CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74879

ADMINISTRATIVE DOCUMENTS

MINUTES OF PHONE CALL

DATE: October 28, 1997

SUBJECT: ANDA 74-879, Ketoprofen ER caps

ORGANIZATION: Elan

PARTICIPANTS: Allen Rudman
Roger Wiley
Sharon Hamm

Elan was contacted and asked to make the following amendments to their application:

1. Stability commitment from Elan similar to the one supplied by Danbury. Elans current protocol allows expiry changes as war rented and does not agree to withdraw failing batches

The firm agreed to send in a new commitment that matches Danbury's.

2. Additional data or explanation to support the three month expiry in the 88L (6 L test container) keg as the current data indicates that the bio batch fails the dissolution spec. at 8 hr at one and two months.

The firm agreed to provide an explanation and additional data based on the current dissolution work that they have performed.

3. A commitment from Danbury to perform identification and visual inspection testing on the capsules in the kegs to ensure that product is correctly labeled and that there is no significant crushing of capsules during shipment.

The firm agree to this.

4. The proposed formulation contains ranges for PVP and ethyl cellulose which are release controlling excipients. This needs to be changed to a single target for the excipients or there needs to be data to support the equivalency of the product formulation at the extremes of the ranges.

The firm said that they will submit an updated formulation with a single target for the all the excipients. They said that based on the validation batches they have already made that they can do this.

The firm will submit a telephone amendment within the next few days.

MINUTES OF PHONE CALL

DATE: October 28, 1997

SUBJECT: ANDA 74-879, Ketoprofen ER caps

ORGANIZATION: Elan

PARTICIPANTS: Allen Rudman
Roger Wiley
Sharon Hamm

Sharon Hamm called and asked if I had seen the November 11, 1996 amendment addressing this question of excipient ranges for PVP and ethyl cellulose which are release controlling excipients. I informed her that I had but that there needs to be either a single target for the excipients or to be data to support the equivalency of the product formulation at the extremes of the ranges. There does not appear to be a correlation and therefore it is not possible to say whether the the product produced at the extremes of the ranges would be bioequivalent.

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

ANDA Number: 74-879 Date of Submission: May 28, 1997

Applicant's Name: Elan Pharmaceutical Research Corp.

Established Name: Ketoprofen Extended-release Capsules 200 mg

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

Do you have 12 Final Printed Labels and Labeling? Yes (I have checked vol.2.1)

Container Labels: 200 mg (100's, 500's, and 1000's)

Satisfactory in FPL as of 5/28/97 submission

Professional Package Insert Labeling:

Satisfactory in FPL as of 5/28/97 submission

Revisions needed post-approval:

1. CONTAINER

   Revise the storage temperature statement to read Controlled Room Temperature

2. INSERT

   a. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics - General

         Add the following as the first paragraph:

ii. Individualization of dosage - First paragraph, first sentence:

b. ADVERSE REACTION - Fourth paragraph, second sentence:

Delete

c. HOW SUPPLIED

See comment under CONTAINER.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Oruvail®

NDA Number: 19-816

NDA Drug Name: Oruvail®

NDA Firm: Wyeth-Ayerst Co.

Date of Approval of NDA Insert and supplement #: S-002, approved 2/8/95
Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Oruvail®

FOR THE RECORD:

1. Review based on the labeling of Oruvail® (Ketoprofen Extended-release Capsules): Wyeth-Ayerst Laboratories, Inc.; Approved February 8, 1995). This is a **combined** insert with Orudis® (Ketoprofen Immediate-release Capsules.

2. Refer to the "FOR THE RECORD" made at the time of he last review of this application and signed by Charlie Hoppes, Chan Park and team leader John Grace in April, 1997.

PLEASE NOTE: (From the previous review)

- **This is the first generic application for Ketoprofen Extended-release capsules.**

- **The model for ketoprofen is a <u>combined</u> insert for both the immediate & controlled release capsules.**

Therefore portions of the labeling for this ANDA differ from the RLD & from the mark-up copy of the model, [which was the basis for a model for the immediate release product].

- This ANDA is for the extended release drug product only, therefore some of the text referring to the immediate release drug product was omitted.

- The mark-up copy of the model in the file folder is for the immediate release drug product. Some of the same text marked "to omit" was also omitted for the extended release drug product. However some of the text was retained since it was drug product specific for the extended release capsule.

- Some of the editorial changes were based on the labeling review for Mylan's immediate release drug product, ANDA 74035na2.1.

- Once this labeling review has been finalized, then a separate model for the "extended-release drug product" can be marked-up for the file folder.

3. The text describing the usage or conditions for which this extended-release product is not indicated has been deleted under DOSAGE AND ADMINISTRATION).

4. Patent/exclusivity's:

Orange Book/17th Ed.- [supplement#2]

No Patent or Exclusivity.

The firm's exclusivity certification statement is accurate. [Vol.B1.1, section III].

5. Storage Conditions:

Insert-
NDA: Store at room temperature, approximately 25°C (77°F). Keep tightly closed.

ANDA: Store at controlled room temperature 20° - 25°C (68° -77°F).

Container-
NDA: Store at room temperature, approximately 25°C (77°F). Keep tightly closed.

ANDA: Store at controlled room temperature 20° - 25°C (68° -77°F). Keep tightly closed.

[See comment under container for pos-approval revision].

6. Dispensing Recommendations:

NDA: Dispense in a tight container.

ANDA: Dispense in a tight, light-resistant container with child-resistant closure.

7. Product Line:

RLD:	100's & unit dose 100's
ANDA:	100's, 500's & 1000's

8. Closure:

100's, 500's & 1000's: non-CRC

9. The capsule imprints listed in the HOW SUPPLIED section are consistent with the firm's stability report. Vol.B1.4, p.425

10. Inactive Ingredients:

The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's composition statement [Vol.B1.2, section VII].

11. **Further revision** considered after "FOR THE RECORD" signed by Charlie Hoppes, Chan Park and team leader John Grace in April, 1997.

CLINICAL PHARMACOLOGY

a. Pharmacokinetics - General

Add the following as the first paragraph:

[redacted]

b. Individualization of dosage - First paragraph, first sentence:

[redacted]

c. Include a part of the first sentence of the third paragraph as follows.

Review cycle: #3 (FPL)

Primary Reviewer: Chan Park /S/ **Date: June 18, 1997**

Secondary Reviewer: Charlie Hoppes **Date:**

Team Leader: John Grace **Date:** 6/23/97

/S/ for John Grace

cc:

ANDA: 74-879
DUP/DIVISION FILE
HFD-613/CPark/CHoppes/JGrace (no cc)
njg/6/20/97/X:\NEW\FIRMSAM\ELAN\LTRS&REV\74879AP.L
Review

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

ANDA Number: 74-879 Date of Submission: December 18, 1996

Applicant's Name: Elan Pharmaceutical Research Corp.

Established Name: Ketoprofen Extended-release Capsules 200 mg

Labeling Deficiencies:

1. CONTAINER - 100's, 500's and 1000's

   We encourage you to revise the storage temperature statement to indicate a temperature range rather than an approximation.

2. INSERT

   a. GENERAL

      Revise to read [ ] throughout text. [hyphenated]

   b. DESCRIPTION

      You have listed both [ ] and "colloidal silicon dioxide" as inactive ingredients. However, only "colloidal silicon dioxide" is found in your Components and Composition statement. Please revise and/or comment.

   c. CLINICAL PHARMACOLOGY

      i. Pharmacokinetics

         A) General

            Delete the last paragraph.

         B) Absorption

            1) First paragraph - Revise to read as follows:

               [ ]

2) Second paragraph:

Delete

3) Delete the third paragraph.

4) Delete where it first appears in the penultimate paragraph.

5) Last paragraph - Revise to read as follows:

C) Multiple dosing

1) Upon further review, add this subsection immediately after the subsection and include the following text as the first paragraph:

2) Revise the table appearing in the draft labeling you have submitted on March 29, 1996, to include only part of the table specific to the ketoprofen extended-release capsules and footnote. Also, revise the table title to read

D) Metabolism - Paragraph 1, sentence 3:

...(see CLINICAL PHARMACOLOGY, *Special Populations*: Renally impaired).

E) Special Populations (Elderly: Clearance and unbound fraction)

1) Delete [redacted] from the second paragraph.

2) Delete the last paragraph.

F) Special Populations (Hepatically impaired)

Upon further review, include the first paragraph as you had proposed in the draft insert labeling submitted on March 29, 1996. However, please replace [redacted] in the first sentence with [redacted]

ii. Clinical Trials (Rheumatoid Arthritis And Osteoarthritis)

A) Revise the heading [redacted] to be of the same prominence as other subsection heading of subsections (*i.e.* Italicized).

B) Upon further review, include the following text as the second sentence of the first paragraph:

Using standard assessments of therapeutic response, there were no detectable differences in effectiveness or in the incidence of adverse events in crossover comparison of ketoprofen immediate-release capsules and ketoprofen extended-release capsules.

d. INDICATIONS AND USAGE

Revise to read [redacted] (see CLINICAL PHARMACOLOGY, Pharmacokinetics)

e. PRECAUTIONS

i. General

A) Delete the second sentence of the first paragraph.

B) Penultimate paragraph, second sentence:

Revise to read

ii. Information For Patients - Last paragraph, first sentence:

...ketoprofen (see PRECAUTIONS, Drug Interactions).

iii. Drug Interactions

A) Upon further review, revise the first paragraph to read as follows:

B) 3. Diuretic

...(see PRECAUTIONS, General).

C) 5. Warfarin

... (see PRECAUTIONS, Drug/Laboratory Test Interactions: ...), ...

f. DOSAGE AND ADMINISTRATION (Rheumatoid Arthritis And Osteoarthritis)

Upon further review, revise to read as follows:

The recommended starting dose of extended-release ketoprofen in otherwise healthy patients is 200 mg administered once a day. A small dose should be utilized initially in small individuals, in debilitated or elderly patients. Immediate-release ketoprofen capsules are recommended for initial dosage titration and 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. (see CLINICAL PHARMACOLOGY, Individualization of Dosage).

During titration with immediate-release ketoprofen capsules, if minor side effects appear, they may disappear at a lower dose which may still have an adequate therapeutic effect. If well tolerated but not optimally effective, the dosage may be increased. Individual patients may show a better response to 300 mg daily as compared to 200 mg, although in well-controlled clinical trials patients on 300 mg did not show greater mean effectiveness. They did, however, show an increased frequency of upper- and lower-GI distress and headaches. It is of interest that women also had an increased frequency of these adverse effects compared to men. When treating patients with 300 mg/day, the physician should observe sufficient increased clinical benefit to offset potential increased risk. Dosages higher than 300 mg/day are not recommended because they have not been adequately studied. Relatively smaller people may need smaller doses. (See CLINICAL PHARMACOLOGY, Individualization of Dosage).

h. HOW SUPPLIED

i. You may delete the following statement:

ii. See comment under CONTAINER.

Please revise your labels and labeling, as instructed above, and submit container labels in final print and insert labeling in final print, or in draft if you prefer.

Please note that we reserve the right to request further changes in your labels and/or 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 all differences annotated and explained.

_____

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

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/4/96

FROM: Bill Russell, CSO, RSB

SUBJECT: Telecon

TO: ANDA 74-879

I called Sharon Hamm to request a revised list of convictions to include "affiliated persons" other than Elan employees. She will revise the list and FedEx it ASAP. I also reminded her that since they were a US applicant, the field copy should go to the district office and a certification to OGD. I also noted that bulk labels were included with the draft labels but there was no bulk packaging so these would probably be used for transit. She confirmed the bulk labels were for shipment only from the manufacturing facility in Ireland to the packaging facility in the US (Schein) and not intended as a marketable container configuration.

APPEARS THIS WAY
ON ORIGINAL

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

Date of Review: July 1, 1996

Date of Submission: March 29, 1996

Primary Reviewer: Jacqueline White, Pharm.D.

ANDA Number: 74-879 Review Cycle: 1st [Draft]

Applicant's Name [as seen on 356(h)]: Elan Pharmaceutical Research Corporation

Manufacturer's Name (If different than applicant): Elan Pharma LTD

Established Name: Ketoprofen Extended-release Capsules, 200 mg

LABELING DEFICIENCIES, WHICH ARE TO BE INCORPORATED WITH THE CHEMISTRY COMMENTS TO THE FIRM:

[NOTE: These deficiencies can be located on the x-drive as detailed in notes from Ted Sherwood regarding the New X-Drive]

LABELING DEFICIENCIES

1. CONTAINER:

   a. Revise to read:

      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 read "(see CLINICAL PHARMACOLOGY, Individualization of Dosage)". 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_a) 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, from the second paragraph.

3) Delete the fourth paragraph,

4) Last paragraph

... absorption of ketoprofen.

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, "No studies have been ..." 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).

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*

... administered as immediate release ketoprofen capsules.

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.

Please revise your labels and labeling, as instructed above, and submit in draft.

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.

NOTE TO THE CHEMIST

None

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

Do you have 12 Final Printed Labels and Labeling? Yes No
If no, list why:

Container Labels:

Carton Labeling:

Unit Dose Blister Label:

Unit Dose Carton Label:

Professional Package Insert Labeling:

Patient Package Insert Labeling:

Auxiliary Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? Yes No

What is the RLD on the 356(h) form:

NDA Number:

NDA Drug Name:

NDA Firm:

Date of Approval of NDA Insert and supplement #:
Has this been verified by the MIS system for the NDA?
Yes No

Was this approval based upon an OGD labeling guidance?
Yes No

If yes, give date of labeling guidance:

Basis of Approval for the Container Labels:

Basis of Approval for the Carton Labeling:

Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis			
PROPRIETARY NAME			
Has the firm proposed a proprietary name? If yes, complete this subsection.			
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
PACKAGING -See applicant's packaging configuration & RLD in FTR.			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	x		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? No Light sensitive product which might require cartoning? yes Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
LABELING			

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

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

FOR THE RECORD:

1. Review based on the labeling of Orudis® (Wyeth-Ayerst Laboratories, Inc.; Approved February 8, 1995). This is a **combined** insert with Oruvail® (Ketoprofen Extended-release Capsules).

   PLEASE NOTE:

   - **The model for ketoprofen is a <u>combined</u> insert for both the immediate & controlled release capsules. Therefore portions of the labeling for this ANDA differ from the RLD & from the mark-up copy of the model, [which was the basis for a model for the immediate release product].**
   - **This ANDA is for the extended release drug product only, therefore <u>some</u> of the text referring to the immediate release drug product was omitted.**
   - **Text referring to the exclusivity for the immediate release drug product was omitted.**
   - **The table & chart in the CLINICAL PHARMACOLOGY section were omitted.**
   - **The mark-up copy of the model in the file folder is for the immediate release drug product. Some of the same text marked "to omit" was also omitted for the extended release drug product. However some of the text was retained since it was drug product specific for the extended release capsule.**
   - **Some of the editorial changes were based on the labeling review for Mylan's immediate release drug product, ANDA 74035na2.1.**
   - **Once this labeling review has been finalized, then a separate model for the "<u>extended-release drug product</u>" can be marked-up for the file folder.**

2. Patent/exclusivity's:

   a. Orange Book/16th Ed.-
   Patent: none pending
   Exclusivity: For Oruvail:"new dosage form" expires 9/24/96

The firm's exclusivity certification statement is accurate. [Vol.B1.1, section III].

b. There is one exclusivity for the immediate release capsule expiring January 6, 1997, for management of moderate to severe pain (I-112). Some of the text of the insert refers to both the immediate release and extended release product. Although this application is for the extended release product, some of the text referring to the pain has been carved out.

NOTE: The following information is from a previous labeling review by a different Labeling Reviewer for the immediate release drug product. [Mylan's immediate release drug product, ANDA 74035na2.1].

The exclusivity was granted (with the approval of the innovator's supplement NDA 18-754, SE1-018) on January 6, 1994. The INDICATIONS section in the Orudis® insert labeling now states it's indicated for the management of the signs and symptoms of rheumatoid arthritis and osteoarthritis, the "management of pain" and primary dysmenorrhea. Since they formerly had an indication of mild to moderate pain, with the inclusion of moderate to severe pain, they now state just "pain" to cover the spectrum. As a result, the generic firm's product must state for mild to moderate pain as listed in the innovator's February 18, 1988, approved labeling previous to the January 6, 1994, labeling.

3. Storage Conditions:

Insert-

NDA: Store at room temperature, approximately 25°C (77°F). Keep tightly closed.

ANDA: Store at room temperature approximately 25°C (77°F).
Protect from direct light, excessive heat and humidity.

Container-

NDA: Store at room temperature, approximately 25°C (77°F). Keep tightly closed.

ANDA: Store at room temperature approximately 25°C (77°F).
Protect from direct light, excessive heat and humidity. Keep tightly closed.
[See comment under HOW SUPPLIED section].

4. Dispensing Recommendations:

NDA: Dispense in a tight container.

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.

ANDA: Dispense in a tight, light-resistant container with child-resistant closure.

5. Product Line:

RLD:	100's & unit dose 100's
ANDA:	100's, 500's & 1000's

6. Closure:

100's, 500's & 1000's: non CRC

7. The capsule imprints listed in the HOW SUPPLIED section are consistent with the firm's stability report. Vol.B1.4, p.425

8. Inactive Ingredients:

The inactive ingredients listed in the DESCRIPTION section are NOT consistent with the firm's composition statement. [Vol.B1.2, section VII]

9. Elan has the statement, "Protect from direct light, excessive heat and humidity" printed on their container labels. This statement is not on the innovator's container label. We find the statement acceptable since this drug product is a capsule formulation.

/S/ 12-5-96 12/5/96

Primary Reviewer Date

/S/ 12/6/96

Team Leader, Labeling Review Branch Date

cc: ANDA 74-879
Dup/Division File
HFD-613/JWhite/CPark/AVezza (no cc:)
HFD-600/RF
njg/12/3/96/x:\new\firmsam\Elam\ltrs&rev\74879na1.l
Review