

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

76170

CORRESPONDENCE

AUG 22 2001

Barr Laboratories, Inc.
Attention: Christine Mundkur
2 Quaker Road
Pomona, NY 10970
|||||

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.

Reference is also made to our "Refuse to Receive" letter dated July 3, 2001 and your amendment dated July 26, 2001.

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

DATE OF APPLICATION: May 11, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 27, 2001

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

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

Should you have questions concerning this application contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

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

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Beth Fritsch

July 26, 2001

505W(2)(A) OK
22-AUG-2001
J. L. [Signature]
ORG AMENDMENT
N/A C

AMENDMENT

REFERENCE: ABBREVIATED NEW DRUG APPLICATION
ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg**.

Reference is also made to the Agencies letter dated July 3, 2001 that stated the following:

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR §314.101(d)(3) for the following reasons:

Comment 1:

You have failed to submit complete comparative in vitro dissolution data between your proposed drug product and the reference listed drug. Dissolution profiles should be generated in aqueous media of the following pH ranges: 1 – 1.5, 4 – 4.5, 6 – 6.5, and 7 – 7.5 and in 0.1 N HCL.

Response 1:

As per the July 16, 2001 telephone conversation between Beth Fritsch, Project Manager, Regulatory Support Branch, Surendra Shrivastava, Reviewer, and Shriniwas Nerurkar, Team Leader, Div. of Bioequivalence, FDA and Christine Mundkur, Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc., FDA agreed that this comment is not a refuse to file issue and can therefore be answered under separate cover at a later point in time as a bioequivalence amendment.

Comment 2:

The following should also be provided:

1. SOP for reassay of samples
2. SOP or criteria for acceptance of reassay values
3. Raw data including individual peaks with areas, etc. for 20 percent of the subjects in the study(ies).



Barr Laboratories, Inc.

ABBREVIATED NEW DRUG APPLICATION

ANDA # 76-170

Lithium Carbonate Extended-Release Tablets, USP 300mg

Response 2:

1. Enclosed please find a copy of SOP BAS_RMT_02, "Selection Criteria for Reanalyses" (Attachment I).
2. Enclosed please find a copy of SOP BAS_RMT_03, "Evaluation of Results After Reinjection Or Reassay Of Samples" (Attachment I).
3. As discussed in the July 16 phone conversation between Barr and FDA referenced above, there are no chromatograms or peak plots for this bioanalytical method because the analysis is not chromatographic in nature. During analysis, each sample and standard was continuously nebulized and the system rapidly recorded five replicate measurements of the signal intensities (counts per second) of both the analyte and internal standard isotopes. For each sample and standard, the ratio of the mean of the five intensities for the analyte isotope to the mean of the five intensities for the internal standard isotope was then calculated and used for the determination of the serum lithium concentration. The individual values of the five replicate measurements, as well as the mean, standard deviation, and coefficient of variation are shown on the instrument printout for each sample or standard. Such instrument printouts constitute the raw data for these bioanalyses. Supplement 01 to each of the two biostudy reports provides such instrument printouts (raw data) for analytical runs representing approximately 20% of the subjects in each biostudy. Supplement 02 to each of the two biostudy reports provides sequence lists showing the mean analyte and internal standard signal intensities, as well as the calculated serum lithium concentrations for all analytical runs. Enclosed please find the following documents:
 - Supplement 01 to the Fasting Biostudy Analytical Report (Study #2427) (Attachment II)
 - Supplement 02 to the Fasting Biostudy Analytical Report (Study #2427) (Attachment III)
 - Supplement 01 to the Food Effect Biostudy Analytical Report (Study #2428) (Attachment IV)
 - Supplement 02 to the Food Effect Biostudy Analytical Report (Study #2428) (Attachment V)

Comment 3:

Please check the appropriate box on the 356h form under the proposed marketing status section.

Response 3:

Acknowledged. The appropriate box on the 356h form under the proposed marketing status section has been checked.

An identical copy of this Amendment has been provided to the Baltimore District Office. A document certification is attached.

This completes the Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Vice President, Quality and Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

January 22, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Nina Nwaba

NLAB

ORIG AMENDMENT

**REFERENCE: ANDA # 76-170
 Lithium Carbonate Extended-Release Tablets, USP 300mg
 BIOEQUIVALENCY AMENDMENT**

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg.**

Reference is also made to the Agencies letter dated November 20, 2001 that stated the following:

Comment 1:

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

Response 1:

Attached please find a copy of the Comparative Report (ARD_RPT-120) for Lithium Carbonate Extended Release Tablets, USP 300mg.

This completes the Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.



Sincerely,

BARR LABORATORIES, INC

A handwritten signature in black ink, appearing to read "Christine Mundkur".

Christine Mundkur
Senior Vice President, Quality
and Regulatory Counsel

Page 13
1/3/02

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

December 28, 2001

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Kassandra Sherrod

ORIGINAL AMENDMENT
N/A.M.

REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
MINOR AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg.**

Reference is also made to the Agency's letter dated November 6, 2001 that stated the following:

Comment 1:

Please revise and resubmit your components and composition to mg/tablet instead of mg/dose.

Response 1:

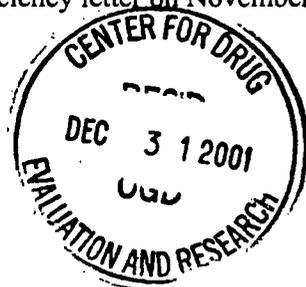
Barr acknowledges the Agency's request. Please see Section VII for an updated components and composition statement.

Comment 2:

DMF is deficient and the holder has been informed.

Response 2:

 responded to their DMF deficiency letter on November 16, 2001. See Attachment I for a copy of the cover letter.



Barr Laboratories, Inc.

December 28, 2001

REFERENCE: **ANDA # 76-170**
 Lithium Carbonate Extended-Release Tablets, USP 300mg
 MINOR AMENDMENT

Comment 3:

Please specify the expected time limit for completion of the manufacturing of the product including packaging.

Response 3:

Barr's expectation is that a batch immediately proceeds through the production stages to bulk finished product and is then packaged as soon as possible. The following table includes the approximate production time necessary to manufacture and package the product based on data obtained from the submission batch.

Product	Limit of Completion of Manufacturing
Manufacturing	
Lithium Carbonate Extended Release Uncoated Tablets	About 6 to 8 days
Lithium Carbonate Extended Release Coated Tablets	About 2 to 3 days
Packaging	
Lithium Carbonate Extended Release Tablets, USP 300mg	About 1 to 2 days

We are however aware of our obligation to monitor the stability of intermediates or finished product which exceed a 30 day hold time as per the Draft Guideline titled, "Stability Testing of Drug Substances and Drug Products" dated 6/98.

In addition, based upon previous observations, Barr has developed a bulk finished product stability program that evaluates the performance of bulk finished product up to, and including, a 12 month CRT interval. See Section XVI for a copy of Barr's bulk product stability protocol. Barr's systems are designed to immediately proceed to the next stage of manufacturing or packaging. However, Barr has put in place a procedure to evaluate blends and finished products when product cannot proceed immediately. In these rare instances a batch will need to be re-evaluated prior to it being released to the next stage. This re-evaluation includes the same critical tests and specifications used for the initial evaluation of the product.

Comment 4:

Indicate the time frame for holding tablets in bulk containers before packaging.

Response 4:

Barr has established a time limitation of 90 days for re-evaluation for holding tablets in bulk containers before packaging. Please note, Barr is not seeking approval for a final bulk package configuration. Per the *Guidance for Industry: Container Closure Systems for Packaging Human Drug and Biologics*, Barr has added the bulk product to the Stability program to support the hold time between bulk finished product and packaging. Bulk Stability data generated to date supports a hold time of up to 11.3 months. See Section XVI for a copy of the stability report which contains the bulk data. As per Barr's SOP, all bulk finished product that have not progressed to the packaging stage within 3 months will be retested.

Bulk stability data, Container closure needed -

6 months max.

Barr Laboratories, Inc.

December 28, 2001

REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
MINOR AMENDMENT

Comment 5:

What are your packaging limits? Include your limits on your packaging order forms

Response 5:

Barr's packaging limits are stated in their Standard Operating Procedure and are therefore not included on individual packaging order forms. The accountability limit for controlled drugs is % and for non-controlled drugs %. Thus, the packaging limits for Lithium Carbonate Extended Release Tablets, USP 300mg are %.

Comment 6:

Core color is included in your compression guidelines on page 12-18 but not on page 12-74 (in-process testing). Please include core color in your in-process table on page 12-74. We note that "Guidelines" on page 12-74 is the same as compression guidelines on page 12-18. Please explain when "specifications" are used, remove all reference to guidelines, and provide in-process tests, methods, and specifications. Include revisions for any changes in methods.

Response 6:

Barr acknowledges the Agency's comment. Please see Section XII for an updated in-process table (12-74).

As stated, the in-process tests and guidelines are included on pages 12-74 and 12-18 of the original ANDA submission. Additionally, page 12-74 also includes the specifications for the in-process tests. The guidelines are tighter ranges used by the operators on the manufacturing floor for set-up and control of the batch and are included on the batch record to ensure that product is manufactured within the approved specifications. The specifications are the validated ranges for manufacture of the product and are specified in Barr's product specification tables which list the specifications for in-process weight, thickness and hardness testing for each product (as applicable). The use of guidelines and specifications is stipulated in a standard operating procedure which is available for review by a District Inspector.

Comment 7:

Please acknowledge that in the case of any dispute that the USP method is the compendial method and overrules your method for the drug product assay and drug release.

Response 7:

Barr acknowledges the Agency's comment.

Comment 8:

Please include specifications in your Marketed Product Stability Protocol (p16-14) for test parameters.

Barr Laboratories, Inc.

December 28, 2001

REFERENCE: **ANDA # 76-170**
 Lithium Carbonate Extended-Release Tablets, USP 300mg
 MINOR AMENDMENT

Response 8:

Barr does not include specifications for test parameters in their Marketed Product Stability Protocol. Rather, the current test method is referenced. The test method and corresponding specification sheet, contain this information. This is the most efficient way to tie current specifications to the protocols.

Comment 9:

Please submit available updated room temperature stability data for the product

Response 9:

Please see Section XVI for an updated Stability Summary Report containing 12M CRT data for batch #403450002R.

Comment 10:

According to literature sources (USP 24, NIST Certificate, JC PDS, analytical profiles, vol 15), Lithium Carbonate may exist in more than one crystalline form. Please provide evidence that appropriate controls are in place and set a specification for purity. In addition, assess the potential for interconversion of the forms during the manufacturing process.

Response 10:

Based on literature sources (USP 24, NIST Certificate, JC PD5 and Analytical Profiles: Vol 15), Lithium Carbonate exists in one crystalline form. According to the article from Analytical Profiles: Vol 15, pg. 376, earlier work suggesting may have been caused by the presence of impurities. To further assess the potential for interconversion of the forms during the manufacturing process, Barr conducted X-ray diffraction studies during product development and recently on the finished blend. We did not observe any change from the raw material to the processed material (wet granulation and drying). Thus, there is no need to set a specification for purity.

Comment 11:

We know that there could be potential dissolution and hardness issues with Lithium Carbonate products on long-term stability. Therefore, include test and specification for hardness in your stability protocol and provide additional controlled room temperature data to support your expiration period.

Barr Laboratories, Inc.

December 28, 2001

REFERENCE: **ANDA # 76-170**
 Lithium Carbonate Extended-Release Tablets, USP 300mg
 MINOR AMENDMENT

Response 11:

Barr's Lithium Carbonate Extended Release Tablets, USP 300mg are film coated. As a general rule, hardness testing is not performed on film coated tablets. However, drug release testing is performed as part of our marketed product stability program. If as stated there is a potential for dissolution and hardness issues with this product, the effects would be seen in the drug release testing results. Therefore, hardness testing will not be added to the stability protocol, but will remain as an in-process control during the manufacture of the product.

As stated in response 9, Section XVI includes an updated Stability Summary Report containing 12M CRT data for batch #403450002R. The dissolution results met specifications at all timepoints.

At this time Barr would like to eliminate the Loss on Drying (LOD) testing from the release and stability requirements for the finished product. In general, the purpose for determining water content in a solid dosage finished product is two-fold. First, water may impact the stability of the active ingredient and cause degradation. Second, water may impact the product performance characteristics and potentially alter the Bio profile of the product. For this particular product however, since the active ingredient of Lithium Carbonate Extended-Release Tablets USP, is an inorganic salt, and Lithium is an element, there is no possibility for water to have any effect on the stability to cause degradation of the active. Therefore, the sole purpose for determining the water content in the Lithium Carbonate Extended-Release Tablets USP, 300mg is to establish any impact on the product performance. Since this is a modified release product, product performance for Lithium Carbonate Extended-Release Tablets, USP 300mg is determined via the Drug Release Test at the following time intervals and corresponding specifications.

Drug Release Test Requirements:

Time (minutes)	Amount Dissolved (%)
15	Between %
45	Between %
90	Between %
120	NLT %

The submission batch of Lithium Carbonate Extended-Release Tablets, USP, 300mg (lot #403450002R) was used to establish stability as per previously submitted stability protocol RD00-321. Along with the other test requirements, the water content (LOD) was determined on this batch under Accelerated, CRT and Bulk storage conditions.

The initial specification for LOD (NMT %) was set based on the limited data available at the end of the accelerated stability period prior to filing. Since that time, additional data was generated and the overall requirement for LOD was re-evaluated.

The formulation composition was reviewed and it was determined that the formulation may possibly be susceptible to picking up water from the environment. A study was then conducted which clearly indicated that the water content increases significantly when the product is exposed to high humidity and also may lose water when exposed to very low humidity. The water levels in this study ranged from %.

Barr Laboratories, Inc.

December 28, 2001

REFERENCE: **ANDA # 76-170**
 Lithium Carbonate Extended-Release Tablets, USP 300mg
 MINOR AMENDMENT

A review of the Drug Release stability data did not indicate any correlation between the different water levels (%) and the product performance. Therefore, this indicates that the water content does not affect the product performance. In order to obtain additional information in this regard, the drug release testing was conducted on the elevated humidity and desiccator stored samples exhibiting water levels from %. The obtained drug release data confirmed that the water content does not impact the Lithium Carbonate Extended-Release Tablets, USP, 300mg performance characteristics (see Figure 1, Section XVI). It is also important to note that the 7.1% water level is the saturation level and the water content would not increase significantly beyond this value.

Since the water content does not in any way impact the stability profile and the performance characteristics of this product, the test is of no value and is not needed for release or stability testing. It is therefore proposed to delete this test from the monograph and stability program. Section XIV contains the quality control and marketed product stability specifications and test records and updated finished product test method in which the Loss on Drying test has been removed. Section XVI contains an updated marketed product stability protocol in which the Loss on Drying test has been removed.

An identical copy of this Amendment has been provided to the Baltimore District Office. A document certification is attached.

This completes the Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

*Update stab. data!
beyond 3 months
up to 12 months
Purified.*

1125

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 4, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Radhika Rajagopalan

N/AM
ORIG AMENDMENT

REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg.**

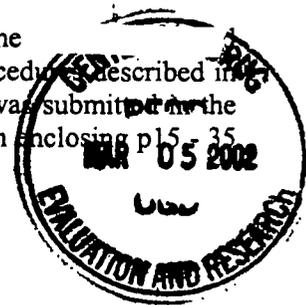
Reference is also made to a February 25, 2002 phone conversation between Radhika Rajagopalan, DCII, FDA and Christine Mundkur, Senior Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc. regarding our Minor Amendment dated December 28, 2001. Radhika requested the following additional information be submitted in a Telephone Amendment.

Bulk container/closure information

The bulk container/closure used for Lithium Carbonate Extended-Release Tablets, USP 300mg consists of doubled polyethylene bags (the primary container). The polyethylene bag is 100% Linear Low Density Polyethylene Prime Virgin USDA and FDA Approved Packaging Grade. The polyethylene bags comply with all FDA/USDA regulations covering direct food contact. All ingredients have been certified to meet the requirements of the FDA regulation 21 CFR 177.1520 PAR © 3.2 x 2.2 and 21 CFR 178. Attached please find a letter from which certifies that the raw materials and processes used in the manufacture of their Polyethylene bags comply with all FDA/USDA regulations. Barr also commits to package bulk tablets within 6 months of manufacture as per the Agency's request.

Assay Method Validation information

Barr developed and validated an in-house method for the tests, which is more accurate and precise than the assay procedure described in USP 24. The equivalency study is summarized in Report # RD00-299, which was submitted in the original ANDA, Section XV 2.2.1 p15-35. For your ease of review, we are again enclosing p15-35 of Report # RD00-299.



Barr Laboratories, Inc.

REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
TELEPHONE AMENDMENT

X-ray diffraction information

As stated in response 10 of the Minor Amendment, Barr conducted X-ray diffraction studies during product development and on the finished blend to demonstrate there is no need to set a specification for purity. As requested, enclosed please find a copy of the X-ray diffraction studies between the reference listed drug (Lithobid®), active material (Lithium Carbonate, USP), in-process material, and finished blend.

LOD information

Also, Barr requested to eliminate Loss on Drying (LOD) testing from the release and stability requirements for the finished product. As per the Agency's request, Barr will continue to monitor and evaluate the overall requirement of LOD testing. Barr has placed the LOD testing back into the release and stability requirements for the finished product with the specification of NMT %. The original specification for LOD was set at NMT %, based on the limited stability data available at the time of submission. After reviewing additional stability data generated to date, including the bulk, it became clear that the specification should more accurately be set at NMT %. As stated in the December 28, 2001 amendment, drug release testing was performed on elevated humidity and desiccant stored samples, which exhibited water levels from %. The obtained drug release data confirmed that the water content does not impact the Lithium Carbonate Extended Release Tablets USP, 300mg performance characteristics. Once additional data is generated from our validation batches, we will re-evaluate whether LOD testing is truly significant.

Attached please find the updated quality control and marketed product stability specifications and test records, and updated finished product test method Version 2.0, in which the LOD has been added. Also, attached is an updated marketed product stability protocol reflecting the addition of the LOD test.

An identical copy of this Telephone Amendment has been provided to the Baltimore District Office. A document certification is attached. This completes the Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 13, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Radhika Rajagopalan

ORIG AMENDMENT



REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg.**

Reference is also made to a March 13, 2002 phone conversation between Radhika Rajagopalan, DCII, FDA and Christine Mundkur, Senior Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc. requesting additional information on our in-process controls for weights. Radhika requested the following additional information be submitted in a Telephone Amendment.

In-Process Controls information

During the manufacturing process, 10 tablets are weighted on a suitable balance, and the average weight of the 10 tablets is documented on the batch record. The average result obtained must fall within the designated guidelines listed on the batch record. Each individual tablet weight must be within the acceptable guideline for individual tablet weights. This guideline is the assay limit of the product less 2%. For example the assay limit for this product is _____, therefore, the guideline is _____

If the average or any individual tablet is outside of its respective guideline but within the specification for an average of 10, then a re-sample of 60 tablets will be performed. If the re-sampled tablets all fall within the approved specification, and the average tablet weight is within the average of ten specification then production may resume. All re-sampled data (individuals and averages) are maintained and included in the batch record.

If the re-sampled tablets do not meet the Individual and Average Specification, then the product produced since the last known good in-process check is segregated and the Manufacturing Team Leader/Supervisor is notified to determine what further action is required.

RECEIVED

MAR 14 2002

OGD / CDER

Barr Laboratories, Inc.

**REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
TELEPHONE AMENDMENT**

An identical copy of this Telephone Amendment has been provided to the Baltimore District Office. A document certification is attached. This completes the Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.

A handwritten signature in cursive script, appearing to read "Christine Mundkur", with a small square mark at the end of the signature.

Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

April 8, 2002

LABELING AMENDMENT

Office of Generic Drugs
CDER/ Food And Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

ORIGINAL RECEIVED

N/AF

REFERENCE: ANDA 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg

Dear Sir or Madam:

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg**.

Reference is also made to the Agency's March 27, 2002 facsimile from the Labeling Review Branch requesting Barr make revisions to their insert labeling and to submit these changes in a Labeling Amendment. On March 28, 2002, Barr submitted printer proof brochures, Revision April 2002, which have been revised according to the recommendations.

The final printed brochures are now being submitted as we committed to do in our March 28th response.

Attached please 12 Final Printed brochures (APRIL 2002 Revision).

This completes the present Labeling Amendment. If you have any questions, please contact me by phone at (845) 348-6894 or by fax at (845) 353-3859.

Sincerely,


Salvatore P. Peritore, M.S., R.Ph.
Associate Director, Regulatory Affairs

Enc

RECEIVED

APR 09 2002

OGD / CDER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

March 28, 2002

ORIG AMENDMENT
NIAFFPL

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

REFERENCE: ANDA 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
LABELING AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg**.

Reference is also made to the Agency's March 27, 2002 facsimile from the Labeling Review Branch requesting Barr make the following revisions to their insert labeling and to submit these changes in a Labeling Amendment:

Labeling Deficiencies:

a. **WARNINGS**

Replace the subsection headings, "Usage in Pregnancy", "Usage in Nursing Mothers" and "Usage in Children" with "Pregnancy", "Nursing Mothers" and "Pediatric Use", respectively and relocate the subsections to the end of the PRECAUTIONS section per 21 CFR 201.57.

b. **PRECAUTIONS**

Revise the seventh sentence to read "...intake (2500-3000mL) at..."

c. **ADVERSE REACTIONS (Neuromuscular)**

Revise to read "...deep tendon reflexes."

d. **DOSAGE AND ADMINISTRATION**

Delete all trailing zeros after decimal points.

e. **Switch the DOSAGE AND ADMINISTRATION section with the OVERDOSAGE section per 21 CFR 201.56.**

RECEIVED

MAR 29 2002

OGD / CDER

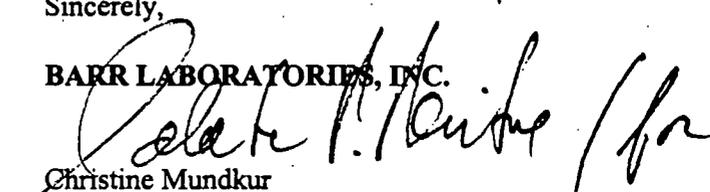
Barr Laboratories, Inc.

Attached please find printer proof brochures, Revision April 2002, which have been revised according to the above recommendations. The final printed brochures will be submitted during the first week of April. Also enclosed is a side-by-side comparison between Barr's last submitted brochure (March 2002 Revision) and the current proposed brochure (April 2002 Revision) annotating and explaining only those sections that are different.

This completes the present Labeling Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.


Christine Mundkur

Vice President, Quality and Regulatory Counsel

RECEIVED

MAR 29 2002

OGD / CDER

Barr Laboratories, Inc.

2 Quaker Road • P.O. Box 2900 • Pomona, NY 10970-0519 • 845/362-1100

May 29, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room 150
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855-2773
Attention: Radhika Rajagopalan

NEW CORRESP
MC

REFERENCE: ANDA # 76-170
Lithium Carbonate Extended-Release Tablets, USP 300mg
TELEPHONE AMENDMENT

Reference is made to our pending Abbreviated New Drug Application submitted on May 11, 2001, under Section 505(j) of the Federal Food, Drug and Cosmetic Act for **Lithium Carbonate Extended-Release Tablets, USP 300mg.**

Reference is also made to a May 29, 2002 phone conversation between Radhika Rajagopalan, DCII, FDA and Christine Mundkur, Senior Vice President Quality and Regulatory Counsel, Barr Laboratories, Inc. requesting a statement made on p14-4 of the original ANDA submission. Attached please find the correction of page 14-4.

An identical copy of this Telephone Amendment has been provided to the Baltimore District Office. A document certification is attached. This completes the Amendment. If you have any questions, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859.

Sincerely,

BARR LABORATORIES, INC.



Christine Mundkur
Senior Vice President, Quality and
Regulatory Counsel

Attn:Radhika Rajagopalan
Fax copy: 301-443-3839

RECEIVED
MAY 30 2002
OGD / CDER

Barr Laboratories, Inc.

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May 11, 2001

Refuse to receive!
03-JUL-2001
Gregory S. Davis

Office of Generic Drugs
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773



**REFERENCE: Abbreviated New Drug Application
 Lithium Carbonate Extended-Release Tablets, USP 300 mg**

In accordance with the regulations promulgated under 505 (j) of the Food, Drug and Cosmetic Act, and as amended, Barr Laboratories, Inc. is submitting this Abbreviated New Drug Application for Lithium Carbonate Extended-Release Tablets, USP 300 mg.

The application is provided in duplicate, as an archival copy, and a review copy. The archival copy of the application is contained in blue binders and consists of **6 volumes**. The review copy is divided into two parts. The chemistry, manufacturing and controls part of the review copy is contained in red binders and consists of **2 volumes**. The bioequivalence part of the review copy is contained in orange binders and consists of **5 volumes**.

Included in this application and in accordance with the Generic Drug Enforcement Act of 1992, is a Debarment Certification Statement. Field Copies of this application has been forwarded to the Baltimore District Office. A Field Copy Certification is also provided in this application.

Certifications of financial interests and arrangements of clinical investigators conducting the bioequivalence study are provided in Section VI.

The CMC and Bioequivalence Sections of this application will be provided in electronic format within 30 days from this date. Barr Laboratories, Inc. will at that time provide a declaration that the information in the electronic submission is the same as the information provided in the paper submission.

The format of this application is in accordance with Office of Generic Drug's Guidance for Industry: Organization of an ANDA, dated February 1999. The information submitted in this application is also in accordance with the October 14, 1994 communication from Dr. Janet Woodcock, (CDER) and Mr. Ronald Chesemore (ORA).

If you have any questions concerning this application, please contact me by phone at (845) 353-8432 or by fax at (845) 353-3859. Your earliest acknowledgment to this application will be very much appreciated.

Sincerely,

BARR LABORATORIES, INC.

Christine Mundkur
Christine Mundkur

Vice President, Quality and Regulatory Counsel

Cc. Baltimore District Office