# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74879**

# CORRESPONDENCE

JUL 28 1997

ANDA 74-879

Elan Pharmaceutical Research Corporation
Attention: Roger Wayne Riley, R.Ph.
1300 Gould Drive
Gainesville GA 30504

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketoprofen Extended-release Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time. This letter supersedes the letter sent on 6/30/97.

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test should meet the following interim specifications:

| | **Amount Dissolved** |
|---|---|
| 1 Hours | not less than % and not more than % |
| 2 Hours | not less than % and not more than % |
| 4 Hours | not less than % and not more than % |
| 6 Hours | not less than % and not more than % |
| 10 Hours | not less than % |

   The interim specifications are based on the further review of the dissolution data on the bioequivalence lot. The final dissolution specifications will be set upon review of the dissolution data on at least 3 production batches.

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/

for Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-879

JUN 30 1997

Elan Pharmaceutical Research Corporation
Attention: Roger Wayne Riley, R.Ph.
1300 Gould Drive
Gainesville GA 30504

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketoprofen Extended-release Capsules 200 mg.

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| | **Amount Dissolved** |
|---|---|
| 1 Hours | not less than % and not more than % |
| 2 Hours | not less than % and not more than % |
| 4 Hours | not less than % and not more than % |
| 6 Hours | not less than % and not more than % |
| 10 Hours | not less than % |

   The interim specifications are based on the further review of the dissolution data on the bioequivalence lot. The final dissolution specifications will be set upon review of the dissolution data on at least 3 production batches.

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/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-879

OCT - 7 1997

Elan Pharmaceutical Research Corporation
Attention: Roger Wayne Riley, R.Ph.
1300 Gould Drive
Gainesville GA 30504

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Ketoprofen Extended-release Capsules 200 mg.

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

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test should meet the following interim specifications:

| | **Amount Dissolved** |
|---|---|
| 1 Hours | not less than % and not more than % |
| 2 Hours | not less than % and not more than % |
| 4 Hours | not less than % and not more than % |
| 8 Hours | not less than % and not more than % |
| 16 Hours | not less than % |

   The interim specifications are based on the further review of the dissolution data on the bioequivalence lot. The final dissolution specifications will be set upon review of the dissolution data on at least 3 production batches.

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/

Rabindra N. Patnaik, Ph.D.
Acting Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

D N

ANDA 74-879

OCT 31 1996

Elan Pharmaceuticals Research Corporation
Attention: Sharon L. Hamm, Pharm.D.
1300 Gould Drive
Gainesville GA 30504

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 Ketoprofen Extended-release Capsules, 200 mg.

Reference is also made to the letter from the Division of Bioequivalence dated October 9, 1996. That letter included incorrect recommendations for dissolution specifications for your product.

Please refer to the following corrected dissolution testing which should be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

| | **Amount Dissolved** | |
|---|---|---|
| 1 Hour | not less than % | and not more than % |
| 2 Hours | not less than % | and not more than % |
| 4 Hours | not less than % | and not more than % |
| 6 Hours | not less than % | and not more than % |
| 10 Hours | not less than % | and not more than % |
| 24 Hours | not less than % | |

These are tentative dissolution specifications. As more results are available, the Office will issue the final dissolution specifications of this product.

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/

Rabindra Patnaik,, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DW

ANDA 74-879

OCT - 9 1996

Elan Pharmaceuticals Research Corporation
Attention: Sharon L. Hamm, Pharm.D.
1300 Gould Drive
Gainesville GA 30504

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 Ketoprofen Extended-release Capsules 200 mg.

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

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 23 apparatus 2 (paddle) at 50 rpm. The test should meet the following specifications:

| | **Amount Dissolved** |
|---|---|
| 1 Hours | not less than [ ] % and not more than [ ] % |
| 2 Hours | not less than % and not more than % |
| 4 Hours | not less than % and not more than % |
| 6 Hours | not less than % and not more than % |
| 12 Hours | not less than [ ] % |

   This is a tentative dissolution specifications. As more results are available, the Office will issue the dissolution specifications of this product.

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 74-879

Elan Pharmaceutical Research Corp.
Attention: Sharon L. Hamm, Pharm.D.
1300 Gould Dr.
Gainesville, GA 30504-3947

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: Ketoprofen Extended-release Capsules, 200 mg

DATE OF APPLICATION: March 29, 1996

DATE OF RECEIPT: April 1, 1996

We also refer to our correspondence dated April 4, 1996.

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:

James Wilson
Project Manager
(301) 594-0310

Sincerely yours,

/S/ 4/24/96

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

ANDA 74-879
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, RSB /S/ 4/23/96 date
HFD-615/WRussell, CSO /S/ 4/24/96 date
HFD-623/VSayeed, Sup. Chem /S/ 4/25/96 date
File\x:\new\firmsam\Elan\ltrs&rev\74879ac.f
F/T hrw 4-12-96
ANDA Acknowledgement Letter!

ANDA 74-879

Elan Pharmaceutical Research, Corp.
Attention: Sharon L. Hamm, Pharm.D.
1300 Gould Drive
Gainesville, GA 30504

DEC 6 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated March 29, 1996 submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketoprofen Extended-release Capsules, 200 mg.

Reference is made to our not approvable letter of September 10, 1996.

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

B. LABELING DEFICIENCIES

1. CONTAINER:

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

b. Delete the following:

2. INSERT:

a. GENERAL COMMENTS

i. Revise to

Revise accordingly throughout the text of the insert labeling.

ii. Please distinguish between your section headings, subsection headings and sub-subsection headings. For example:

**CLINICAL PHARMACOLOGY**

**Pharmacokinetics**
*Elimination*
Special Populations
*Elderly*

b. DESCRIPTION

i. List the botanical source of starch.

ii. We note that [ ] is listed as an inactive ingredient. However, black S-1-8100HV appears in your Components and Composition statement. Please comment and/or revise.

iii. You have listed [ ] as an inactive ingredient, however "colloidal silicon dioxide" is listed in your Components and Composition statement. Please revise and/or comment.

iv. Each extended-release capsule, for oral administration, contains...

c. **CLINICAL PHARMACOLOGY**

i. **Pharmacodynamics**

Delete the second paragraph.

ii. **Pharmacokinetics**

A) *General*

Revise to read as follows:

The systemic availability ($F_s$) when the oral formulation is compared with IV administration is approximately 90% in humans. For 75 mg to 200 mg single doses, the area under the curve has been shown to be dose proportional.

Ketoprofen is >99% bound to plasma proteins, mainly to albumin.

B) *Absorption*

1) Delete the first paragraph, [ ]

2) Delete the text, "(See ... below)" from the second paragraph.

3) Delete the fourth paragraph, [ ]

4) Last paragraph

C)

Delete this subsection entirely.

D) ***Elimination***

1) First paragraph -

2) Second paragraph -

E) ***Special Populations***

1) *Elderly: Clearance and unbound fraction*

Second paragraph -

Last paragraph -

2) *Renally Impaired*

Start a new paragraph with the sentence, and revise to read as follows:

> No studies have been ... extended-release capsules. It is recommended that only the immediate release ketoprofen capsules be used to treat patients with significant renal impairment (See Individualization of Dosage).

3) *Hepatically Impaired*

Delete the first paragraph and revise

the second paragraph to read as follows:

> No studies have ... extended-release capsules. It is recommended that only immediate release ketoprofen be used to treat patients who have hepatic impairment and serum albumin levels below 3.5 g/dL (see Individualization of Dosage).

iii. **Clinical Trials**

A) *Rheumatoid Arthritis and Osteoarthritis*

Delete the second sentence of the first paragraph.

B)

Delete this subsection

iv. **Individualization of Dosage**

Revise this subsection to read as follows:

> In patients with significant renal impairment, immediate release ketoprofen should be used. In elderly patients, renal function may be reduced with apparently normal serum creatinine and/or BUN levels. Therefore, immediate release ketoprofen capsules are the recommended formulation of ketoprofen.
>
> It is recommended that for patients with impaired liver function and serum albumin concentration less than 3.5 g/dL, immediate release ketoprofen capsules rather than the extended-release capsules should be used. All patients with metabolic impairment, particularly those with both hypoalbuminemia and reduced renal function, may have increased levels of free (biologically active) ketoprofen and should be closely monitored. The dosage may be increased to the range recommended for the general population, if necessary, only after good individual tolerance has been ascertained.
>
> Because hypoalbuminemia and reduced renal function both increase the fraction of free drug (biologically active form), patients who

have both conditions may be at greater risk of adverse effects. Therefore, it is recommended that such patients also be started on lower doses of immediate release ketoprofen and closely monitored.

As with other nonsteroidal anti-inflammatory drugs, the predominant adverse effects of ketoprofen are gastrointestinal. To attempt to minimize these effects, physicians may wish to prescribe ketoprofen be taken with antacids, food, or milk. Although food delays the absorption (see CLINICAL PHARMACOLOGY), in most of the clinical trials ketoprofen was taken with food or milk.

Physicians may want to make specific recommendations to patients about when they should take ketoprofen in relation to food and/or what patients should do if they experience minor GI symptoms.

d. **PRECAUTIONS**

i. General

Penultimate paragraph, second sentence -

Patients on long-term treatment with NSAIDs, including ketoprofen, should have their hemoglobin or hematocrit checked if they develop signs or symptoms of anemia.

ii. Information for Patients

Delete the first sentence.

iii. Drug Interactions

A) Revise the second sentence of the first paragraph to read as follows:

B) *Antacids*

e. **ADVERSE REACTIONS**

i. First paragraph -

...835 immediate release ketoprofen treated...from 4 to 54 weeks and in 622 patients treated with ketoprofen extended-release capsules in trials lasting from 4 to 16 weeks.

ii. Second paragraph -

...symptoms. In crossover trials in 321 patients with rheumatoid arthritis or osteoarthritis, there was no difference in either upper or lower gastrointestinal symptoms between patients treated daily with 200 mg of ketoprofen extended-release capsules or 75 mg of immediate release ketoprofen t.i.d. (225 mg/day). Peptic ulcer...

f. **DOSAGE AND ADMINISTRATION**

i. Rheumatoid Arthritis and Osteoarthritis

Revise this subsection to read as follows:

> The recommended starting dose of extended-release ketoprofen in otherwise healthy patients is 200 mg administered once a day. A smaller dose should be utilized initially in small individuals, in debilitated or elderly patients. Ketoprofen extended-release capsules are recommended for chronic treatment of those patients whose optimum dose is 200 mg/day. The recommended maximum daily dose of ketoprofen is 300 mg/day.

ii. Delete the subsection [ ] since this drug product is not indicated for these conditions.

g. **HOW SUPPLIED**

i. Add the statement, "Keep tightly closed".

ii. Include the 10 digit NDC number for each package size.

Revise your package insert labeling, as instructed above, and submit in draft as a labeling amendment to your application. 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.

To facilitate review of your next submission and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with the differences annotated.

Sincerely yours,

/S/ 12/6/96

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

cc: ANDA 74-879
Dup/Division File
HFD-613/JWhite/CPark/JGrace (no cc)
HFD-600/RF
njg/12/4/96/x:/new\firmsam\Elan\ltrs&rev\74879lo.
Letter out

ANDA 74-879

Elan Pharmaceutical Research Corporation
Attention: Sharon L. Hamm, Pharm. D.
1300 Gould Dr.
Gainesville, GA 30504-3947

SEP 10 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated April 1, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ketoprofen Extended-release Capsules, 200 mg.

Reference is also made to your correspondence dated April 4, 1996.

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

A. Chemistry Deficiencies

B. Labeling Deficiencies:

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:

a. Since this drug product is not covered by an official monograph in the USP, the analytical methods must be validated by an FDA field laboratory. Samples for the methods validation will be requested by the FDA at the appropriate time.

b. The dissolution specifications for the drug products will be reviewed and established by the Division of Bioequivalence.

c. All DMFs referenced in this ANDA have to be found satisfactory at the time of approval of the ANDA. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality. Any unsatisfactory review/evaluation will delay the approval of the ANDA.

d. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs 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 MAJOR 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,

/S/ - 9/9/96

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

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

September 5, 1997

YOA ORIG AMENDMENT

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 74-879: Ketoprofen Extended Release Capsules 200mg - Response to Minor Amendment Telefax Deficiency**

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Ketoprofen Extended Release Capsules 200mg. In addition, reference is made to the Minor Amendment telefax deficiency from the agency dated May 23, 1997.

We regret the delay in responding to the minor amendment telefax, however, we have had numerous interactions with the Division of Bioequivalence in an attempt to finalize the dissolution specifications, in advance of updating the corresponding analytical specifications and methods. Although we do not as yet have final concurrence on the dissolution specifications, we are submitting this amendment with the understanding that the Division of Bioequivalence is prepared to issue final specifications within the week. Further, from our teleconference on Wednesday, September 3, 1997, Dr. Patniak agreed to telephone the CMC reviewer and make him aware of what has transpired within the division (beyond Elan's control) since October 1996 that has led to this delay in issuing final specifications. We, therefore, respectively request that the CMC review be expedited (with receipt of this response) as a result of the delay.

In light of this background, we are enclosing herein revised analytical protocols for Ketoprofen 200mg ER Capsules (Attachment 1), Ketoprofen SR Beads (Attachment 2) and Ketoprofen SR Beads for Encapsulation (Attachment 3). Included within the attachment after each protocol is a single page summary with details of revisions which include calibration of the dissolution apparatus, conformance to USP XXIII for "sinkers" as part of the dissolution technique, detailed instructions for preparation of media, encapsulation of beads prior to analytical testing, an alternate automated dissolution method, etc.

RECEIVED

SEP 08 1997

GENERIC DRUGS

In addition, we are including in Attachment 4 an updated stability report which provides data through 18 months for the pivotal batch (lot # C5J1932) at controlled room temperature, which is in addition to the accelerated data and corresponding room temperature data through 3 months previously submitted in the original ANDA. A summary of this same report was provided in correspondence to the Division of Bioequivalence on August 20, 1997.

We would also like to clarify that within the application as previously submitted, it was our intention that either Élan laboratories (Athlone) or Danbury Pharmacal in New York could be equally qualified for the conduct of any QC testing or supporting stability testing, as defined in the accompanying finished product specs and methods.

We trust that the enclosed update provides additional clarity with respect to the current analytical methods, specifications, testing laboratories, and product stability. Further, it is our hope that the reviewer can now expeditiously complete review of this application given that the DMF holder has responded in full, the labeling review is complete, and biostudies have been found acceptable. The only remaining issue is resolution of final dissolution specifications which we expect to receive within the week and we will notify you immediately upon receipt.

If you have any questions regarding the contents of this submission, please do not hesitate to contact me.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, N. America Regulatory Affairs

cc Rabindra Patniak

RWW/bh

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

VIA TELEFAX:
September 9, 1997

BIOAVAILABILITY

Rabindra Patniak, Ph.D.
Division of Bioequivalence
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 74-879: Ketoprofen Extended Release Capsules 200mg - Correspondence**

Dear Dr. Patniak:

As requested in our last telephone conversation, we have undertaken additional dissolution testing for Ketoprofen Extended Release Capsules 2, in an effort to more broadly characterize the profile beyond the initial pivotal clinical lot performance. We are enclosing as Attachment 1 a profile plot of the dissolution results from four additional runs. This incorporates the pivotal bio-batch (Lot #C5J1932) which is approximately 18 months old, along with results from three recently manufactured lots (DD1202, DD1209, DD1063; in addition to being a manufactured lot, DD1063 is also a process validation lot). Recognizing the desire to target the dissolution specification range around the mean of the dissolution results, we have plotted the data with this in mind. Upon review of the data, we would recommend a dissolution specification which addresses this need, while recognizing the necessary flexibility to accommodate routine manufacturing, analytical variability, and product aging as follows:

| | |
|---|---|
| Hour 1: | [ % |
| Hour 2: | % |
| Hour 4: | % |
| Hour 8: | % |
| Hour 18: | NLT __% |

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SEP 10 1997
GENERIC DRUGS

For a more detailed review of the individual and mean results, please refer to the data display in Attachment 2.

As previously discussed, we will follow up with you directly to discuss these findings and to agree on a final specification. We had preferred to meet with you at your office to discuss these data/specifications, however in the interest of time and because of the urgency we request a teleconference with you and the reviewer to discuss these data prior to the issuance of final specifications. Thank you.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

October 7, 1997

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 74-879: Ketoprofen Extended Release Capsules 200mg-Dissolution Specifications Issued by Division of Bioequivalence/Analytical Protocols**

Dear Mr. Sporn:

Reference is made to our pending Abbreviated New Drug Application for Ketoprofen Extended Release Capsules 200mg, (ANDA 74-879). In addition, reference is made to the submission to your office dated September 5, 1997 which provided for revised analytical protocols.

At the time of the aforementioned submission we were still in discussion with Dr. Patniak in the Division of Bioequivalence regarding dissolution specifications. We have now received written confirmation of these specifications and a copy of the correspondence is provided under Attachment 1.

Subsequent to receipt of this correspondence we have now incorporated these dissolution specifications into the analytical protocols previously submitted on September 5 and they are provided as follows:

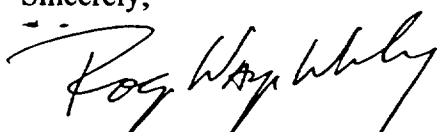
Attachment 2: Ketoprofen 200mg ER Capsules (rev 6)

Attachment 3: Ketoprofen SR Beads (rev 5)

Attachment 4: Ketoprofen SR Beads for Encapsulation (rev 4)

If your have any questions regarding the contents of this submission, please do not hesitate to contact me.

Sincerely,



Roger Wayne Wiley, R.Ph
Director, North America Regulatory Affairs

élan

March 29, 1996

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

**RE: Ketoprofen Extended-Release Capsules 200 mg**
**Original ANDA Submission**

Dear Mr. Sporn:

Élan Pharmaceutical Research Corporation is enclosing herein an original Abbreviated New Drug Application (ANDA) for a 200 mg Ketoprofen Extended-Release Capsule that is bioequivalent to the listed drug, ORUVAIL®, manufactured by Wyeth-Ayerst pursuant to NDA 19,816. This application is being submitted on behalf of Élan Corporation, plc of Athlone, Ireland.

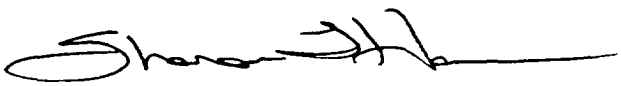
This ANDA consists of twelve volumes. The archival copy (blue jacket) contains all the information required in the ANDA and a technical review copy (red jacket) which contains all of the information in the archival copy with the exception of the Bioequivalence section (VI). The Bioequivalence section (VI) is provided in orange jackets. Additional copies (4) of the Methods Validation Package are also included and identified accordingly.

Furthermore, this letter certifies that concurrent with the filing of this ANDA, a true Field Inspection Copy of the chemistry/technical section of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is included with the submission to be held at the Agency's Documentation Management Branch until requested. The manufacture of Ketoprofen Extended Release Capsules will be at Elan's Athlone, Ireland facility.

*élan pharmaceutical research corp.*
1300 Gould Drive, Gainesville, Georgia 30504-3947, USA
Telephone: (770) 534-8239, Fax: (770) 534-8247

Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely yours,



Sharon L. Hamm, *Pharm. D., R.Ph.*
*Head, North America Regulatory Affairs & Compliance*

SH:tf

K:/ketoprof/subm/fda0329.doc

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

**VIA FAX (301) 594-0180**

October 14, 1997

NEW CORRESP
NC

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

**RE: ANDA 74-879: Ketoprofen Extended Release Capsules 200 mg**
**Commitment for Methods Validation**

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application for Ketoprofen Extended Release Capsules 200 mg (ANDA 74-879).

Elan Pharmaceutical Research Corporation commits to cooperate with the Agency to resolve method validation issues that may be revealed to the Office of Generic Drugs during the review of the methods validation package.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

RECEIVED
OCT 15 1997
GENERIC DRUGS

élan pharmaceutical research corp.

1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

November 25, 1997

BIOAVAILABILITY
11/28/97

ORIG AMENDMENT
N/AB

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER
Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 74879: Ketoprofen Dissolution Data For Lot DD1212/Telephone Amendment**

Dear Mr. Sporn:

Attached is the dissolution data requested by Allen Rudman and faxed to the Division on November 19, 1997.

In the event you need to contact me, I can be reached at (770) 538-6360 or telefax (770) 531-0835.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

Attachments

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1300 Gould Drive
Gainesville, Georgia 30504, USA
Telephone (770) 534-8239
Fax (770) 534-8247

August 20, 1997

NEW CORRESP BIOAVAILABILITY

Rabindra Patniak, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Metro Park North II
Document Control Room, Room 150
7500 Standish Place
Rockville, MD 20855-2773

**RE: ANDA 74-879; Dissolution Specifications for Ketoprofen Extended Release Capsules 200mg**

Dear Dr. Patniak

Reference is made to our abbreviated new drug application for Ketoprofen Extended Release Capsules 200mg. In addition, reference is made to your correspondence dated July 28, 1997 regarding revised dissolution specifications for this drug product (Attachment I).

We believe there is an error in the specifications provided in the aforementioned correspondence. The specifications established for the 1, 2 and 4 hour time points are correct and representative of the data from the pivotal bio-batch (Lot # C5J1932), however, the specification of "not less than % and not more than %" at 6 hours is not reflected in the data provided for this same batch. *In fact, the pivotal ANDA batch fails to meet this specification in all packages at all accelerated stability stations.* This dissolution data was presented in the original ANDA submission (Vol 4/pages 462, 468 and 480) is provided in Attachment 2 of this submission for your reference.

As previously stated we concur with your assessment of specifications for the 1, 2, and 4 hour time points as stated in your letter dated July 28, 1997 (Attachment 1) as this is reflective of the pivotal bio-batch. For dissolution specifications at the 6 and 10 hour intervals we refer to your letter of October 31, 1996 (Attachment 3). Our review indicates that these specifications are reflective of the data presented in the ANDA with the exception of the 6 hour specification which is more appropriate as "not less than __% and not more than __%."

The resulting specifications are as follows:

| | **Amount Dissolved** | |
|---|---|---|
| 1 Hours | not less than % and not more than % | (per agency letter of 7/28/97) |
| 2 Hours | not less than % and not more than % | (per agency letter of 7/28/97) |
| 4 Hours | not less than % and not more than % | (per agency letter of 7/28/97) |
| 6 Hours | not less than __% and not more than % | (revised from agency letter of 10/31/96) |
| 10 Hours | not less than % and not more than % | (per agency letter of 10/31/96) |

Finally, we wish to provide additional data which further supports these specifications. In addition to the pivotal batch dissolution release study provided in the original ANDA, Elan and the commercial distributor Schein, have now generated dissolution data for up to 18 months from the pivotal stability program as reported in Attachment 4 herein. We have also generated initial release dissolution data for 13 full scale lots which have been manufactured as part of the process validation/inventory management phase of this products development. A table which summarizes the dissolution data from these 13 lots is provided in Attachment 5.

A review of the stability and subsequent full scale manufactured lots dissolution performance provides increased assurance of consistent in-vitro release performance for which the proposed revised specifications would be appropriate.

We trust that this additional data will document the appropriateness of the proposed revised specifications, beyond the profile of the pivotal bio-batch. In the event there is a need for further iterations of these proposed specifications and given the numerous interactions and subsequent delay of approval because of this issue, we request a meeting between your division and Elan be held to discuss any further proposals. Thank you in advance for your consideration of these data and the proposed specifications.

Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are 770 534-8239 (phone) and 770 531-0835 (fax).

Sincerely,

PP. Helen Ryan

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

élan pharmaceutical research corp.

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May 28, 1997

N/Am

AMENDMENT

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD. 20855-2773

**RE: MINOR AMENDMENT**
**ANDA 74-879: Ketoprofen Extended-Release Capsules 200 mg**
**Final Printed Labeling/Response to Labeling Deficiencies**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Ketoprofen Extended-release Capsules 200 mg (ANDA 74-879) dated March 29, 1996. In addition, reference is made to the labeling deficiencies letter dated December 6, 1996 and most recently the labeling deficiency telefax dated May 12, 1997 (Attachment I).

Provided in Attachment II are revised final printed labeling (container labels and package insert) which incorporates the changes advised in the telefax dated May 12, 1997.

Provided in Attachment III are documents which compare the revisions to labeling previously revised per the December 6, 1996 correspondence and now per the telefax of May 12, 1997 from OGD.

Twelve sets of final printed labeling (container labels 100's, 500's and 1,000's and package inserts) are provided in the red (CMC) jacket and three sets of final printed labeling are provided in the blue (archives) and navy blue/Mr. Chan Park (desk copy) jackets.

RECEIVED

MAY 29 1997

In the event you need to contact me I can be reached at (770)538-6360 or telefax (770) 531-0835.

Sincerely

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

K:\KETOPR97\SUBM\FDA0528A.DOC5/28/975:05 PMMAB

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March 12, 1997

NDA ORIG AMENDMENT
N/AC

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

RE: NDA #74-879: Ketoprofen Extended Release Capsules 200mg
Minor Chemistry Amendment

Dear Sirs:

Reference is made to our Abbreviated New Drug Application for Ketoprofen Extended Release Capsules 200 mg submitted March 31, 1996, and currently under review in your Division.

We are amending this application as a result of notification received from[ ](see attached correspondence), the drug substance supplier, that a revised DMF has been submitted which incorporates an alternate process for Ketoprofen production, providing an improved organic volatile impurity profile, yet with equivalent physico-chemical characteristics to the original process.

Although[ ]has indicated this is an alternate method of synthesis, it would be our intention to routinely acquire the improved process material, due to the improvement in impurity profile. Furthermore, we are aware that Ketoprofen bulk drug substance supplied by[ ] to Élan and utilized in the manufacture of drug product for the pivotal biostudy and now ongoing process validation incorporate drug substance manufactured by the alternate method.

In addition, Élan has conducted physico-chemical characterization of Ketoprofen drug substance lots received from[ ](produced by both methods) and have confirmed their equivalency.

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As a result of this background we request incorporation of this process revision as a minor amendment to this application.

Thank you.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

K:\KETOPROF\SUBM\FDA22197.DOC3/12/97MAB

élan

December 20, 1996

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

**RE: ANDA 74,879/Classification of Chemistry Amendment**

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated April 1, 1996 for Ketoprofen Extended-release Capsules 200mg (ANDA 74-879). In addition, reference is made to the deficiency letter for chemistry dated September 10, 1996 and Elan's response to these questions dated November 8, 1996.

The purpose of this correspondence is to request consideration by the agency to re-classify the aforementioned deficiency letter and corresponding response from a **MAJOR** to a **MINOR** amendment. It appears that the original estimate of agency review time was calculated based on an expectation that there would be submission of data for review in response to a majority of the questions. We believe the actual review time required is considerably less than the original estimate based on the fact that a number of the responses actually required no additional data. Specifically:

> Question 6, which requested additional technical information for [ ] in the container/closure system used for packaging of drug product, is answered by a statement confirming that no [ ] are used in packaging of the drug product.

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Question 7, which requested clarification of the batch number numbering system versus use of a control number, is answered in a single paragraph by defining the use of the control and batch numbering systems and does not involve the submission of data or corrective material.

Question 4, which recommended the addition of a specification for content and particle size for ethylcelluose required Elan to either comply with the recommendation or provide explanation as to why compliance wasn't practical. This response is provided within two paragraphs of text.

Question 2, regarding the statement of composition for the gelatin capsules along with CFR references, is answered by inclusion of a capsule certificate of analysis and copies from the CFR of relevant citations for the components.

Questions 3, 5 and 8, involved the addition or updating/revision of specifications to analytical protocols.

Questions 9 and 10 required addition of an identification test to the analytical protocol (as recommended) and submission of a Methods Validation report for the analysis of the related compound, 2-(3-carboxyphenyl) propinic acid.

Finally, the response to question number 1 required a detailed explanation for the ranges of excipients in the manufacture of production batches.

To reiterate, we can understand the original estimate for review as **MAJOR** based on the number of questions, however, we believe the time required for a chemist's review is significantly less than the original estimation given the fact that the majority of questions ultimately required a response or clarification and no new or additional data was submitted. Therefore, we respectfully request that the amendment be reclassified as a **MINOR** amendment (effective receipt date of this letter).

Your attention to this matter is appreciated. I can be contacted by telephone at (770) 538-6360 or telefax (770) 531-0835 if necessary.

Sincerely,

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

élan

December 18, 1996

NDA ORIG AMENDMENT

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Document Control Room, Room 150
7500 Standish Place
Rockville, MD. 20855-2773

**RE: ANDA 74-879: Ketoprofen Extended-Release Capsules 200mg**
**Response to Labeling Deficiencies**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Ketoprofen Extended-release Capsules 200mg (ANDA 74-879) dated March 29, 1996. In addition, reference is made to the labeling deficiences letter dated December 6, 1996 (Attachment I)

Attached are the revised (4 copies) draft labels and labeling for the drug product (Attachment II). In addition, a side by side comparison of the original Élan labeling compared to the revised labeling (per OGD December 6, 1996 recommendations) is also provided (Attachment III).

In regards to the two comments regarding (Agency letter: b. DESCRIPTION - comments ii and iii) S-1-8100HV and [ ] the labeling has been revised to correct these errors.

In addition, we have revised the labeling as you have requested and trust that our revised use of type fonts regarding section headings and sub-headings are now acceptable.

In the event you need to contact me I can be reached at (770)538-6360 or telefax (770) 531-0835.

Sincerely

Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

RWW/bh

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élan

November 22, 1996

Mr. Douglas Sporn
Office of Generic Drugs (HFD-615)
CDER Food and Drug Administration
Metro Park North II
Document Control Room, Room 150
7500 Standish Place
Rockville, MD. 20855-2773

**RE: ANDA 74-897: Ketoprofen Extended-release Capsules 200mg**
**Division of Bioequivalence Proposed Dissolution Specifications**

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application for Ketoprofen Extended-release Capsules 200mg (ANDA 74-897). In addition, reference is made to your letter dated October 31, 1996 (attached) which provided your tentative dissolution specifications proposed for this product.

We request further review and consideration to revise the proposed dissolution specifications presented in the aforementioned, October 31, 1996, correspondence. Specifically, we request that the agency re-consider 1) the necessity of dissolution specifications at 6 (six) time points and 2) the impact of the proposed one-hour and two-hour dissolution specifications. Discussion of these points follows:

1) Necessity of Dissolution Specifications at six time points:

The dissolution timepoints provided in the original submission of the Ketoprofen ANDA proposed controlling the product based on five timepoints which is consistent with typical USP 23 monographs and other applications approved by FDA . Please note that the tentative specifications in your communication dated October 9, 1996 proposed five timepoints in accordance with standard requirements for modified release formulations, however, in your second communication dated October 31, 1996 the proposed specifications included a total of six timepoints in the specifications.

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1300 Gould Drive, Gainesville, Georgia 30504-3947, USA
Telephone: (770) 534-8239. Fax: (770) 534-8247

The inclusion of a sixth timepoint represents a significant and unnecessary burden in terms of analytical testing and we would suggest that five timepoints are standard and adequate. With the addition of your requested one-hour timepoint, fifty-percent of dissolution is accounted for with the 1, 2 and 4 hour sampling points. We propose to delete sampling at the 6th hour and complete the profile with a 10th and 24 hour sample.

We wish to point out that dissolution testing is performed both on individual component batches prior to blending, on the blend of individual components prior to encapsulation and on bulk capsule product prior to packaging. Consequently the proposed sampling at five timepoints (1,2,4,10 and 24 hours) in addition to the in-process testing of sustained release beads and bead blends provides adequate characterization of the early, mid and late stages of the dissolution curve profile.

2) Impact of the proposed one-hour and two-hour dissolution specifications:

We are concerned that the tentative dissolution ranges particularly at the one and two hour timepoints proposed in your correspondence dated October 31, 1996 are obviously much narrower that the standard __% ranges which are routinely applied to release specifications. In addition, we would also point out that the one hour value has not been part of our specifications up until now and we do not have a substantive database on which to rely.

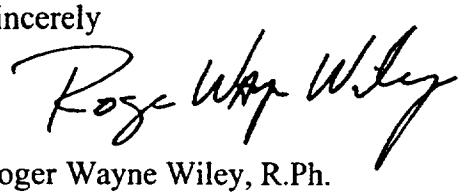
Therefore, we propose that the tentative specifications at the one and two hour time points be revised to __ % at the first hour and __ % at the second hour. We find the tentative specifications at 4, 10 and 24 hours as proposed in the aforementioned correspondence acceptable.

In summary, based on the above points we propose the following dissolution specifications for consideration taking into account the 1-hour timepoint and a total of five timepoints which are considered adequate to control the product:

| **Timepoints (hours)** | **Specification(%)** |
|---|---|
| 1 | [ |
| 2 | |
| 4 | |
| 10 | |
| 24 | NLT _] |

Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely



Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

Attachments

élan

November 8, 1996

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

NDA ORIG AMENDMENT
AC

**RE: ANDA 74-879/Major Amendment/Response To Chemistry Deficiency**

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated April 1, 1996 for Ketoprofen Extended-Release Capsules, 200 mg. (ANDA 74-879). In addition, reference is made to the deficiency letter for chemistry dated September 10, 1996.

We have responded to each of the deficiencies cited in the aforementioned letter in a question/answer format with FDA questions in italics and Elan's response in bold standard type.

A. Chemistry Deficiencies

*élan pharmaceutical research corp.*
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Telephone: (770) 534-8239. Fax: (770) 534-8247

Redacted 9

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secret and/or

confidential

commercial

information

Chem

B. Labeling Deficiencies:

*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.*

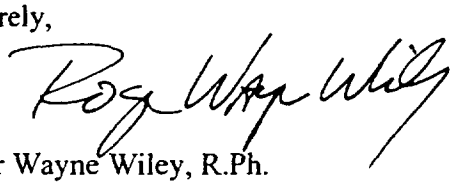
**The deficiency letter instructs that our response should incorporate a response to the labeling deficiencies, however, correspondence on labeling deficiencies has not yet been received.**

**I contacted Mr. Jim Wilson, Program Support, for advice on how to proceed. Mr. Wilson advised that we could go ahead and submit our response to the chemistry deficiencies and respond separately to the labeling deficiencies when they arrive.**

**In addition, we acknowledge comments a-d provided at the close of the September 10, 1996 correspondence.**

**Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are (770 534-8239 (phone) and (770) 531-0835 (fax).**

Sincerely,



Roger Wayne Wiley, R.Ph.
Director, North America Regulatory Affairs

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NEW CORRESP

September 16, 1996

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

**RE: ANDA #74-879: Ketoprofen Extended-Release Capsules 200 mg**
**Not Approvable Correspondence**

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application for Ketoprofen Extended-Release Capsules 200 mg and your "not approvable" letter dated September 10, received by us today. We have reviewed your noted deficiencies however, understand that these cannot be responded to until we receive under separate cover any labeling deficiencies relative to this pending application. In accordance with the provisions of 21 CFR 314.120, we hereby notify you of our intent to amend the application to address the noted chemistry deficiences and any future labeling deficiencies in full. We understand that this amendment constitutes an agreement to extend the review period for this application. Thank you for your review efforts thus far.

Sincerely,

Sharon L. Hamm, Pharm. D., R.Ph
Vice President, Regulatory Affairs

SH/bh

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k:/ketoprof/subm/fda91696.doc

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NC

NEW CORRESP

April 4, 1996

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

**RE: ANDA #74-879: Ketoprofen Extended-Release Capsules 200 mg**
**New Correspondence**

Dear Mr. Sporn:

Reference is made to our recently submitted ANDA for Ketoprofen Extended-Release Capsules 200 mg. As requested by your staff, we are enclosing herein a revised debarrment statement which incorporates "affiliated persons", along with certification for Élan employees. An original and two copies of the revised certification is enclosed.

Thank you.

Sincerely yours,

Sharon L. Hamm, *Pharm. D., R.Ph.*
*Head, North America Regulatory Affairs & Compliance*

SH/bh

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***élan pharmaceutical research corp.***
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élan

March 29, 1996

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

APR 0 1 1996

**RE: Ketoprofen Extended-Release Capsules 200 mg**
**Original ANDA Submission**

Dear Mr. Sporn:

Élan Pharmaceutical Research Corporation is enclosing herein an original Abbreviated New Drug Application (ANDA) for a 200 mg Ketoprofen Extended-Release Capsule that is bioequivalent to the listed drug, ORUVAIL®, manufactured by Wyeth-Ayerst pursuant to NDA 19,816. This application is being submitted on behalf of Élan Corporation, plc of Athlone, Ireland.

This ANDA consists of twelve volumes. The archival copy (blue jacket) contains all the information required in the ANDA and a technical review copy (red jacket) which contains all of the information in the archival copy with the exception of the Bioequivalence section (VI). The Bioequivalence section (VI) is provided in orange jackets. Additional copies (4) of the Methods Validation Package are also included and identified accordingly.

Furthermore, this letter certifies that concurrent with the filing of this ANDA, a true Field Inspection Copy of the chemistry/technical section of the ANDA (including a copy of the 356h form and a certification that the contents are a true copy of those filed with the Office of Generic Drugs) is included with the submission to be held at the Agency's Documentation Management Branch until requested. The manufacture of Ketoprofen Extended Release Capsules will be at Elan's Athlone, Ireland facility.

*élan pharmaceutical research corp.*
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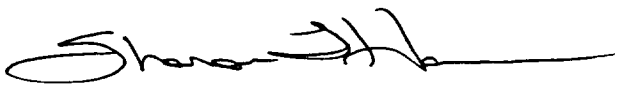
Telephone: (770) 534-8239. Fax: (770) 534-8247

Please direct any written communications regarding this ANDA to the undersigned or Helen Ryan at the above address. If you need to call or fax me, my numbers are (770) 534-8239 (phone) and (770) 531-0835 (fax).

Sincerely yours,



Sharon L. Hamm, *Pharm. D., R.Ph.*
*Head, North America Regulatory Affairs & Compliance*

SH:tf

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