CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-754

CORRESPONDENCE

LEMMON

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

AMENDMENT
N/AM

March 14, 1997

MINOR AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 74-754
KETOROLAC TROMETHAMINE TABLETS USP, 10 mg
MINOR AMENDMENT

Dear Mr. Sporn:

We submit herewith an amendment to the above referenced Abbreviated New Drug Application in accord with the instructions provided in your February 28, 1997 **tentative approval** letter for this file. At this point in time, no changes have been made to the conditions under which this ANDA was tentatively approved with regards to labeling, chemistry, manufacturing, or controls. This amendment is being submitted approximately 60 days prior to the May 16, 1997 expiration of U.S. Patent No. 4,089,969 held by Syntex in association with their NDA 19-645 for Toradol® Tablets. This information is being submitted for retention in your files and to facilitate the issuance of **final approval** of ANDA 74-754.

Sincerely,

Deborah Jaskot

DAJ/pe

RECEIVED
MAR 17 1997
GENERIC DRUGS

3-21-97

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

ANDA # 74-754

KETOROLAC TROMETHAMINE TABLETS, 10 mg

MINOR AMENDMENT

In accord with the final rule published in the Federal Register of September 8, 1993, LEMMON Company hereby certifies that the field copy is a true copy of the technical section of this submission and has been provided to the Philadelphia District Office.

Deborah Jaskot

Deborah A. Jaskot
Sr. Director, Regulatory Affairs

3/14/97
Date

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

November 22, 1996

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA #74-754
KETOROLAC TROMETHAMINE TABLETS USP, 10 mg
AMENDMENT TO PATENT CERTIFICATION

Dear Mr. Sporn:

In accord with a direct request made in your letter dated March 26,1996, a revised patent certification was submitted to this file which recognized an expiration date of July 14,1998, for U.S. Patent No. 4,089,969. In light of the more recent publication of Cumulative Supplement 8 to the FDA's official listing of Approved Drug Products (the Orange Book) which now identifies May 16, 1997, as the expiration of Syntex's U.S. Patent No. 4,089,969, in association of their NDA 19-645 for Toradol® Tablets, we herewith submit a newly revised patent certification statement. Copies of the relevant pages from the above-referenced FDA document are provided herein for your convenience. The enclosed amended certification is intended to replace the previously submitted version.

Sincerely,

Deborah Jaskot

Deborah A. Jaskot
Senior Director, Regulatory Affairs

DAJ/pe
Enclosure

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

Deborah A. Jaskot
Director, Regulatory Affairs

September 30, 1996

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RECEIVED
OCT 0 1996

ORIG AMENDMENT
N/AA

ANDA #74-754
KETOROLAC TROMETHAMINE TABLETS, 10 mg
AMENDMENT - ADDITION OF CONTRACT TESTING FACILITY

Dear Mr. Sporn:

We submit herewith an amendment to the above-referenced pending ANDA to provide for X-ray diffraction testing by a contract facility of the active ingredient Ketorolac Tromethamine. The proposed contract facility is:

X-ray diffraction testing will be performed in accord with LEMMON's Raw Material Procedures Manual. Enclosed is a letter from , certifying compliance to GMP and GLP requirements.

We wish to bring to your attention the fact that has been approved for X-ray diffraction testing of another compound in two other LEMMON ANDAs. was approved for X-ray diffraction analysis on July 25, 1996, for ANDA 73-524/S-003, Carbamazepine Chewable Tablets , 100 mg, and also ANDA 70-541/S-022, Carbamazepine Tablets USP, 200 mg.

This information is submitted for your continued review and approval of ANDA 74-754.

Sincerely,

DAJ/eml
Enclosure

1.1 dup.

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

Deborah A. Jaskot
Director, Regulatory Affairs

September 30, 1996

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AA

ANDA #74-754
KETOROLAC TROMETHAMINE TABLETS, 10 mg
AMENDMENT - ADDITION OF CONTRACT TESTING FACILITY

Dear Mr. Sporn:

We submit herewith an amendment to the above-referenced pending ANDA to provide for X-ray diffraction testing by a contract facility of the active ingredient Ketorolac Tromethamine. The proposed contract facility is:

X-ray diffraction testing will be performed in accord with LEMMON's Raw Material Procedures Manual. Enclosed is a letter from certifying compliance to GMP and GLP requirements.

We wish to bring to your attention the fact that has been approved for X-ray diffraction testing of another compound in two other LEMMON ANDAs. was approved for X-ray diffraction analysis on July 25, 1996, for ANDA 73-524/S-003, Carbamazepine Chewable Tablets , 100 mg, and also ANDA 70-541/S-022, Carbamazepine Tablets USP, 200 mg.

This information is submitted for your continued review and approval of ANDA 74-754.

Sincerely,

DAJ/eml
Enclosure

LEMMON

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

Deborah A. Jaskot
Director, Regulatory Affairs

ORIG AMENDMENT

June 19, 1996

RECEIVED

JUN 24 1996

GENERIC DRUGS

MINOR AMENDMENT

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA # 74-754
KETOROLAC TROMETHAMINE TABLETS, 10 mg
MINOR AMENDMENT - CHEMISTRY, MANUFACTURING, CONTROLS and LABELING

Dear Mr. Sporn:

We herewith submit an amendment to the above referenced abbreviated new drug application in response to the Chemistry and Labeling Deficiency Letters dated March 20, 1996 and March 29, 1996 respectively. The comments are addressed in the order in which they were presented.

A. Chemistry, Manufacturing and Controls

7. Blend uniformity testing will be performed on every lot manufactured. (See page 6 of 12 in the master production batch record in attachment #4)

B. Labeling

1. Reference is made to the telephone conversation of April 17, 1996 between Andy Shapiro, Manager, Professional Affairs and Jerry Phillips, Acting Director of Labeling and Program Support. During the conversation, Jerry Phillips stated that the requested temperature range (20 - 25°C) was part of a proposed guideline and not a requirement, therefore, the temperature range we originally proposed (15 - 30°C) is acceptable. All other revisions requested have been made.

2. Twelve copies of final printed labeling are provided. (See attachment #7)

In addition we note and acknowledge the following:

1. All DMF's referenced in this ANDA must be found satisfactory at the time of approval of the ANDA and some of the DMF holders may have to be inspected by the Division of Manufacturing and Product Quality. Any unsatisfactory review/evaluation will delay approval of the ANDA.

2. The firms referenced in the ANDA relative to the manufacture and testing of the product must be in compliance with cGMP's at the time of approval.

This information is submitted for your review and approval of ANDA 74-754. If there are any further questions, please do not hesitate to call (215) 256-8400 X 4249.

Sincerely,

Deborah Jaskot/PE

Enclosure

LEMMON

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

Deborah A. Jaskot
Director, Regulatory Affairs

NOTED 5/21/96

May 14, 1996

NEW CORRES BIOAVAILABILITY 3 month

NC/BIO

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE RESPONSE

RECEIVED
MAY 16 1996
GENERIC DRUGS

ANDA # 74-754
KETOROLAC TROMETHAMINE TABLETS USP, 10 mg
BIOEQUIVALENCE RESPONSE

Dear Mr. Sporn:

We herewith submit an amendment to the above referenced abbreviated new drug application in response to the letter dated March 20, 1996 from Dr. Keith Chan of the Division of Bioequivalence. The comments are addressed (in the order in which they were presented) by on our behalf in the following report. As requested, a copy of the March 20, 1996 correspondence is also included herein.

This information is submitted for your review and approval of ANDA 74-754. If there are any further questions, please do not hesitate to call (215) 256-8400 X 4249.

Sincerely,

Deborah Jaskot /pe

DAJ/bn
Enclosures

A,1

ANDA 74-754

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville PA 18960

SEP 30 1996

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketorolac Tromethamine Tablets USP 10 mg.

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

2. The dissolution testing should be conducted as specified in the USP 23 and should be incorporated into your stability and quality control programs.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

//Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-754

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

MAR 29 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated September 21, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketorolac Tromethamine Tablets USP, 10 mg.

Reference is made to our not approvable letter of March 26, 1996.

The following comments pertain to labeling deficiencies only as discussed in item B of our cited correspondence above.

1. CONTAINER: 10 mg - 100's, 500's and 1000's

Revise the storage statement to read as follows:

Store at controlled room temperature
20-25°C(68-77°F)
[See USP]

2. INSERT

a. GENERAL COMMENTS

i. When referring to micrograms use the abbreviation "mcg" instead of "μg".

ii. Delete USP following the established name, except in the TITLE, DESCRIPTION and HOW SUPPLIED sections.

iii. Delete terminal zeros following decimal points.

b. Boxed WARNING

i. Delete the subsection, INTRATHECAL OR EPIDURAL ADMINISTRATION

ii. LABOR, DELIVERY AND NURSING

Revise the first sentence to read:

> The use of ketorolac tromethamine in labor and delivery is CONTRAINDICATED because ...

c. DESCRIPTION

Revise the first sentence of the second paragraph to read:

> Ketorolac tromethamine is a racemic ...

d. INDICATIONS AND USAGE

Delete the second paragraph.

e. CONTRAINDICATIONS

Delete the following sentence:

> Ketorolac tromethamine IV/IM is CONTRAINDICATED for neuraxial (epidural or intrathecal) administration due to its alcohol content.

f. PRECAUTIONS

i. Drug Interactions

A) Change the proprietary names of the antiepileptic and psychoactive drugs to their corresponding established names.

B) Delete the penultimate paragraph.

ii. Use in the Elderly (≥ 65 years of age)

Revise this subsection to read:

... elderly with ketorolac tromethamine. The incidences and severity of ...

g. ADVERSE REACTIONS (The adverse reactions listed below were reported in clinical trials as probably related to ketorolac tromethamine).

Incidence Greater Than 1%

Delete the last sentence: Injection-site pain was reported by 2% of patients in multi-dose studies.

h. DOSAGE AND ADMINISTRATION

Delete the subsection heading "Ketorolac Tromethamine-IV/IM" and revise to read:

Ketorolac Tromethamine-IV/IM may ... exceed 5 days.

Ketorolac Tromethamine Tablets are indicated ONLY ...

i. HOW SUPPLIED

i. Please indicate that your tablet is unscored.

ii. Please refer to our comment under CONTAINER.

Please revise your container labels and package insert labeling, and submit in final print with your amendment to our March 26, 1996, letter. Please note that we reserve the right to request further changes in your labels and labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

This letter addressed unique issues involving only labeling. Again, we refer you to our letter of March 26, 1996, for the requirements to reopen the file on this application.

Sincerely yours,

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:

Letter out

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

ANDA 74-754

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville, PA 18960

MAR 26 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated September 21, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketorolac Tromethamine Tablets USP, 10 mg.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Comments:

The labeling portion of your application is currently under review. The Division of Labeling and Program Support will notify you, under separate cover, of all labeling deficiencies within 10 working days of the date of this letter. Your response must be complete and incorporate ALL deficiencies, including any pending labeling deficiencies.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

1. All DEF(s) referenced in this AND have to be found satisfactory at the time of approval of the AND. Some of the DEF holders may have to be inspected by our Division of Manufacturing and Product Quality. Any unsatisfactory review/evaluation will delay the approval of the AND.

2. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMP(s) at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the

bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

R. Patel

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-754

MAR 20 1996

Lemmon Company
Attention: Debbie Jaskot
650 Cathill Road
Sellersville, PA 18960

Dear Ms. Jaskot:

Reference is made to the Abbreviated New Drug Application, submitted on September 21, 1995 for Ketorolac Tromethamine Tablets, 10 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

1. Due to the irregularity of the terminal data points, the estimation of Kel (hence AUCinf) is not reliable for the following subjects:

   For the fasting study:

   subject 8 and 9 (test formulation) and subject 10 and 11 (reference formulation), and,

   For the fed study:

   subject 4 and 6 (test formulation, fasting leg) and subject 2 and 6 (test formulation, fed leg).

   Hence, we request the following information

   a. Please delete the above referenced subjects in both the fasting and fed studies and redo the statistical analysis of AUCinf for both studies.

   b. As supportive analysis, you may want to use an appropriate pharmacokinetic model to fit the data of the above subjects, then estimate Kel and AUCinf. Rerun the ANOVA and appropriate statistical testings.

2. With regard to the fed study, detailed information on chromatographic interference on subject 9 should be provided. All chromatograms for this subject should be submitted for evaluation.

3. Data on photo-decomposition of ketorolac should be provided. Comparative data on the extent of the stability of the samples under both normal conditions and light-protected conditions should be provided. The extent of the photo-decomposition of the samples by during the HPLC run should be provided.

4. Complete data with all calculations should be shown to substantiate the choice of using 1/Response as weighting factor vs. other weighting schèmes, such as $1/(\text{Response})^2$ or no weight in the regression of the standard curves.

5. Please provide the date of manufacture as well as information on theoretical and actual yield for the test formulation used in the fasting and fed studies.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, CSO, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

/Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-754

Lemmon Company
Attention: Deborah A. Jaskot
650 Cathill Road
Sellersville PA 18960

NOV 20 1995

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: Ketorolac Tromethamine Tablets USP, 10 mg

DATE OF APPLICATION: September 21, 1995

DATE OF RECEIPT: September 25, 1995

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

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

Should you have questions concerning this application contact:

James Wilson
Consumer Safety Officer
(301) 594-0310

Sincerely yours,

1/95

Jerry Phillips
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

LEMMON

LEMMON COMPANY
650 Cathill Road
Sellersville, PA 18960
Phone: (215) 256-8400
Fax: (215) 721-9669

Deborah A. Jaskot
Director, Regulatory Affairs

S. Middleton
505(j)(2)(A)
10/30/95

September 21, 1995

Charles Ganley, M.D.
Acting Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
KETOROLAC TROMETHAMINE TABLETS USP, 10 mg

Dear Dr. Ganley:

We submit herewith an abbreviated new drug application for the drug product Ketorolac Tromethamine Tablets USP, 10 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs Policy and Procedure Guide #30-91. These copies are presented in a total of 13 volumes; 6 for the archival copy and 7 for the review copy. The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Ketorolac Tromethamine Tablets USP, 10 mg, manufactured by LEMMON Company, to the reference listed drug Toradol®, manufactured by Syntex, under both fasting and post-prandial conditions.

We look forward to your review and comment.

Sincerely,

Deborah Jaskot

DAJ/eml
Enclosures

RECEIVED
SEP 25 1995
GENERIC DRUG