# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 75078

## ADMINISTRATIVE DOCUMENTS

# ANDA APPROVAL SUMMARY

ANDA:75-078 DRUG PRODUCT:Etodolac Capsules

FIRM:Taro DOSAGE:Capsules STRENGTH: 200, 300 mg

CGMP STATEMENT/EIR UPDATE STATUS:EER acceptable as of 8/19/97.

BIO STUDY:Acceptable per Bio review dated 9/14/97 (M.Park).

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): FDA MV was completed on 4/7/98 and was found acceptable.

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?):

Three months of RT (25°C/60%RH) and accelerated (40°C/75%RH) stability data are provided for the 200 mg strength capsules on pp.2884-2886. Six months of accelerated (40°C/75%RH) stability data are also provided for the 300 mg strength capsules on p.2992. Second tier dissolution testing with the addition of enzyme to the dissolution medium was employed in the dissolution testing.

In a subsequent amendment the firm provided up to 9 and 12 months CRT (25°C/60%RH) stability data respectively for the 200 mg and 300 mg capsule strength and indicated that based on these data there has not been a need to use the second tier dissolution testing using enzyme.

Note: Per E-mail dated 11/24/97 from H. Malinowski the two tier gelatin capsules dissolution testing with enzyme added to the dissolution medium is now acceptable based on the USP <711> dissolution change effective 12/1/97.

Containersused in the study are the same as those listed under container/closure system of the application.

LABELING:Acceptable per labeling review dated 3/26/98 (C.Park).

STERILIZATION VALIDATION (IF APPLICABLE):N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.?):

NDS source: OK

200 mg: capsules
300 mg: capsules

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

Same as the biobatches.

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

Master instructions for manufacturing capsules (200 mg) and capsules (300 mg) are provided. Manufacturing process is essentially the same as those of the test batches.

| Reviewer: | Dated completed: |
| --- | --- |
| J. Fan | 4/2/98 |
| | 4/16/98 (Revised) |

HFD-623/J.Fan/ 4/16/98
HFD-623/V.Sayeed, Ph.D.
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F/t by:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 75078

CORRESPONDENCE

April 9, 1998

Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

AC

Reference: **ANDA 75-078**
**Etodolac Capsules, 200 mg & 300 mg**
**Telephone Amendment**

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on February 14, 1997 for Etodolac Capsules, 200 & 300 mg, under Section 505(j) of the Federal Food, Drug and Cosmetic Act, and to our amendment submitted September 7, 1997.

Reference is also made to telephone conversations on April 6, 7, and 8, 1998 with Mr. James Wilson and Dr. Vilayat Sayeed of the OGD, and representatives from Taro. Mr. Wilson requested that Taro revise the release and stability specifications for this drug product to incorporate the following limits for unknown impurities:



Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

This completes our response to this telephone request.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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04/09/98 4:37 PM

March 24, 1998

TARO

EPL

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

N/A

Reference: **ANDA 75-078**
**Etodolac Capsules 200 & 300 mg**
**Telephone Amendment**

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on February 14, 1997 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etodolac Capsules 200 and 300 mg.

Reference is also made to a phone call from Mr. Chan Park on March 24, 1998 to Lorraine Sachs in which it was requested that we update the package insert to specify the imprintings that will be on the capsule. It was also requested, in this phone call that we re-submit 12 final printed labels for both the 200 and 300 mg bottles.

Enclosed please find the final printed labeling for the 200 and 300 mg bottles, as well as final printed labeling for the package insert.

This concludes our response to the Agency's phone call of March 24, 1998.

If you should have any questions, please contact the undersigned.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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MAR 25 1998
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03/24/98 4:24 PM

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 800-544-1449, 914-345-9001 Sales Fax: 914-345-8727 http://www.taropharma.com

February 6, 1998

Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Reference: **ANDA 75-074**
**Etodolac Tablets, 400 mg**

**ANDA 75-078**
**Etodolac Capsules, 200 mg & 300 mg**
**Telephone Amendment**

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on February 10, 1997 for Etodolac Tablets, 400 mg and on February 14, 1997 for Etodolac Capsules, 200 & 300 mg, under Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the Methods Validation Letter dated February 6, 1998 from the FDA Philadelphia District Laboratory requesting samples and documentation for ANDA 75-074, Etodolac Tablets, 400 mg.

Taro hereby commits to work in conjunction with the District Laboratory to complete the validation of the methods for both the above referenced ANDA's within 30 days of the approval of each ANDA.

We are providing herewith copies of the following letters:

1. ANDA Validation Letter dated February 6, 1998, sent by the FDA Philadelphia District Laboratory to Taro requesting samples and documentation for the validation of methods for ANDA 75-074, Etodolac Tablets, 400 mg

2. Letter from Taro to the FDA Philadelphia District Laboratory providing samples and documentation for both ANDA 75-074, Etodolac Tablets, 400 mg and ANDA 75-078, Etodolac Capsules, 200 & 300 mg, in the event that the laboratory can concurrently schedule the validation of samples for both ANDA's.



Sincerely,

Lorraine W. Sachs

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs
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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

1 copy. See contents in 7507

September 8, 1997

ARCHIVAL COPY

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

AMENDMENT

Reference: **ANDA 75-078**
**Etodolac Capsules 200 and 300 mg**
**Major Amendment**

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on February 14, 1997 under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etodolac Capsules, 200 and 300 mg.

Reference is also made to your letter dated July 25, 1997 in which you stated the following:

**Comment A.1.a**

PAGES 2 - 12
CMC

SEP 09 1997

GENERIC DRUGS

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 800-544-1449, 914-345-9001 Sales Fax: 914-345-8727 http://www.taropharma.com

In addition to the comments above, we have responded to the following labeling deficiencies:

**1. Container - 100's**
**A. ANDA 75-074 (Tablets)**

**a) We encourage the use of boxing, contrasting colors, or other means to differentiate the strength of this drug product from the strengths of your proposed capsule products (ANDA 75-078).**

**b) You may include the following:**
**Each tablet contains:**
**Etodolac ..... 400 mg**

**c) Revise the storage statement to read "Store at controlled room temperature 15° - 30°C (59° - 86°F)".**

**d) Include the statement "Dispense in a light-resistant container.".**

e) **Revise the "Usual Dosage" statement to read "Usual Dosage: See accompanying package insert.".**

**B. ANDA 75-078 (Capsules)**

**a. Refer to the comments (a) and (e) for ANDA 75-074.**

**b. Revise the storage statement to read "Store at controlled room temperature 15° - 30°C (59° - 86°F), protected from moisture".**

**c. You may include the following:**

**Each capsule contains:**
**Etodolac ..... xxx mg**

**d. Include the statement "Dispense in a well-closed container as defined in the USP" to be in accord with the reference listed drug.**

**2. INSERT (ANDA 75-078)**
**a. GENERAL**

**i. We acknowledge your proposal for a combined package insert for two separate applications for etodolac tablets and capsules. Please note that these applications must be approved at the same time, or further revisions may be necessary.**

Response
We acknowledge your comment and, at this time have separated the inserts to be for either Tablets or Capsules.

**ii. Use "mcg" rather than "μg" throughout the text.**

**iii. Use the term "to" rather than hyphen when expressing a range.**

**iv. "(see Clinical Pharmacology, CLINICAL TRIALS)" rather than "(see Clinical Trials)" throughout the text. Please note that "Clinical Studies" is a subsection under the "Clinical Pharmacology" section.**

v. **Please distinguish different levels of section headings consistently by using headings of different prominence throughout the text. Also, revise accordingly wherever references are made to these headings in the text. We offer the following as an example:**

**Clinical Pharmacology**
**PHARMACOKINETICS**
**Absorption**
**Antacid Effects**

**b. DESCRIPTION**

i. **Paragraph 2, sentence 1:**

**You may delete this statement [redundant] or revise to read "The molecular formula ...". [rather than "empirical"]**

ii. **You have listed "molecular weight" twice using different numbers. You may delete "Molecular Weight: 287.36" or revise to read "287.37".**

iii. **Delete the last paragraph and revise the third and fourth paragraphs to read as follows:**

**Each tablet, for oral administration, contains 400 mg of etodolac. In addition, each tablet contains the following inactive ingredients: Color lakes, ...**

iv. **You may omit "Color Lakes" and "CI numbers".**

v. **Please alphabetize the list of inactive ingredients.**

**b. PRECAUTIONS (Laboratory tests) - Paragraph 1, sentence 1:**

**.... NSAIDs, should ... [add "comma"]**

**c. HOW SUPPLIED**

iv. **Add "unscored" to the description of your tablet.**

v. **Revise the storage statement to read "Store at controlled room temperature 15° - 30°C (59° - 86°F)" for tablets.**

We acknowledge the agency's comments and have revised our labeling accordingly. Enclosed please find:

12 final printed bottle labels
12 final printed package inserts

In addition please find a side-by-side comparison of our revised labeling (supplemental pages S80 - S108).

This completes our response to the Agency's letter of July 25, 1997.

If you should have any further questions, or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

June 9, 1997

TARO

BIOAVAILABILITY
NEW CORRESP
NC/Bio

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Attn: Ms. Saundra T. Middleton, HFD-615

RE: ANDA 75-074, Etodolac Tablets, 400 mg
~~ANDA 75-078~~ Etodolac Capsules, 200 & 300 mg
**General Correspondence**

Dear Ms. Middleton:

At your request, we are forwarding to the Division of Bioequivalence a copy of a disk which contains the data for the two 2 way crossover bioavailability studies done on the 400 mg tablets and the 300 mg capsules (protocols 960933 and 960484, respectively).

We apologize for any inconvenience which was caused. Please contact the undersigned at (914)345-9001 if you require any further information.

Sincerely,

Lorraine W. Sachs, RAC
Senior Regulatory Affairs Scientist
Taro Pharmaceuticals U.S.A., Inc.

enclosure

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JUN 10 1997
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June 17, 1997

TARO

Ms. Lizzie Sanchez
Division of Bioequivalence
Office of Generic Drugs
Food and Drug Administration
7500 Standish Place
MPN-II, Room E-130 (HFD-650)
Rockville, MD 20855

NEW CORRESP
BIOAVAILABILITY

**RE:** **ANDA 75-074**
Etodolac Tablets, 400 mg
**Bioequivalence Telephone Amendment**

**ANDA 75-078**
Etodolac Capsules, 200 &300 mg
**Bioequivalence Telephone Amendment**

Dear Ms. Sanchez:

In response to your telephone request on Friday, June 13, 1997, enclosed please find corrected copies of pages 1918 through 1921 of ANDA 75-078. These pages incorrectly indicated a 15 minute dissolution profile timepoint. The correct timepoint is 20 minutes.

In addition, upon reviewing these pages and the corresponding pages in ANDA 75-074, another typographical error was discovered. Page 1871f of ANDA 75-074 and page 1913 of ANDA 75-078 incorrectly indicate that the dissolution medium used was 0.1 M hydrochloric acid. The correct medium used for Etodolac tablet and capsule dissolution is pH 7.5 phosphate buffer. Therefore, we have also corrected these pages and are submitting them at this time.

We apologize for any inconvenience caused and thank you for bringing this matter to our attention.

Sincerely,
TARO PHARMACEUTICALS U.S.A., INC.

Lorraine W. Sachs, RAC
Senior Regulatory Affairs Scientist

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Taro Pharmaceuticals U.S.A. Inc. Five Skyline Drive, Hawthorne, N.Y. 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

April 10, 1997

CORRESP

BIOAVAILABILITY

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

**Re: ANDA 75-078**
**Etodolac Capsules 200 & 300 mg**
**General Correspondence**

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application # 75-078, submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etodolac Capsules 200 & 300 mg.

Reference is also made to a telephone conversation between Laurence Galvin (301 594-2290) of the Division of Bioequivalence and Tim Anderson and Lorraine Sachs of Taro. During this phone call, Mr. Galvin requested that we send a copy of the diskette which contains the individual plasma concentration from the bioequivalence study.

We have enclosed this diskette per Mr. Galvin's request. This diskette was inadvertently omitted from the original submission, and was forwarded separately via Federal Express on February 19, 1997 (see attached letter). However, according to Mr. Galvin, it was not received by the Division of Bioequivalence.

Thank you for your consideration in this matter.

Sincerely,

Lorraine W. Sachs, RAC
Senior Regulatory Affairs Scientist
Taro Pharmaceuticals U.S.A., Inc.

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April 1, 1997

NEW CORRESP

NC

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Att: Harvey Greenberg, HFD-615

75078

Reference: **Etodolac Capsules 200 & 300 mg**
**Telephone Amendment**

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etodolac Capsules 200 & 300 mg.

Reference is also made to a phone call from Harvey A. Greenberg of the Office of Generic Drugs (301 594-0315) on March 31, 1997 during which it was requested that we send an original signed 356h form for the above-referenced ANDA.

If there are any questions with regards to this response, please do not hesitate to contact me.

Cordially,

Timothy A. Anderson, M.S., M.B.A.
Vice President, Regulatory Affairs

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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

March 27, 1997

NEW CORRESP
NC

TARO

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

Reference: **Etodolac Tablets 400 mg**
**Telephone Amendment**

75078

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Etodolac Tablets 400 mg.

Reference is also made to a phone call from Harvey A. Greenberg of the Office of Generic Drugs (301 594-0315) on March 26, 1997 during which it was requested that we send a Patent Certification for a Paragraph II Certification and a revised Exclusivity Statement.

Enclosed please find the Patent Certification for a Paragraph II Certification (page S1), a revised Exclusivity Statement (pages S2 and S3), a revised 356h form specifying "Lodine Tablets" and correcting what first appeared as "Lodine Capsules" (page S4), and a completed current 356h form.

This completes our response to the Agency's phone call of March 26, 1997.

If there are any questions with regards to this response, please do not hesitate to contact me.

Cordially,

Timothy A. Anderson, M.S., M.B.A.
Vice President, Regulatory Affairs

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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

NEW CORRESP
NC

February 19, 1997

BIOAVAILABILITY

Office of Generic Drugs
CDER, Food and Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

**Re: ANDA for Etodolac Capsules, 200 and 300 mg**
**General Correspondence**

75078

Dear Sir/Madam:

Reference is made to the above mentioned ANDA which Taro Pharmaceuticals U.S.A., Inc. submitted to your office on February 14, 1997.

We inadvertently omitted the enclosed diskette which contains the individual plasma concentrations from the bioequivalence study.

We apologize for this oversight and request that you include this diskette with the bioequivalence working copy which is contained in the orange binders.

We are also including a revised FDA form 356h. This 356h includes the which was not listed on the 356h form submitted on February 14, 1997.

Thank you for your consideration in this matter.

Sincerely,

Lorraine W. Sachs, RAC
Senior Regulatory Affairs Scientist
Taro Pharmaceuticals U.S.A., Inc.

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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

February 14, 1997

Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville, MD 20855

Dear Sir/Madam:

**Re: ANDA for Etodolac Capsules, 200 & 300 mg**

Taro Pharmaceutical Industries Ltd. ("Taro") submits today an original, abbreviated new drug application (ANDA) seeking approval to market 200 & 300 mg Etodolac capsules which are bioequivalent to the listed drug, Lodine capsules, manufactured by Wyeth-Ayerst Laboratories pursuant to NDA 18-922.

This ANDA consists of 5 volumes. Taro is filing an archival copy (in blue folders) of the ANDA that contains all the information required in the ANDA, and a technical review copy (in red folders) which contains all the information in the archival copy with the exception of the Bioequivalence section (Section VI). In addition, a field copy for this ANDA is also submitted herewith (as Taro is located in Haifa Bay, Israel). Taro hereby certifies that the "field copy" is a true copy of the technical sections of the ANDA (also included is a copy of this letter, the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs). This "field copy" is contained in a burgundy folder.

In reviewing this ANDA submission, there are certain clarification points relevant to the entire ANDA submission that the reviewer should be aware of in order to facilitate the review. The clarifications directly follow this letter. Taro hopes these points can be kept in mind when reviewing this submission.

In accordance with the Patent Certification guidelines issued by the Agency, please refer to the signed Patent Certification.

Also, please find Taro's Certification of Compliance with the Generic Drug Enforcement Act of 1992, as well as the "field copy" certification, both located immediately after the 356h Application Form.

The Stability Commitment is located in Section XVII, and the signed certifications of compliance with current Good Manufacturing Practices is located in Section IX.



Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

Please note that our US agent, Taro Pharmaceuticals U.S.A., Inc., can be contacted at the following address:

Taro Pharmaceuticals U.S.A., Inc.
Five Skyline Drive
Hawthorne, NY 10532
Tel.: 914-345-9001
Attention: Mr. Timothy A. Anderson
Vice-President, Regulatory Affairs

Thanking you for your prompt handling of this submission.

Sincerely,

Timothy A. Anderson, M.S., M.B.A.
Vice President, Regulatory Affairs
Taro Pharmaceuticals U.S.A., Inc.