CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-390

ADMINISTRATIVE DOCUMENTS

(Supercedes APPROVAL SUMMARY signed off 3/8/00)

APPROVAL SUMMARY

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

ANDA Number: 75-390 **Date of Submission: February 16, 2001**
Applicant's Name: **Alphapharm PTY. Ltd.**
Established Name: **Naproxen Delayed-release Tablets, 375 mg and 500mg**

APPROVAL SUMMARY

1. **Do you have 12 Final Printed Labels and Labeling?** Yes
2. **Container Labels**: (100's and 1000's)
   Satisfactory in **final print** as of July 19, 1999 submission.

   (See blue jacket volume 4.1; response 4; page 269 through the end of jacket **FOR CONTAINER LABELS ONLY)** 375 mg and 500 mg bottles of 100 and 1000 tablets. **(See OTHER COMMENTS below)**

3. **Professional Package Insert Labeling**:
   Satisfactory in **final print** as of the February 16, 2001 submission

   (See blue jacket volume 5.1; response 2; pages 4 through 15)
4. **Revisions needed post-approval**: None

BASIS OF APPROVAL:

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: EC NAPROSYN®
NDA Number: N 20-067
NDA Drug Name: Naproxen Delayed-release Tablets, 375mg & 500 mg
NDA Firm: Syntex
Date of Approval of NDA Insert and supplement #: Oct 14, 1994
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? Yes. Sept 1997.
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

OTHER COMMENTS: Note that as of the February 16, 2001 submission, the firm (Alphapharm) has deleted any reference to the unit-dose CARTON of 100 tablets and does NOT intend to market this packaging configuration.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

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?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
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?			X
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?			X
Packaging			
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? Light sensitive product which might require cartoning? 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	
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			
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?		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?	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 bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
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.		X	

FOR THE RECORD:

1. The reference listed drug for this product is EC-Naprosyn® (Syntex Co.; NDA 20-067; Approved October 14, 1994).
2. The applicant certifies that there are no patents or exclusivities in existence for this product. See Vol. 1.1, page 9 and 11.
3. The product is manufactured by: Alphapharm Pty. Ltd, Cnr Garnet and Antimony Streets,Carole Park Queensland, 4300 Australia See Vol. 1.9, page 3885.
4. Outside firms are used for testing only. See Vol. 1.9, page 3976.
5. Container/Closure Statement
   Bottles of 100: 100 mL white HDPE
   Closure: 38 mm white wadded PP screw cap.
   Liner Type: foamseal PS22 Liner
   Bottles of 1000: 750 mL white HDPE
   Closure: 53 mm white wadded PP screw cap.
   Liner Type: Foamseal PS22 Liner
   Bottles of 1000: 950 mL white HDPE
   Closure: 53 mm white wadded PP screw cap.
   Liner Type: Foamseal PS22 Liner
   Bulk packaging:
   4 Litre: Bag size and type: 710 mm x 550 mm x 38 □m Plastic bag composed of PolyethyleneResin.
   20 Litre: Bag size and type: 710 mm x 550 mm x 38 □m Plastic bag composed of Polyethylene Resin. See Vol. 1.11, page 4840-4845.
6. Product Line
   375 mg tablet: white round imprinted with G-NP-375" on one side.Light resistant bottles of 100 and 1000
   500 mg tablet: white round imprinted with G-NP-500" on one side. Light resistant bottles of 100 and 1000.
7. Components/Composition
   Innovator:
   Active: Naproxen 375 mg or 500 mg
   Inactive: Croscarmellose Sodium triethyl citrate
   Povidone Sodium hydroxide
   magnesium stearate Purified water
   methacrylic copolymer simethicone emulsion
   talc
   Applicant:
   Active: Naproxen 375mg or 500 mg
   Inactive: Croscarmellose Sodium *titanium dioxide
   Povidone *simethicone emulsion
   magnesium stearate #black ink
   sodium hydroxide #ink thinner
   *methacrylic copolymer
   *purified talc *=enteric coating
   *polyethylene glycol #=printing process
   See Vol. 1.8, page 3245.
8. Storage and Dispensing
   NDA: Store at 15-30°C (59-86°F) in well-closed containers.
   ANDA: Store at 15-30°C (59-86°F) in well-closed containers. Dispense in light-resistant containers. See Vol. 1.13, page 35.
9. **Note: That T. Watkins did the last review (Approval Summary) signed off on 3/8/00. This is my first review of this application.**

Date of Review: 4/12/01 **Date of Submission: February 16, 2001**
Reviewer: Jim Barlow **Date:**

Team Leader: John Grace **Date:**

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cc:

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

ANDA Number: 75-390

Date of Submission: August 13, 1998
Date of Amendment: October 5, 1998

Applicant's Name: Alphapharm PTY. Ltd.

Established Name: Naproxen Delayed-release Tablets, 375 mg and 500mg

Labeling Deficiencies:

1. CONTAINER (100'S and 1000'S)

   a. Revise "CAUTION: Federal Law..." statement to read "℞ only".

   b. Revise the established name to read Naproxen Delayed-release Tablets instead of Naproxen Tablets.

   c. Delete "enteric coated" from the label.

2. UNIT DOSE CARTON (100'S)

   a. Revise "CAUTION: Federal Law..." statement to read "℞ only".

   b. Revise the established name to read Naproxen Delayed-release Tablets instead of Naproxen Tablets.

   c. Delete "enteric coated" from the established name.

   d. Add "unit dose" to the carton.

3. UNIT DOSE BLISTER STRIPS

   a. Satisfactory in draft, however, you may delete the street address to save space.

4. INSERT

   a. DESCRIPTION

i. Revise the chemical name to read as follows:

(+)-6-Methoxy-∝-methyl-2-napthaleneacetic acid.

ii. Revise the third sentence of paragraph one of this section to read as follows:

Naproxen has the following structural formula:

iii. Revise the first sentence of paragraph two of this section to read as follows:

Naproxen is practically odorless,...

b. CLINICAL PHARMACOLOGY

i. Delete "(NSAID)" from the first sentence of this section.

ii. Include the following immediately after the first sentence in the *Pharmacokinetics* subsection.

The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days and the degree of naproxen accumulation is consistent with this half-life.

iii. Include the following to immediately follow the last sentence in the *Absorption* subsection.

When 500 mg of naproxen delayed-release tablets were given twice a day to fasted subjects (n=24), the following was observed after 1 week of dosing:

C_{max} (mcg/mL)	94.9	(18%)*
T_{max} (hours)	4	(39%)*
AUC_{0-12hr} (mcg·hr/mL)	845	(20%)*

*mean value (coeffiecient of variation)

iv. Revise the section relating to children under the *Special Populations* subsection to read as follows:

Children: In children of 5 to 16 years of age with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen oral suspension were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in children and adults. Pharmacokinetic studies of naproxen were not performed in children of less than 5 years of age. Naproxen delayed-release tablets have not been studied in subjects under the age of 18.

c. CLINICAL STUDIES

i. Revise the first sentence of the first paragraph of this section to read as follows:

...rheumatoid arthritis, osteoarthritis, juvenile arthritis, and ankylosing spondylitis.

ii. Delete the third paragraph of this section which begins as follows:

In a clinical trial comparing...

iii. Revise the first sentence of the fourth paragraph of this subsection to read as follows:

In clinical studies in patients with rheumatoid arthritis, osteoarthritis, and juvenile arthritis, naproxen...

iv. Delete paragraphs 6 and 7 of this section.

v. Include the following to appear immediately after paragraph 8 of this section.

Three 6-week, double- blind multicenter studies with naproxen delayed-release tablets (375 or 500 mg BID, n=385) and naproxen immediate-release tablets (375 or 500 mg BID, n=279) were conducted comparing naproxen delayed-release tablets with naproxen immediate-release tablets including 355 rheumatoid arthritis and osteoarthritis who had a recent history of NSAID related GI symptoms. These studies indicated that

naproxen delayed-release tablets and naproxen immediate-release tablets showed no significant differences in efficacy or safety and had similar prevalence of minor GI complaints. Individual patients, however may find one formulation preferable to the other.

d. INDIVIDUALIZATION OF DOSAGE

i. Include the following to appear as the first paragraph of this section:

Because naproxen delayed-release tablets dissolve in the small intestine rather than in the stomach, the absorption of the drug is delayed compared to other naproxen formulations (see CLINICAL PHARMACOLOGY).

ii. Revise the first sentence of the first paragraph of this section to read as follows:

...is to choose a formulation and a starting dose...

iii. Delete "(see DOSAGE AND ADMINISTRATION)" from the first paragraph of the *Osteoarthritis/ Rheumatoid Arthritis/Ankylosing Spondylitis* subsection.

iv. Include the following to immediately follow the third sentence in paragraph to of the *Osteoarthritis/ Rheumatoid Arthritis/ Ankylosing Spondylitis* subsection.

When treating patients with naproxen 1500 mg/day, the physician should observe sufficient increase clinical benefit to offset the potential increased risk.

v. Include the following to appear as the last subsection of the INDIVIDUALIZATION OF DOSAGE section.

Juvenile Arthritis: The use of naproxen oral suspension allows for more flexible dose titration.

The recommended total daily dose is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg give twice a day) (see

DOSAGE AND ADMINISTRATION).

e. INDICATIONS AND USAGE

i. Revise the first paragraph of this section to read as follows:

Naproxen delayed-release tablets are indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis. Naproxen oral suspension is recommended for juvenile rheumatoid arthritis in order to obtain the maximum dosage flexibility based on the child's weight.

f. WARNINGS

i. Revise the first sentence of paragraph three of this section to read as follows:

...and bleeding or any differences between naproxen products in their propensity to cause peptic ulceration and bleeding.

g. PRECAUTIONS

i. Include the following as the first sentence of the *General* subsection.

General: **NAPROXEN DELAYED-RELEASE TABLETS SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN CONTAINING PRODUCTS SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.**

ii. Revise the *Pediatric Use* subsection to read as follows:

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for juvenile arthritis are based on well-controlled studies (see DOSAGE AND ADMINISTRATION). There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in juvenile arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen oral suspension, see

DOSAGE AND ADMINISTRATION section), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

h. ADVERSE REACTIONS

i. Revise the first sentence of the second paragraph of this section to read as follows:

...or osteoarthritis are listed below.

ii. Include the following to appear as the fourth paragraph of this section:

In controlled clinical trials with about 80 children and in well monitored open-label studies with about 400 children with juvenile arthritis, treated with naproxen, the incidence of rash and prolonged bleeding times were increased, the incidence of gastrointestinal and central nervous system reactions were about the same, and the incidence of other reactions were lower in children than in adults.

i. DOSAGE AND ADMINISTRATION

i. Revise the first paragraph of this section to read as follows:

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

The recommended dose of naproxen delayed-release tablets is 375 or 500 mg twice daily. To maintain the integrity...

ii. Delete paragraphs four and five and replace them with the following:

Juvenile Arthritis

The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses (i.e., 5 mg/kg given twice a day). Naproxen tablets are not well suited to this dosage so use of naproxen oral suspension is recommended for this indication.

j. HOW SUPPLIED

Revise this section to include scoring configuration information, e.g., unscored.

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed container and blister pack labels, along with 12 copies of final printed unit dose carton and insert labeling.

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