	(b) (4)
1	33	5.0		51	5.9	
1.5	54	9.2		74	6.3	
2	87	11.2		94	4.3	
2.5	103	1.5		101	1.4	

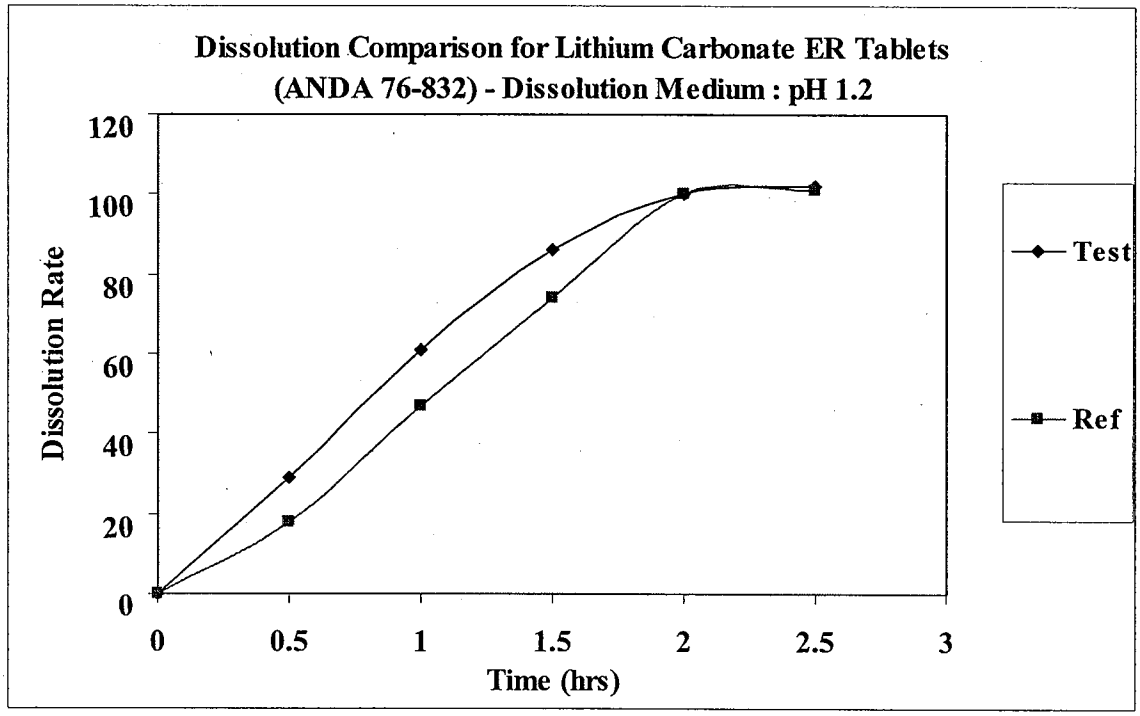
(information on pages 117, 120, vol. C1.1)

Sampling Time (hr)	Medium: **pH 6.8 Tris Buffer** Volume: 900 mL USP Apparatus: I Rotation: 100 rpm					
	Test Product, Roxane's Lithium Carbonate ER Tablets Strength: 300 mg Lot No. 029080			Reference Product, Solvay's Lithobid® ER Tablets Strength: 300 mg Lot No. 91996		
	Mean	%CV	Range	Mean	%CV	Range
0.5	22	5.3	(b) (4)	13	7.6	(b) (4)
1	46	4.2		31	8.1	
1.5	69	3.7		53	10.8	
2	87	4.1		82	8.8	
2.5	97	1.7		99	1.5	

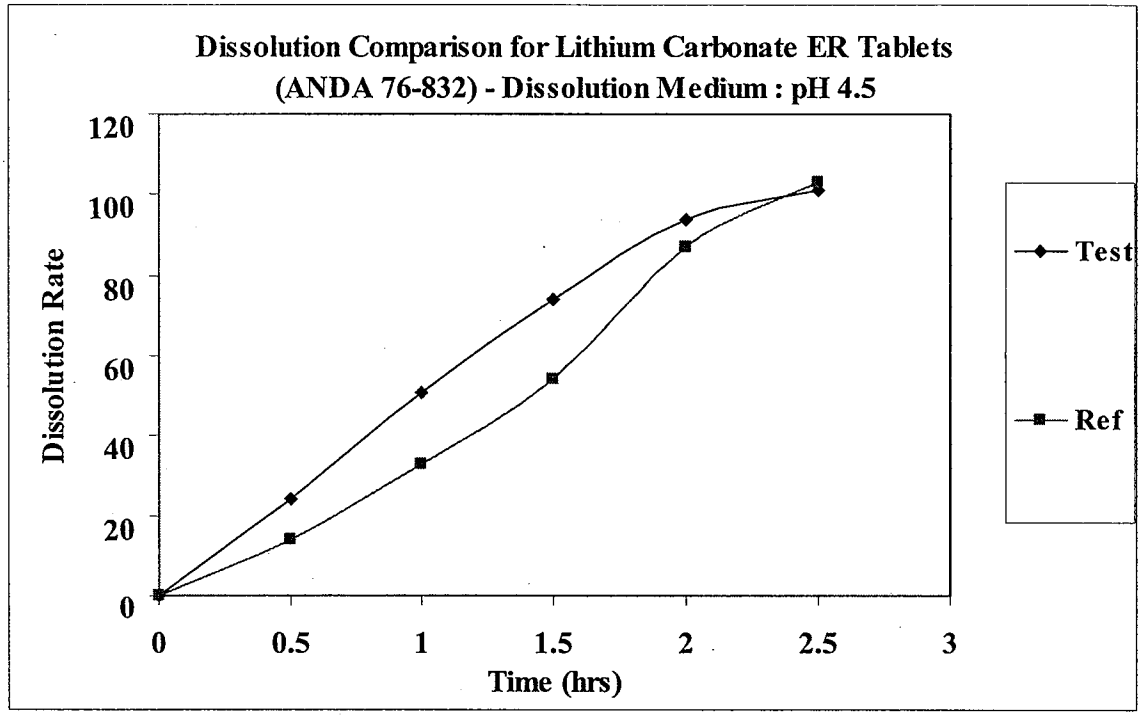
Figure 3 Dissolution Profiles



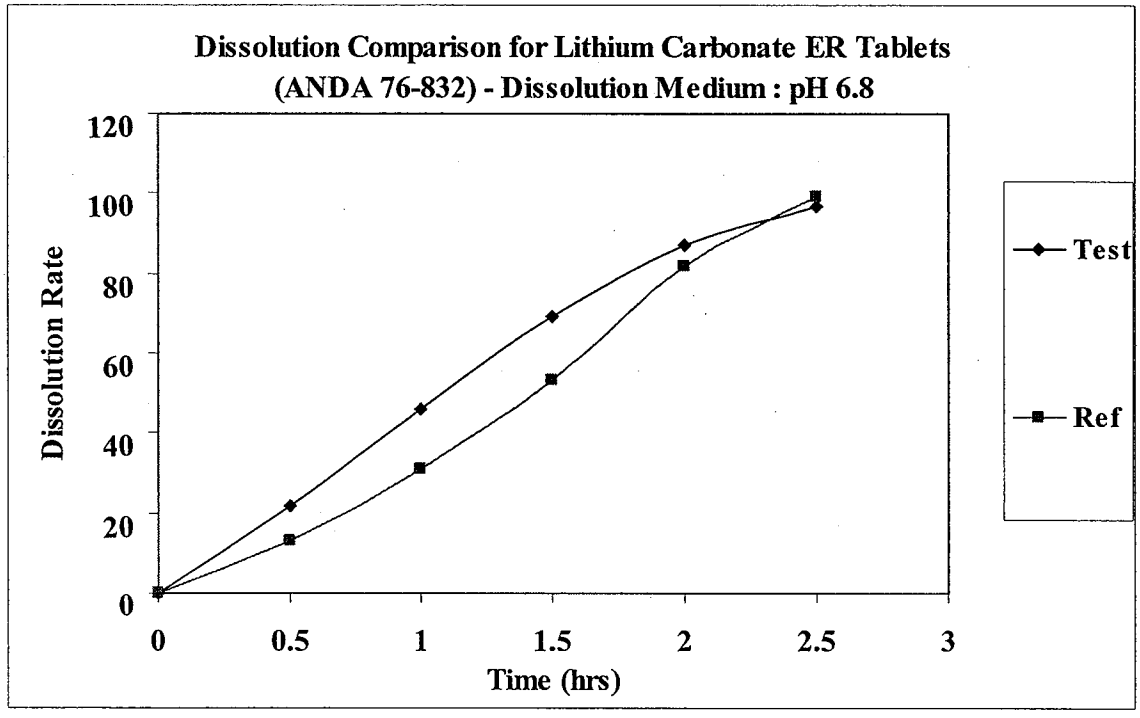
F2= 55.30



F2=50.74



F2=43.84



F2=48.09

D. Consult Reviews:

None

E. SAS Output

Study Type	Plasma Data	PK Data	SAS Code	SAS Output
Fasting Study	76832_Fast_300mg_ Plasma.txt	76832_Fast_300mg_ PK.txt	76832_Fast_300mg_ sas.txt	76832_Fast_300mg_ output.txt
Fed Study	76832_Fed_300mg_ Plasma.txt	76832_Fed_300mg_ PK.txt	76832_Fed_300mg_ sas.txt	76832_Fed_300mg_ output.txt

F. Additional Attachments

-----Original Message-----
From: Tran, Nhan L
Sent: Thursday, May 20, 2004 2:39 PM
To: Wahba, Zakaria Z
Cc: Huang, Yih Chain
Subject: RE: Review 76832 (Roxane's Lithium Carbonate ER Tablets, 300 mg)

Zak:

For your Lithium ER tablets, I do not think the spec in the PF, Test #2 can be used for your product, simply because your product appears to release faster than the product in Test #2. And I think YC is right that we cannot just accept the firm specs. The specs suggested by the firm are too wide to be accepted. Based on the data submitted, and based on the general guidance for setting specifications, I suggest the following:
30 min: 10-30%
90 min: 55-75%
150 min: NLT 85%.

Thanks,

-----Original Message-----
From: Wahba, Zakaria Z
Sent: Tuesday, May 18, 2004 6:01 PM
To: Tran, Nhan L
Cc: Wahba, Zakaria Z; Huang, Yih Chain
Subject: FW: Review 76832 (Roxane's Lithium Carbonate ER Tablets, 300 mg)

Nhan,

Your comments on the dissolution testing are greatly appreciated.
Thanks
Zak

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:76-832 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lithium Carbonate Extended Release Tablets USP, 300 mg.

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

Your proposed dissolution specifications are not acceptable. Based on the data submitted, the Division of Bioequivalence recommends the following:

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 interim specifications:

Time (minutes)	Amount dissolved
30	between 10% - 30%
90	between 55% - 75%
150	NLT 85%

Sincerely yours,

for Barbara M Saint

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

CC: ANDA 76-832
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba 2W 5/27/04
HFD-658/ YC Huang YH 5/27/2004
for HFD-650/ D. Conner BD 5/27/04

v:\\firmsnz\Roxane\LTRS&REV\76832n0803.doc

BIOEQUIVALENCE – Incomplete Submission date: 08/26/03

1. FASTING STUDY (STF),(Study #LITH-11) oic — Strength: 300 mg, Outcome: IC
   Clinical Study Site: Novum Pharmaceuticals
   Analytical Site: (b) (4)

2. FOOD STUDY (STP),(Study #LITH-12) oic — Strength: 300 mg, Outcome: IC
   Clinical Study Site: Novum Pharmaceuticals
   Analytical Site: (b) (4)

3. FASTING_ PILOT STUDY (STF), (Study #LITH-10) — Strength: 300 mg, Outcome: NC
   Clinical Study Site: Novum Pharmaceuticals oic
   Analytical Site: (b) (4)

4. Study Amendment (STA), ~~04/08/04~~ 5/7/04 oic wc — Strength: 300 mg, Outcome: ~~IC~~ wc

5. Study Amendment (STA), 05/26/04 wc — Strength: 300 mg, Outcome: ~~IC~~ wc

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: **Incomplete**
WINBIO COMMENTS: **Incomplete**

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-832 SPONSOR : Roxane

DRUG AND DOSAGE FORM : Lithium Carbonate Extended-release Tablets USP

STRENGTH(S) : 300 mg

SEP 10 2004

TYPES OF STUDIES : Fasting, fasting pilot and fed

CLINICAL STUDY SITE(S) : Novum Pharmaceuticals

ANALYTICAL SITE(S) : (b) (4)

STUDY SUMMARY : For the fasting BE study, lithium results are (point estimate, 90% CI): $LAUC_t$ of 0.99, 94.69-103.15%; $LAUC_i$ of 0.99, 95.05-103.44% and LCmax of 0.95, 84.67-105.63%. For the non-fasting BE study, lithium results are (point estimate, 90% CI): $LAUC_t$ of 1.00, 97.43-101.79%; $LAUC_i$ of 0.98, 96.26-100.59% and LCmax of 1.00, 94.27-106.83%.

DISSOLUTION : Roxane accepts dissolution method and specifications.

DSI INSPECTION STATUS

Inspection needed:	Inspection status:	Inspection results:
First Generic ___ New facility _____ For cause ____ Other ____	Inspection requested: Inspection completed:	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes_____ No__X_____
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes ___X_____Amendment Date__11-Jun-2004_____

PROJECT MANAGER:
Beth Fritsch Beth Fritsch DATE: 9/3/04

PRIMARY REVIEWER : Zak Wahba Ph.D. BRANCH: III

INITIAL : Zak Wahba DATE : 9/3/04

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

INITIAL : YCH DATE : 9/3/2004

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

INITIAL : Dale P. Conner DATE : 9/3/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076832

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

9/17/03 Filing Ack for SOSI Y2 YA Concur 18 Sept 2003

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

August 26, 2003

Abbreviated New Drug Application
Lithium Carbonate Extended Release Tablets USP, 300 mg

Dear Madam/Sir:

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Lithium Carbonate Extended Release Tablets USP, 300 mg. This ANDA consists of eight volumes. This ANDA was formatted in accordance with the Guidance for Industry, Organization of an ANDA, February 1999.

The reference listed drug is LITHOBID® (Lithium Carbonate, USP) Slow-Release Tablets, 300 mg, manufactured by Solvay Pharmaceuticals, Inc. The active ingredient is Lithium Carbonate, USP.

Four complete copies of the draft labeling are contained in the Archival and CMC Review copies of this application. The drug product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. An *in vivo* bioequivalence study report is also included in this application. Furthermore, two copies of the ANDA Section XV, Analytical Methods, are enclosed separately along with this application.

Please note that electronic versions of the bioequivalency data (in SAS Transport format) and of the FDA Form 356H, the Table of Contents, and this cover letter (in pdf format) are provided as per the Guidance for Industry, Providing Regulatory Submissions in Electronic Format – ANDAs, June 2002. These electronic documents are provided on a CD in a separate Archival (blue) binder. These documents are the only portions of this ANDA provided in electronic format.

Samples and the methods validation package will be submitted upon the request and direction of the Office of Generic Drugs. Roxane Laboratories, Inc. commits to provide full cooperation to resolve any problems that may arise during the methods validation testing as part of the "Post-Approval" for the above listed drug product.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

DIV

ANDA 76-832

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

SEP 22 2003

Dear Madam:

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

NAME OF DRUG: Lithium Carbonate Extended-release Tablets USP, 300 mg

DATE OF APPLICATION: August 26, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 27, 2003

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:

Nicole Park
Project Manager
(301) 827-5849

Sincerely yours,

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

ANDA 76-832
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement:
HFD-615/M. Shimer, Chief, RSB_____date
HFD-615/S. Middleton, CSO_____date
Word File
V:\FIRMSNZ\ROXANE\LTRS&REV\76832.ACK
F/T StM 9/17/03
ANDA Acknowledgment Letter!

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

N/AF

January 22, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Nicole Park

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP, 300 mg

LABELING AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Ms. Park:

We wish to amend ANDA 76-832. This is in response to the labeling revisions requested by Mr. Kuong Lee (Labeling Review Branch) in the facsimile deficiency letter dated January 9, 2004. A copy of the letter is attached. Please note that all the revisions requested, except for the inclusion of the USP drug release test have been incorporated in the attached revised container and package inert. The reason for this is that we have not received the comments from the Division of Bioequivalence whether our proposed dissolution method, submitted in the ANDA, is acceptable.

Roxane's formulation, which has been shown to be bioequivalent to the reference listed drug, LITHOBID® (Lithium Carbonate, USP) Slow-Release Tablets, 300 mg cannot be adequately characterized using the USP Test I. Because of these findings, Roxane proposed a drug release method that we believe fully characterizes our product and thus can be used to adequately control batch to batch variability. This drug release method uses the same conditions as the USP Drug Release Test 2 except for the earlier sampling time points.

Attached are twelve copies of the final printed labeling (container label and package inert). Also attached is one (1) copy of the side-by-side comparison of the revised labeling with the previous labeling submitted in the original ANDA.

We have also submitted a copy of this amendment to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097

JAN 2 3 2004

Please note that electronic versions of this cover letter and of the Form FDA 356h (in pdf format) are provided as per the Guidance for Industry, Providing Regulatory Submissions in Electronic Format – ANDAs, June 2002. These electronic documents are provided on a CD in a separate Archival (blue) binder. These letters and the Form FDA 356h are the only portion of this Amendment provided in electronic format.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
~~Associate Director~~, DRA-Multisource Products

MINOR AMENDMENT

ANDA 76-832

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)

FEB 17 2004

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Elizabeth A. Ernst FAX: 614-276-2470

FROM: Nicole Lee PROJECT MANAGER: (301) 827-5849

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lithium Carbonate Extended-release Tablets USP, 300 mg.

Reference is also made to your amendment(s) dated: January 22, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of 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. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

M

FEB 17 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-832 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lithium Carbonate Extended-release Tablets, 300mg

The deficiencies presented below represent MINOR deficiencies.

1. (b) (4)
2.
3.
4.
5.
6.
7.
8.

9. (b) (4)

10.

11.

12.

13. Your stability report forms should be revised to specify the product manufacturing date, product expiration and packaging dates.

Sincerely yours,

Brenda D. Gonneau /for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Boehringer Ingelheim
Roxane Laboratories

2.1

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

FPL

Attention: Koung Lee

February 18, 2004

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP 300 mg
Labeling Amendment

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs, DRA-Multisource Products for Roxane Laboratories, Inc.

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Wu:

We wish to amend ANDA 76-832. Enclosed please find the final printed bottle labels and corresponding side-by-sides which annotate our revision.

This amendment contains 12 final printed copies of the labeling for your review.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by telefax at (614) 276-2470.

Respectfully,

Elizabeth A. Ernst, R.N., B.S.N.
Associate Director, Regulatory Affairs
DRA-Multisource Products for Roxane Laboratories, Inc.

RECEIVED
FEB 19 2004
OGD/CDER

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT

N/am

Roxane Laboratories, Inc.

March 16, 2004

Attention: Nicole Lee

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP, 300 mg

MINOR AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Ms. Lee:

We wish to amend ANDA 76-832. Enclosed please find a point-by point response to the questions in the facsimile deficiency letter dated February 17, 2004 (copy attached).

We have also submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs, at (614) 241-4133.

Respectfully,

Virginia J. Fojas for

Elizabeth Ernst
Associate Director, DRA-Multisource

3.1

ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

May 7, 2004

Attention: Steve Mazzella

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP, 300 mg

BIOEQUIVALENCY AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com
P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Mazzella:

We wish to amend ANDA 76-832, Lithium Carbonate Extended Release Tablets, 300 mg. This is in response to your telephone request on May 5, 2004 requesting copies of the SOPs used by the CRO who performed the bioanalytical testing on this drug product, which describes how bioanalytical analysis is conducted, as well as those that pertain to how the company handles the analytical repeats and rejects exceptions. The requested SOP was obtained from (b) (4) a CRO located in (b) (4) who performed the bioanalytical testing. A copy of (b) (4) SOP No. AL-G-1520-11, Reporting of Data Generated from the Analysis of Biological Matrices is attached. This SOP applies to all data generated by Bioanalysis Mass Spectrometry, (b) (4) (b) (4) including the (b) (4) which was used for the determination of lithium in human serum.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

RECEIVED
MAY 10 2004
OGD/CDER

3.1

ORIGINAL

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AB

May 26, 2004

Attention: **Steve Mazzella**

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP, 300 mg

BIOEQUIVALENCY AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Mazzella:

We wish to amend ANDA 76-832, Lithium Carbonate Extended Release Tablets, 300 mg. This is in response to your telephone request on May 25, 2004 requesting clarification whether the formulation used in our pivotal study was Formulation A or B.

Roxane Laboratories conducted a pilot study under protocol number LITH-10 to evaluate the potential bioequivalence of 2 different formulations of Roxane's lithium carbonate extended release tablets, 300 mg. The 2 formulations were (ANDA page 171):

Formulation A: Roxane Lot Number 029080
Formulation B: Roxane Lot Number 029111

The results of this pilot study indicated that Roxane's Formulation A (Lot number 029080) was bioequivalent to the reference product. This formulation (Lot number 029080) was therefore selected for the pivotal fasted (protocol LITH-11, ANDA page 177) and fed (protocol LITH-12, ANDA page 859) studies.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs at (614) 241-4133.

Respectfully,

Virginia Z. Fojas for

Elizabeth Ernst
Associate Director, DRA-Multisource

RECEIVED
MAY 27 2004
OGD / CDER

3.1

BIOEQUIVALENCY AMENDMENT

ANDA 76-832

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)

JUN 04 2004

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Elizabeth Ernst FAX: 614-276-2470

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

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on August 26, 2003, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lithium Carbonate Extended Release Tablets USP, 300 mg.

Reference is also made to your amendment(s) dated: May 7, 2004 and May 26, 2004.

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 submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

JUN 0 4 2004

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:76-832 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lithium Carbonate Extended Release Tablets USP, 300 mg.

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

Your proposed dissolution specifications are not acceptable. Based on the data submitted, the Division of Bioequivalence recommends the following:

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 interim specifications:

Time (minutes)	Amount dissolved
30	between 10% - 30%
90	between 55% - 75%
150	NLT 85%

Sincerely yours,

Barbara M Davit

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

Boehringer Ingelheim
Roxane Laboratories

BIOAVAILABILITY

ORIG AMENDMENT
N/AB

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

June 11, 2004

Attention: Nicole Lee

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP, 300 mg

BIOEQUIVALENCY AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

Dear Ms. Lee:

We wish to amend ANDA 76-832. Enclosed is a courtesy copy of the Bioequivalency Amendment in response to the facsimile deficiency letter dated June 4, 2004, received from Steve Mazzella, Division of Bioequivalence (copy attached, see **Attachment A**). As requested, the drug release limits in the product specification have been revised for both release and stability as follows:

Time (minutes)	% LA Amount Released (for Release and Stability)
30	**From** (b) (4) **to** 10 - 30%
90	**From** **to** 55 - 75%
150	**From** **to** NLT 85%

A copy of the revised Roxane Product Specification for Lithium Carbonate Extended Release Tablets USP, 300 mg, Specification No. 1610-03 is attached (see **Attachment B**).

In addition, the revised drug release limits have also been incorporated in the Post Approval Stability Protocol and Stability Commitment (Document No. ST-COM-1459-03-02) and the Stability Experience Report (Document No. ROX-SP-1459-AC-AD-03-02) for ANDA Batch 029080. The stability report contains initial, 3months accelerated data (40°C/75%RH) and 12 months room temperature data (25°C/60%RH). The tabulated stability data are presented on pages 11 to 14 of this report. Copies of these documents are attached (see **Attachments C and D**).

Because of the limited amount of drug release data (3 months at 40°C/75%RH and up to 12 months at 25°C/60%RH on the ANDA batch), Roxane is proposing that the revised limits be re-evaluated after 10 commercial batches have been tested, to determine whether these revised limits have been consistently and satisfactorily met for release and stability. If needed, a Prior Approval Supplement will be filed to the ANDA with the proposed revised specifications at that time.

RECEIVED
JUN 14 2004
OGD/DUEP

We have submitted the Bioequivalency Amendment to Mr. Steve Mazzella, Division of Bioequivalence, and we have submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs, at (614) 241-4133.

Respectfully,

Virginia Z. Fojas for

Elizabeth Ernst
Associate Director, DRA-Multisource

MINOR AMENDMENT

ANDA 76-832

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)

JUL 2 2 2004

APPLICANT: Roxane Laboratories, Inc. TEL: 614-272-4785

ATTN: Elizabeth A. Ernst FAX: 614-276-2470

FROM: Nicole Lee PROJECT MANAGER: (301) 827-5791

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 26, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Lithium carbonate extended-release tablets, 300 mg.

Reference is also made to your amendment dated February 18 and March 16, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of 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. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

M for N Lee

JUL 2 2 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-832 APPLICANT: Roxane Laboratories, Inc.

DRUG PRODUCT: Lithium Carbonate Extended-release Tablets, 300 mg

The deficiencies presented below represent MINOR deficiencies.

(b) (4)

1.

2.

3.

4.

5.

6. [redacted] (b) (4)

Sincerely yours,

Brenda L. Gommerstadt for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Roxane Laboratories, Inc.

August 20, 2004

ORIG AMENDMENT
N/AM

Attention: Nicole Lee

ANDA 76-832
Lithium Carbonate Extended Release Tablets USP, 300 mg

MINOR AMENDMENT

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Ms. Lee:

We wish to amend ANDA 76-832. Enclosed please find a point-by point response to the questions in the facsimile deficiency letter dated July 22, 2004 (copy attached).

Please note that electronic versions of the FDA Form 356H and this cover letter (in pdf format) are provided as per the Guidance for Industry, Providing Regulatory Submissions in Electronic Format – ANDAs, June 2002.

We have also submitted a copy of this amendment to Ms. Kathleen D. Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Virginia Fojas, Manager, Regulatory Affairs, at (614) 241-4133.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource

Verified 10/28/04 Rawlest

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : ANDA 76832/000
Org Code : 600
Priority :

Sponsor: ROXANE
1809 WILSON RD
COLUMBUS, OH 43228

Stamp Date : 27-AUG-2003
PDUFA Date :
Action Goal :
District Goal: 27-JUL-2004

Brand Name :
Estab. Name: LITHIUM CARBONATE
Generic Name:
Dosage Form: (EXTENDED-RELEASE TABLET)
Strength : 300 MG

FDA Contacts: N. LEE Project Manager (HFN-617) 301-827-5791
B. ARNWINE Team Leader (HFD-645) 301-827-5849

Overall Recommendation: ACCEPTABLE on 17-MAY-2004by J. D AMBROGIO(HFD-322) 301-827-9049

ACCEPTABLE on 30-APR-2004by S. FERGUSON(HFD-322) 301-827-9009

Establishment : CFN : (b) (4) FEI : (b) (4)

(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-MAY-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1510690 FEI : 1510690

ROXANE LABORATORIES INC

1809 WILSON RD

COLUMBUS, OH 43228

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : TTR OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-OCT-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1527529 FEI : 1527529

ROXANE LABORATORIES INC

330 OAK ST

COLUMBUS, OH 43216

DMF No: AADA:

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-SEP-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-832 Applicant Roxane
Drug Li Carbonate ER Tablets USP Strength(s) 300mg

APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 6 Oct 2004 Initials MMS	Date 10/25/04 Initials RWilfar

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = NDA# 18-027
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked N/A
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ N/A
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐
Type of Letter:
Comments: No patents/exclusivities ∴ eligible for Full Approval

2. Project Manager, Y Kong Team 7 Review Support Branch	Date 10/5/04 Initials	Date Initials

Original Rec'd date 8-26-03 ✓
Date Acceptable for Filing 8-27-03
Patent Certification (type)
Date Patent/Exclus.expires
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☐ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 5-17-04
Date of Office Bio Review 9/3/04 (3.1 vol)
Date of Labeling Approv. Sum 3/3/04 (2.1 vol)
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐

Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ OGD Regulatory Counsel, Post-MMA Language Included ☐ Comments: N/A		Date Initials

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III Comments: CMC OK		Date 10/26/04 Initials

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

N/A.

6. Vacant RLD=Lithobid Slow Extended-release Tablets 300mg NDA 18-027 Date_____
Deputy Dir., DLPS Initials_____
Slayback Pharmaceuticals

7. Peter Rickman Date 10/28/04
Director, DLPS Initials Richard Lee for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 5/17/04 (Verified 10/28/04). No O.A.I. alerts noted. FPL found acceptable for approval 3/3/04. Bioequivalence studies (fasting and non-fasting) found acceptable 5/29/04. Dissolution specifications (interim) also found acceptable. Bio test sites have acceptable OSI inspection histories. Office-Level bio endorsed 9/3/04. CMC found acceptable 10/25/04. Methods validation was not requested - both the API and drug product are compendial.

8. Robert L. West Date 10/28/2004
Deputy Director, OGD Initials Robert West for
Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☐
Comments: There are no unexpired patents or exclusivity listed in the current Orange Book for this drug product.
This ANDA is recommended for approval.

9. Gary Buehler Date 10/28/04
Director, OGD Initials Richard Lee for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Rem. Issue ☐

10. Project Manager, Team Y. Kong Date 10/28/04
Review Support Branch Initials YK
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
12:08 Time notified of approval by phone 12:11 Time approval letter faxed
FDA Notification:
10/28/04 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
10/28/04 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc