CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 075416Orig1s000

Name: Naproxen Sodium Extended-release Tablets 500 mg (base)

Sponsor: Andrx Pharmaceuticals, Inc.

Approval Date: August 27, 2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter(s)	**X**
Labeling	**X**
Labeling Review(s)	**X**
Medical Review(s)	
Chemistry Review(s)	**X**
Bioequivalence Review(s)	**X**
Statistical Review(s)	
Microbiology Review(s)	
Other Review(s)	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

APPROVAL LETTER

ANDA 75-416

AUG 27 2002

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Naproxen Sodium Extended-release Tablets, 500 mg (base). We also acknowledge receipt of your amendment dated May 11, 2000, providing for the addition of a 375 mg (base) tablet strength.

Reference is made to our Tentative Approval letter for your 500 mg (base) strength tablet dated March 17, 2000, our Tentative Approval letter for the 375 mg (base) and 500 mg (base) strength tablets dated July 5, 2001, and to your amendments dated January 22, June 11, July 22, August 14, and August 16, 2002.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. However, because of patent issues explained below, we are unable to approve both strengths of the drug product at this time. Therefore, only the 500 mg (base) strength of the drug product is approved. The 375 mg (base) strength remains tentatively approved and will not receive final approval until the patent issues discussed below are satisfactorily resolved. The Division of Bioequivalence has determined your Naproxen Sodium Extended-release Tablets, 500 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Naprelan Extended-release Tablets, 500 mg (base), of Elan Pharmaceutical Research Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

> The dissolution testing should be conducted in 900 mL of pH 7.5 Phosphate Buffer at 37°C using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following "interim" specifications:

Time (hr)	% Dissolved
0.5	(b) (4)
3	
6	
14	Not less than (b) (4)

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data for the first three production size batches. Data should be submitted as a "Special Supplement – Changes Being Effected" when there are no revisions to be made to the "interim" specifications, or when the final specifications proposed are tighter than the "interim" specifications. In all other instances, the data provided should be in the form of a Prior Approval Supplement.

The listed drug product referenced in your application, Naprelan Extended-release Tablets, 375 mg (base) and 500 mg (base), of Elan Pharmaceutical Research Corporation, is subject to a period of patent protection which expires on June 10, 2014, (U.S. Patent No. 5,637,320 – the '320 patent). Your application contains Paragraph IV Certifications to this patent made individually upon submission of each strength under Section 505(j)(2)(A)(vii)(IV) of the Act. These individual certifications state that your manufacture, use, or sale of this drug product will not infringe on the patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against Andrx Pharmaceuticals, Inc. (Andrx) for infringement of the '320 patent. The infringement action must be taken before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received by the NDA and patent holders. You have notified the Agency that Andrx has complied with the requirements of Section 505(j)(2)(B) of the Act, and that as a result, litigation remains ongoing in the United States District Court for the Southern District of Florida involving a challenge to the '320 patent (Elan Corporation, PLC v. Andrx Pharmaceuticals, Inc., Civil Action No. 98-7164-CIV-JORDAN).

We note that your June 11, 2002, amendment requests that the agency grant final approval to both the 375 mg (base) and 500 mg (base) strengths of the drug product based upon what you have termed a "final judgement" rendered in the case noted above. This "final judgement" was entered on March 14, 2002 by the district court in favor of Andrx and declared the '320 patent to be invalid. However, we are unable to base approval of this application on the decision rendered in the referenced district court. Please refer to the agency's Guidance Document dated March 2000, entitled "Court Decisions, ANDA Approvals, and 180-Day Exclusivity Under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act ." This guidance was issued in response to recent litigation and defines the agency's interpretation of the term "court" for the purpose of the timing of ANDA approvals and the commencement of 180-day exclusivity. The Guidance states that effective with its issuance in March 2000, the agency will interpret the term "court" as found in section 505(j)(5)(B)(iii)(I) and 505(j)(5)(B)(iv) to mean the first court that renders a decision finding the patent at issue invalid, unenforceable, or not infringed. Thus, the agency may approve an ANDA based upon a district court decision if it was accepted for

filing after the Guidance issued and no ANDAs containing paragraph IV patent certifications for the same drug product were accepted for filing prior to the issuance of the Guidance. Please note that an ANDA for both strengths of Naproxen Sodium Extended-release Tablets was accepted for review prior to the issuance of the Guidance. Thus, with respect to this drug product, the agency will apply the decision of "court" to mean "the court that enters final judgement from which no appeal can be or has been taken" (21 CFR 314.107(e)(1).

However, the agency is granting approval for your 500 mg (base) strength based upon the recognition that the 30-month period identified in section 505(j)(5)(B)(iii) of the Act, during which time the agency was precluded from approving this strength, has expired. With respect to the 375 mg (base) strength, our records indicate that the 30-month period will expire on December 16, 2002. Therefore, final approval for the 375 mg (base) strength cannot be granted until the expiration of the 30-month period provided for in section 505(j)(5)(B)(iii). This period began on the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), and could be extended or reduced by the court because of the failure of either party to reasonably cooperate in expediting the action.

Under section 505(A) of the Act, certain changes in the conditions described in this ANDA for the 500 mg (base) strength require an approved supplemental application before the change can be made.

Post-marketing requirements for this ANDA for the 500 mg (base) strength) are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of the 500 mg (base) strength.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaign. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81 (b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

In order to provide for the final approval of youre Naproxen Sodium Extended-release Tablets, 375 mg (base), please submit a supplemental application containing the information requested beginning with the last paragraph on page 2 through page 3 of the tentative approval letter dated July 5, 2001. This information should be clearly designated in your cover letter as a "SUPPLEMENTAL APPLICATION – EXPEDITED REVIEW REQUESTED". If applicable, the amendment should also provide a copy of an order, judgement, or a settlement agreement between the parties, whichever is applicable, or a

licensing agreement between you and the patent holder, or any other relevant information.

If you have questions about the status of this application, and prior to your submission of the supplemental application referenced above, please contact Craig Kiester, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler 8/27/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

If you have questions about the status of this application, and prior to your submission of the supplemental application referenced above, please contact Craig Kiester, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-416
Division File
FIELD COPY
HFD-92
HFD-610/P.Rickman
HFD-330/
HFD-205/

Endorsements:
HFD-620/S.Dhanesar/ 7/31/02
HFD-623/A.Mueller/ 8-1-02
HFD-617/R.West for C.Kiester/7/31/02
HFD-613/J.Barlow/ 8/27/2002
HFD-613/J.Grace/ 8/27/2002

F/T by:
Revised:RLWest:7/31/02
V:\FIRMSAM\ANDRX\LTRS&REV\75416AP.DOC

APPROVAL (500 MG (BASE) STRENGTH

TENTATIVE APPROVAL (Third) 375 MG (BASE) STRENGTH

8/2/2002

8/2/2002

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

TENTATIVE APPROVAL LETTERS

ANDA 75-416

MAR 17 2000

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Naproxen Sodium Extended-release Tablets, 500 mg (base).

Reference is also made to your amendments dated September 30, and October 27, 1998; June 21, September 27, October 12, and November 19, 1999; and January 14, and February 7, 2000.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is tentatively approved. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product), and is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Naprelan Extended-release Tablets, 500 mg (base), of Elan Pharmaceutical Research Corporation, is subject to a period of patent protection which expires on June 10, 2014, (U.S. Patent No. 5,637,320). Your application contains a Paragraph IV Certification to this patent under Section 505(j)(2)(A)(vii)(IV) of the Act. This certification states that your manufacture, use, or sale of this drug product will not infringe on the patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against Andrx Pharmaceuticals, Inc. (Andrx) for infringement of the patent that is the subject of the certification (the '320 patent). This action must be taken before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified the Agency that Andrx has complied with the requirements of Section 505(j)(2)(B) of the Act, and that as a result, litigation is currently underway in the United States District Court for the Southern District of Florida involving a challenge to the

'320 patent (Elan Corporation, PLC v. Andrx Pharmaceuticals, Inc., Civil Action No. 987164). Therefore, final approval cannot be granted until:

1. a. The expiration of the 30-month period provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii) (I), (II), or (III)], or,

   c. the '320 patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, please submit a MINOR amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment should be clearly designated in your cover letter as a minor amendment. It should identify changes, if any, in the conditions under which this drug product was tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing and controls data, as appropriate. Alternatively, a statement that no such changes have been made to this application should be made, if appropriate. The amendment should also provide a copy of an order, judgement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. This amendment also serves to reactivate the application prior to final approval.

Any significant changes in the conditions outlined in this abbreviated application as well as the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures (CGMPs) are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendment referred to above, the Agency may, at any time prior to the final date of approval, request that you submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments may result in rescission of this tentative approval determination, or a delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Bonnie McNeal, Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

/S/ Janet Woodcock, M.D. 3/17/00

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

Refer to admn. record.

Rweist
3/17/00

ANDA 75-416

JUL 5 2001

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

Dear Madam:

This is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Naproxen Sodium Extended-release Tablets, 500 mg (base). We also acknowledge receipt of your amendment dated May 11, 2000, providing for the addition of a 375 mg (base) tablet strength.

Reference is made to our Tentative Approval letter for your 500 mg (base) strength tablet dated March 17, 2000, and to your amendment dated February 12, 2001.

We have completed the review of this abbreviated application as amended and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application which now provides for both the 375 mg (base) and 500 mg (base) strengths remains tentatively approved. This determination is based upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices (CGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The listed drug product referenced in your application, Naprelan Extended-release Tablets, 375 mg (base) and 500 mg (base), of Elan Pharmaceutical Research Corporation, is subject to a period of patent protection which expires on June 10, 2014, (U.S. Patent No. 5,637,320). Your application contains Paragraph IV Certifications to this patent made separately upon submission of each strength under Section 505(j)(2)(A)(vii)(IV) of the Act. These individual certifications state that your manufacture, use, or sale of this drug product will not infringe on the patent. Section 505(j)(5)(B)(iii) of the Act provides that approval of an abbreviated new drug application shall be made effective immediately, unless an action is brought against Andrx Pharmaceuticals, Inc. (Andrx) for infringement of the patent that is the subject of the certification (the '320 patent). This action must be taken before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(I) is received. You have notified the Agency that Andrx has complied with the requirements of Section 505(j)(2)(B) of the Act, and that as a result, litigation remains underway with

respect to the 375 mg (base) strength in the United States District Court for the Southern District of Florida involving a challenge to the '320 patent (Elan Corporation, PLC v. Andrx Pharmaceuticals, Inc., Civil Action No. 987164). We note your statement informing the agency that the 30-month period identified in Section 505(j)(5)(iii) of the Act, during which time the agency was precluded from approving your application for the 500 mg (base) strength has expired.

However, please note that an abbreviated application for Naproxen Sodium Extended-release Tablets, 375 mg (base) and 500 mg (base) containing a Paragraph IV Certification to the '320 patent was accepted for filing by this Office prior to the filing of your application. This application remains under review. Consequently, upon approval that application's applicant is eligible for 180-days of generic drug market exclusivity. Pending resolution of the legal issues noted below, your application will not be eligible for final approval until 180-days after the first commercial marketing of the drug by the applicant who preceded you in submitting the application. We refer you to the Agency's guidance document entitled "180-Day Generic Drug Exclusivity Under the Hatch-Waxman Amendments" (June 1998) for additional information on this issue.

In addition to the 180-day exclusivity issue noted above, final approval for both strengths cannot be granted until:

1. a. The expiration of the 30-month period for the 375 mg (base) strength provided for in section 505(j)(5)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

   b. the date of a court decision [505(j)(5)(B)(iii) (I), (II), or (III)], or,

   c. the '320 patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, please submit a MINOR amendment 90 days prior to the date you believe your application will be eligible for final approval. This amendment should be clearly designated in your cover letter as a MINOR AMENDMENT – FINAL APPROVAL REQUESTED. It should identify changes, if any, in the conditions under which both strengths of this drug product were tentatively approved, and should include updated information such as final-printed labeling, chemistry, manufacturing and controls data, as appropriate. Alternatively, a statement that no such changes have been made to this application should be made, if appropriate. If applicable, the amendment should also provide a copy of an order, judgement, or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. This amendment also serves to reactivate the application prior to final approval.

Any significant changes in the conditions outlined in this abbreviated application as well as the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures (CGMPs) are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendment referred to above, the Agency may, at any time prior to the final date of approval, request that you submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments may result in rescission of this tentative approval determination, or a delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the Agency issues the final approval letter, this drug product will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

If you have questions about the status of this application, or prior to your submission of the minor amendment referenced above, please contact Tim Ames, MBA, R.Ph., Project Manager, at (301) 827-5848, for further instructions.

Sincerely yours,

Gary Buehler 7/5/01
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-416
Division File
Field Copy
HFD-610/R. West
HFD-210/B. Poole
HFD-330
HFD-205

Endorsements:
HFD-623/J.Fan/ 3/9/01
HFD-623/A.Mueller/ Hand Summary for 3/13/2001
HFD-617/T.Ames/3/8/01 3/13/01
HFD-613/J.Barlow/3/8/01 3/13/01
HFD-613/J.Grace/ 3/13/2001

(b) (4)

12 Month EER on 3/14/01 is needed

V:\firmsam\ltrs&rev\andrx\75416~~ltr1~~.doc
F/T by: DJ 3/8/01 1546TA2.doc

APPROVAL

PACT

7/5/2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

LABELING

NAPROXEN SODIUM

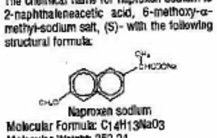
EXTENDED-RELEASE TABLETS
Equivalent to 500 mg naproxen

℞ Only

AUG 2 7 2002

APPROVED

DESCRIPTION
Naproxen sodium is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs).
The chemical name for naproxen sodium is 2-naphthaleneacetic acid, 6-methoxy-α-methyl-sodium salt, (S)- with the following structural formula:



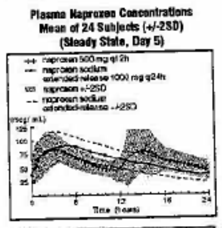
Naproxen sodium
Molecular Formula: $C_{14}H_{13}NaO_3$
Molecular Weight: 252.24

Naproxen sodium is an odorless crystalline powder, white to creamy in color. It is soluble in methanol and water.
Naproxen sodium extended-release tablets contain 550 mg of naproxen sodium, equivalent to 500 mg of naproxen and 50 mg sodium respectively. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, ethyl acrylate/methyl methacrylate copolymer, fumaric acid, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and propylene glycol. The tablet coating contains hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

CLINICAL PHARMACOLOGY
Naproxen is a nonsteroidal anti-inflammatory drug (NSAID), with analgesic and antipyretic properties. As with other NSAIDs, its mode of action is not fully understood; however, its ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Pharmacokinetics
Although naproxen itself is well absorbed, the sodium salt form is more rapidly absorbed resulting in higher peak plasma levels for a given dose. Approximately 30% of the total naproxen sodium dose in naproxen sodium extended-release tablets is present in the dosage form as an immediate release component. The remaining naproxen sodium is in the form of a sustained-release matrix. After oral administration, plasma levels of naproxen are detected within 30 minutes of dosing, with peak plasma levels occurring approximately 5 hours after dosing. The observed terminal elimination half-life of naproxen from both immediate release naproxen sodium and naproxen sodium extended-release tablets is approximately 15 hours. Steady state levels of naproxen are achieved in 3 days and the degree of naproxen accumulation in the blood is consistent with this.

Plasma Naproxen Concentrations
Mean of 24 Subjects (+/-2SD)
(Steady State, Day 5)



Pharmacokinetic Parameters at Steady State Day 5 (Mean of 24 Subjects)

Parameter (units)	Naproxen 500 mg Q12h/5 days (1000 mg) Mean	SD	Range	Naproxen sodium extended-release 2 x 500 mg tablets (1000 mg) Q24h/5 days Mean	SD	Range
AUC 0-24 (mcg·h/mL)	1446	166	1167-1658	1448	145	1173-1174
Cmax (mcg/mL)	95	13	71-117	94	13	74-127
Cavg (mcg/mL)	60	7	48-77	60	6	49-74
Cmin (mcg/mL)	36	9	13-51	33	7	23-48
Tmax (hrs)	3	1	1-4	5	2	2-10

Absorption
Naproxen itself is rapidly and completely absorbed from the GI tract with an *in vivo* bioavailability of 95%. Based on the pharmacokinetic profile, the absorption phase of naproxen sodium extended-release tablets occurs in the first 4-6 hours after administration. This coincides with dissolution of the immediate-release component in the stomach, the transit of the sustained release matrix through the small intestine and into the proximal large intestine.
The absorption rate from the sustained release component of naproxen sodium extended-release tablets is slower than that for conventional naproxen sodium tablets. It is this prolongation of drug absorption processes which maintains plasma levels and allows for once daily dosing.

Food Effects
No significant food effects were observed when twenty-four subjects were given a single dose of naproxen sodium extended-release tablets 500 mg either after an overnight fast or 30 minutes after a meal. In common with conventional naproxen and naproxen sodium formulations, food causes a slight decrease in the rate of naproxen absorption following administration of naproxen sodium extended-release tablets.

Distribution
Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin-bound. At doses of naproxen greater than 500 mg/day there is a less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses. However the concentration of unbound naproxen continues to increase proportionally to dose. Naproxen sodium extended-release tablets exhibit similar dose proportional characteristics.

Metabolism
Naproxen is extensively metabolized to 6-0-desmethyl naproxen and both parent and metabolites do not induce metabolizing enzymes.

Elimination
The elimination half-life of naproxen sodium extended-release tablets and conventional naproxen is approximately 15 hours. Steady state conditions are attained after 2-3 doses of naproxen sodium extended-release tablets. Most of the drug is excreted in the urine, primarily as unchanged naproxen (less than 1%), 6-0-desmethyl naproxen (less than 1%) and their glucuronide or other conjugates (66-92%). A small amount (<5%) of the drug is excreted in the feces. The rate of excretion has been found to coincide closely with the rate of clearance from the plasma. In patients with renal failure metabolites may accumulate.

Special Populations

Pediatric Use

No pediatric studies have been performed with naproxen sodium extended-release tablets, thus safety of naproxen sodium extended-release tablets in pediatric populations has not been established.

Renal Insufficiency

Naproxen pharmacokinetics have not been determined in subjects with renal insufficiency. Given that naproxen is metabolized and conjugates are primarily excreted by the kidneys, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency.

CLINICAL STUDIES

Rheumatoid Arthritis

The use of naproxen sodium extended-release tablets for the management of the signs and symptoms of rheumatoid arthritis was assessed in a 12 week double-blind, randomized, placebo and active-controlled study in 348 patients. Two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily and naproxen 500 mg tablets twice daily (1000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study.

Osteoarthritis

The use of naproxen sodium extended-release tablets for the management of the signs and symptoms of osteoarthritis of the knee was assessed in a 12 week double-blind, placebo and active-controlled study in 347 patients. Two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily and naproxen 500 mg tablets twice daily (1000 mg) were more effective than placebo. Clinical effectiveness was demonstrated at one week and continued for the duration of the study.

Analgesia

The onset of the analgesic effect of naproxen sodium extended-release tablets was seen within 30 minutes in a pharmacokinetic/pharmacodynamic study of patients with pain following oral surgery. In controlled clinical trials, naproxen has been used in combination with gold, D-penicillamine, methotrexate and corticosteroids. Its use in combination with salicylate is not recommended because there is evidence that aspirin increases the rate of excretion of naproxen and data are inadequate to demonstrate that naproxen and aspirin produce greater improvement over that achieved with aspirin alone. In addition, as with other NSAIDs the combination may result in higher frequency of adverse events than demonstrated for either product alone.

Special Studies

In a double-blind randomized, parallel group study, 18 subjects received either two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily or naproxen 500 mg tablets (1000 mg) twice daily for 7 days. Mucosal biopsy scores and endoscopic scores were lower in the subjects who received naproxen sodium extended-release tablets. In another double-blind, randomized, crossover study, 23 subjects received two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily, naproxen 500 mg tablets (1000 mg) twice daily and aspirin 650 mg four times daily (2600 mg) for 7 days each. There were significantly fewer duodenal erosions seen with naproxen sodium extended-release tablets than with either naproxen or aspirin. There were significantly fewer gastric erosions with both naproxen sodium extended-release tablets and naproxen than with aspirin.
The clinical significance of these findings is unknown.

INDIVIDUALIZATION OF DOSAGE

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

Naproxen sodium extended-release tablets like other NSAIDs show considerable variation in response. The recommended starting dose of naproxen sodium extended-release tablets in adults is two 375 mg tablets (750 mg) once daily, or two 500 mg tablets (1000 mg) once daily. Patients already taking naproxen 250 mg, 375 mg or 500 mg twice daily (morning and evening) may have their total daily dose replaced with naproxen sodium extended-release tablets as a single daily dose.
During long-term administration, the dose of naproxen sodium extended-release tablets may be adjusted up or down depending on the clinical response of the patient.
In patients who tolerate lower doses of naproxen sodium extended-release tablets well, the dose may be increased to three 500 mg tablets (1500 mg) once daily for limited periods when a higher level of anti-inflammatory/analgesic activity is required. When treating patients, especially at the higher dose levels, the physician should observe sufficient increased clinical benefit to offset the potential increased risk. (See **CLINICAL PHARMACOLOGY**). The lowest effective dose should be sought and used in every patient.
Symptomatic improvement in arthritis usually begins within one week; however, treatment for two weeks may be required to achieve a therapeutic benefit. A lower dose should be considered in patients with renal or hepatic impairment or in elderly patients (see **PRECAUTIONS**). Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly it is prudent to use the lowest effective dose.

Analgesia, Dysmenorrhea, Bursitis, and Tendinitis

The recommended starting dose is two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily. For patients requiring greater analgesic benefit, three naproxen sodium extended-release 500 mg tablets (1500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two 500 mg tablets (1000 mg).

Acute Gout

The recommended dose on the first day is two or three naproxen sodium extended-release 500 mg tablets (1000-1500 mg) once daily, followed by two 500 mg tablets (1000 mg) once daily, until the attack has subsided.

INDICATIONS AND USAGE

Naproxen sodium extended-release tablets are indicated for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, and acute gout. They are also indicated in the relief of mild to moderate pain and the treatment of primary dysmenorrhea.

CONTRAINDICATIONS

All naproxen products are contraindicated in patients who have had allergic reactions to prescription as well as to over-the-counter products containing naproxen. Anaphylactoid reactions may occur in patients without previous known exposure or hypersensitivity to aspirin, naproxen, or other NSAIDs, or in individuals with a history of angioedema, urticaria, bronchospastic reactivity (e.g. asthma), and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and hypotension associated with NSAIDs before starting therapy is important. In addition, if such symptoms occur during therapy, treatment with naproxen sodium extended-release tablets should be discontinued.

CONTRAINDICATIONS

All naproxen products are contraindicated in patients who have had allergic reactions to prescription as well as over-the-counter products containing naproxen. Anaphylactoid reactions may occur in patients without previous known exposure or hypersensitivity to aspirin, naproxen, or other NSAIDs, or in individuals with a history of angioedema, urticaria, bronchospastic reactivity (e.g. asthma), and nasal polyps. Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome. Therefore, careful questioning of patients for such things as asthma, nasal polyps, urticaria, and bronchospastic reactivity associated with hypersensitivity to aspirin must be made before starting therapy. In addition, if such symptoms occur during therapy, treatment with naproxen sodium should be discontinued.

WARNINGS

Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy

Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulcerations and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients treated chronically with naproxen or several chronic NSAIDs, symptomatic ulcers, gross bleeding, and perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date with all naproxen products have not identified any subset of patients not at risk of developing peptic ulceration and bleeding or any differences between different naproxen products in that propensity to cause peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

General

NAPROXEN SODIUM EXTENDED-RELEASE TABLETS SHOULD NOT BE USED CONCOMITANTLY WITH OTHER NAPROXEN PRODUCTS SINCE THEY ALL CIRCULATE IN THE PLASMA AS THE NAPROXEN ANION.

The antipyretic and anti-inflammatory activities of the drug may reduce fever and inflammation, thus diminishing their utility as diagnostic signs.

Because of adverse eye findings in animal studies with drugs of this class, it is recommended that ophthalmic studies be carried out if any change or disturbance in vision occurs.

Renal Effects

As with other NSAIDs, long term administration of naproxen to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis, hematuria, proteinuria, and occasionally nephrotic syndrome associated with naproxen-containing products and other NSAIDs since they have been marketed.

A second form of renal toxicity has been seen in patients taking naproxen as well as other NSAIDs. In patients with preexisting conditions with reduction in renal blood flow or blood volume, renal prostaglandins have a supportive role in the maintenance of renal perfusion. Administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, diuretic use, and the elderly. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Naproxen and its metabolites are eliminated primarily by the kidneys; therefore the drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Caution should be used if the drug is given to patients with creatinine clearance of less than 30 mL/minute because accumulation of naproxen has been seen in such patients.

Hepatic Effects

As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy. The ALT (SGPT) is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with naproxen. Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with naproxen as with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, fever, etc.),

naproxen should be discontinued. Chronic alcoholic liver disease and probably other diseases with decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Fluid Retention and Edema

Peripheral edema has been observed in some patients receiving naproxen. Naproxen sodium extended-release tablets contain 37.5 mg or 50 mg of sodium (1.5 mEq or 2.0 mEq respectively). This should be considered in patients whose overall intake of sodium must be severely restricted. For these reasons, naproxen sodium extended-release tablets should be used with caution in patients with fluid retention, hypertension or heart failure.

Information for Patients

Naproxen sodium extended-release tablets, like other drugs of its class, are not free of side effects. This formulation of naproxen can cause discomfort and, rarely, there are more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. NSAIDs are often essential agents in the management of arthritis and have a major role in the treatment of pain but they also may be commonly employed for conditions which are less serious. Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS,** and **ADVERSE REACTIONS**) and likely benefits of treatment with naproxen sodium extended-release tablets. Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during therapy with naproxen.

Laboratory Tests

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow patients chronically treated with naproxen sodium extended-release tablets for the signs and symptoms of ulceration and bleeding, and should inform them of the importance of this follow-up and what they should do if certain signs and symptoms do appear. Patients with initial hemoglobin values of 10 grams or less who are to receive long-term therapy should have hemoglobin values determined periodically. (See **WARNINGS — Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy**).

Drug Interactions

The use of NSAIDs in patients who are receiving ACE inhibitors may potentiate renal disease states (See **PRECAUTIONS — *Renal Effects***). *In vitro* studies have shown that naproxen anion, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound (see **CLINICAL PHARMACOLOGY — Pharmacokinetics**).

Theoretically, the naproxen anion itself could likewise be displaced. Short-term controlled studies failed to show that taking the drug significantly affects prothrombin times when administered to individuals on coumarin-type anticoagulants. Caution is advised nonetheless, since interactions have been seen with other nonsteroidal agents of this class. Similarly, patients receiving the drug and a hydantoin, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.

Concomitant administration of naproxen and aspirin is not recommended because naproxen is displaced from its binding sites during the concomitant administration of aspirin, resulting in lower plasma concentrations and peak plasma levels.

The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported. Naproxen and other NSAIDs can reduce the antihypertensive effect of propranolol and other beta-blockers.

Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly.

Caution should be used if naproxen is administered concomitantly with methotrexate. Naproxen, naproxen sodium and other NSAIDs have been reported to reduce the tubular secretion of methotrexate in an animal model, possibly increasing the toxicity of methotrexate.

Drug/Laboratory Test Interactions

Naproxen may decrease platelet aggregation and prolong bleeding time. This effect should be kept in mind when bleeding times are determined. The administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.

Naproxen may interfere with some urinary assays of 5-hydroxyindoleacetic acid (5HIAA).

Carcinogenesis

A two year study was performed in rats to evaluate the carcinogenic potential of naproxen at doses of 8 mg/kg/day, 16 mg/kg/day, and 24 mg/kg/day (50 mg/m^2, 100 mg/m^2, and 150 mg/m^2). The maximum dose used was 0.28 times the systemic exposure to humans at the recommended dose. No evidence of tumorgenicity was found.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats at 20 mg/kg/day (125 mg/m^2/day, 0.23 times the human systemic exposure), rabbits at 20 mg/kg/day (220 mg/m^2/day, 0.27 times the human systemic exposure) and mice at 170 mg/kg/day (510 mg/m^2/day, 0.28 times the human systemic exposure) with no evidence of impaired fertility or harm to the fetus due to the drug. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naproxen sodium extended-release tablets should be used during pregnancy only if the potential benefits justify the potential risks to the fetus.

Nonteratogenic Effects

There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in the late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of ductus arteriosus), use during third trimester should be avoided.

Nursing Mothers

The naproxen anion has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma. Because of the possible adverse effects of prostaglandin-inhibiting drugs on neonates, use in nursing mothers should be avoided.

Pediatric Use

No pediatric studies have been performed with naproxen sodium extended-release tablets, thus safety of naproxen sodium extended-release tablets in pediatric populations has not been established.

Geriatric Use

Clinical studies of naproxen sodium extended-release tablets did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Aging may affect the pharmacokinetics of naproxen. Studies indicate tht although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients (see **INDIVIDUALIZATION OF DOSAGE**). Elderly or debilitated seem to tolerate GI ulcerations and bleeding less well than other individuals taking NSAIDS (see **WARNINGS, Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy**). Additionally, elderly patients may be more sensitive to dose dependent reduction in renal prostaglandin formation while taking NSAIDs (see **PRECAUTIONS, Renal Effects**).

ADVERSE REACTIONS

As with all drugs in this class, the frequency and severity of adverse events depends on several factors: the dose of the drug and duration of treatment; the age, the sex, physical condition of the patient; any concurrent medical diagnoses or individual risk factors.

The following adverse reactions are divided into three parts based on frequency and whether or not the possibility exists of a causal relationship between drug usage and these adverse events. In those reactions listed as "Probable Causal Relationship" there is at least one case for each adverse reaction where there is evidence to suggest that there is a causal relationship between drug usage and the reported event.

The adverse reactions reported were based on the results from two double-blind controlled clinical trials of three months duration with an additional nine month open-label extension. A total of 542 patients received naproxen sodium extended-release tablets either in the double-blind period or in the nine month open-label extension. Of these 542 patients, 232 received naproxen sodium extended-release tablets, 167 were initially treated with naproxen and 143 were initially treated with placebo. Adverse reactions reported by patients who received naproxen sodium extended-release tablets are shown by body system. Those adverse reactions observed with naproxen but not reported in controlled trials with naproxen sodium extended-release tablets are italicized.

The most frequent adverse events from the double-blind and open-label clinical trials were headache (15%), followed by dyspepsia (14%), and flu syndrome (10%). The incidence of other adverse events occurring in 3%-9% of the patients are marked with an asterisk.

Those reactions occurring in less than 3% of the patients are unmarked.

Incidence Greater Than 1% (Probable Causal Relationship)

Body as a Whole — Pain (back)*, pain*, infection*, fever, injury (accident), asthenia, pain chest, headache (15%), flu syndrome (10%).

Gastrointestinal — Nausea*, diarrhea*, constipation*, abdominal pain*, flatulence, gastritis, vomiting, dysphagia, dyspepsia (14%), *heartburn*, stomatitis.*

Hematologic — Anemia, ecchymosis.

Respiratory — Pharyngitis*, rhinitis*, sinusitis*, bronchitis, cough increased.

Renal — Urinary tract infection*, cystitis.

Dermatologic — Skin rash*, *skin eruptions*, ecchymoses*, purpura.*

Metabolic and Nutrition — Peripheral edema, hyperglycemia.

Central Nervous System — Dizziness, paresthesia, insomnia, *drowsiness*, lightheadedness.*

Cardiovascular — Hypertension, *edema*, dyspnea*, palpitations.*

Musculoskeletal — Cramps (leg), myalgia, arthralgia, joint disorder, tendon disorder.

Special Senses — *Tinnitus*, hearing disturbances, visual disturbances.*

General — *Thirst.*

Incidence Less Than 1% (Probable Causal Relationship)

Body as a Whole — Abscess, monilia, neck rigid, pain neck, abdomen enlarged, carcinoma, cellulitis, edema general, LE syndrome, malaise, mucous membrane disorder, allergic reaction, pain pelvic.

Gastrointestinal — Anorexia, cholecystitis, cholelithiasis, eructation, GI hemorrhage, rectal hemorrhage, stomatitis aphthous, stomatitis ulcer, ulcer mouth, ulcer stomach, periodontal abscess, cardiospasm, colitis, esophagitis, gastroenteritis, GI disorder, rectal disorder, tooth disorder, hepatosplenomegaly, liver function abnormality, melena, ulcer esophagus, *hematemesis, jaundice, pancreatitis, necrosis.*

Renal — Dysmenorrhea, dysuria, kidney function abnormality, nocturia, prostate disorder, pyelonephritis, carcinoma breast, urinary incontinence, kidney calculus, kidney failure, menorrhagia, metrorrhagia, neoplasm breast, nephrosclerosis, hematuria, pain kidney, pyuria, urine abnormal, urinary frequency, urinary retention, uterine spasm, vaginitis, *glomerular nephritis, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis.*

Hematologic — Leukopenia, bleeding time increased, eosinophilia, abnormal RBC, abnormal WBC, thrombocytopenia, *agranulocytosis, granulocytopenia.*

Central Nervous System — Depression, anxiety, hypertonia, nervousness, neuralgia, neuritis, vertigo, amnesia, confusion, coordination, abnormal diplopia, emotional lability, hematoma subdural, paralysis, *dream abnormalities, inability to concentrate, muscle weakness.*

Dermatologic — Angiodermatitis, herpes simplex, dry skin, sweating, ulcer skin, acne, alopecia, dermatitis contact, eczema, herpes zoster, nail disorder, skin necrosis, subcutaneous nodule, pruritus, urticaria, neoplasm skin, *photosensitive dermatitis, photosensitivity reactions resembling porphyria cutaneous tarda, epidermolysis bullosa.*

Special Senses — Amblyopia scleritis, cataract, conjunctivitis, deaf, ear disorder, keratoconjunctivitis, lacrimation disorder, otitis media, pain eye.

Cardiovascular — Angina pectoris, coronary artery disease, myocardial infarction, deep thrombophlebitis, vasodilation, vascular anomaly, arrhythmia, bundle branch block, abnormal ECG, heart failure right, hemorrhage, migraine, aortic stenosis, syncope, tachycardia, *congestive heart failure.*

Respiratory — Asthma, dyspnea, lung edema, laryngitis, lung disorder, epistaxis, pneumonia, respiratory distress, respiratory disorder, *eosinophilic pneumonitis.*

Musculoskeletal — Myasthenia, bone disorder, spontaneous bone fracture, fibrotendinitis, bone pain, ptosis, spasm general, bursitis.

Metabolic and Nutrition — Creatinine increase, glucosuria, hypercholesteremia, albuminuria, alkalosis, BUN increased, dehydration, edema, glucose tolerance decrease, hyperuricemia, hypokalemia, SGOT increase, SGPT increase, weight decrease.

General — *Anaphylactoid reactions, angioneurotic edema, menstrual disorders, hypoglycemia, pyrexia (chills and fevers).*

Incidence Less Than 1% (Causal Relationship Unknown)

Other adverse reactions listed in the naproxen package label, but not reported by those who received naproxen sodium extended-release tablets are shown in italics. These observations are being listed as alerting information to the physician.

Hematologic — *Aplastic anemia, hemolytic anemia.*

Central Nervous System — *Aseptic meningitis, cognitive dysfunction.*

Dermatologic — *Epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome.*

Gastrointestinal — *Non-peptic GI ulceration, ulcerative stomatitis.*

Cardiovascular — *Vasculitis.*

OVERDOSAGE

Significant naproxen overdosage may be characterized by drowsiness, heartburn, indigestion, nausea, or vomiting. Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced seizures, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening. The oral LD_{50} of the drug is 500 mg/kg in rats, 1200 mg/kg in mice, 4000 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

Should a patient ingest a large number of tablets, accidentally or purposefully, the stomach may be emptied and usual supportive measures employed. In animals 0.5 g/kg of activated charcoal was effective in reducing plasma levels of naproxen. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding.

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

The usual daily dose of naproxen sodium extended-release tablets is two 375 mg tablets (750 mg) once daily, or two 500 mg tablets (1000 mg) once a day. Both larger and smaller doses may be required in individual patients (see **INDIVIDUALIZATION OF DOSAGE**). Regardless of indication, the dosage should be individualized to achieve effective dose and minimize adverse events, however the maximum daily dose is three naproxen sodium extended-release 500 mg tablets once daily.

Management of Pain, Primary Dysmenorrhea, and Acute Tendinitis and Bursitis

The recommended starting dose is two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily. For patients requiring greater analgesic benefit, three naproxen sodium extended-release 500 mg tablets (1500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two naproxen sodium extended-release 500 mg tablets (1000 mg).

Acute Gout

The recommended dose on the first day is two to three naproxen sodium extended-release 500 mg tablets (1000-1500 mg) once daily, followed by two 500 mg tablets (1000 mg) once daily, until the attack has

Management of Pain, Primary Dysmenorrhea, and Acute Tendinitis and Bursitis

The recommended starting dose is two naproxen sodium extended-release 500 mg tablets (1000 mg) once daily. For patients requiring greater analgesic benefit, three naproxen sodium extended-release 500 mg tablets (1500 mg) may be used for a limited period. Thereafter, the total daily dose should not exceed two naproxen sodium extended-release 500 mg tablets (1000 mg).

Acute Gout

The recommended dose on the first day is two to three naproxen sodium extended-release 500 mg tablets (1000-1500 mg) once daily, followed by two 500 mg tablets (1000 mg) once daily, until the attack has subsided.

HOW SUPPLIED

Naproxen sodium extended-release tablets are available as follows:

500 mg: white, capsule-shaped tablet imprinted with "Andrx 826"; in bottles of 75, NDC 62037-826-75; in bottles of 100, NDC 62037-826-01; and bottles of 1000, NDC 62037-826-10. Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

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

Dispense in a well-closed container.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Ft. Lauderdale, FL 33314

Rev. date: 08/02

Andrx
PHARMACEUTICALS, INC.

NDC 62037-826-10

NAPROXEN SODIUM

EXTENDED-RELEASE TABLETS

500 mg*

Rx ONLY

1000 Tablets

*Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

Usual Dosage: See accompanying information.

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

Dispense in a well-closed container.

APPROVED
AUG 27 2002

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7070 (12/00)

N 3 62037-826-10 8

UNVARNISHED AREA

LOT:

EXP.:

(b) (4)

0900

75-416
AP 8/27/02
Margo

Andrx
PHARMACEUTICALS, INC.

NDC 62037-826-01

NAPROXEN SODIUM

EXTENDED-RELEASE TABLETS

500 mg*

Rx ONLY

100 Tablets

*Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

Usual Dosage: See accompanying information.

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

Dispense in a well-closed container.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7090 (12/00)

N 3 62037-826-01 6

UNVARNISHED AREA

LOT:

EXP.:

0050

Andrx
PHARMACEUTICALS, INC.

NDC 62037-826-01

NAPROXEN SODIUM

EXTENDED-RELEASE TABLETS

500 mg*

Rx ONLY

100 Tablets

*Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

Usual Dosage: See accompanying information.

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

Dispense in a well-closed container.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

7090 (12/00)

N 3 62037-826-01 6

UNVARNISHED AREA

LOT:

EXP.:

APPROVED
AUG 27 2002

(b) (4)

Andrx
PHARMACEUTICALS, INC.

NDC 62037-826-75

NAPROXEN SODIUM

EXTENDED-RELEASE TABLETS

500 mg*

Rx ONLY

75 Tablets

*Each tablet contains 550 mg naproxen sodium equivalent to 500 mg naproxen.

Usual Dosage: See accompanying information.

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

Dispense in a well-closed container.

Manufactured by:
Andrx Pharmaceuticals, Inc.
Fort Lauderdale, FL 33314

N 3 62037-826-75 7

7069 (12/00)

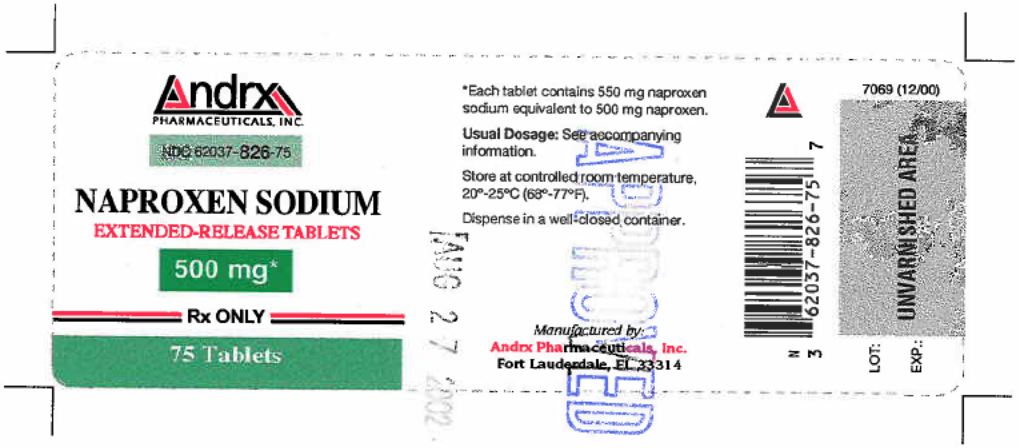
UNVARNISHED AREA

LOT:

EXP.:

AUG 27 2002

0038



(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

LABELING REVIEWS

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

ANDA Number: 75-416 Date of Submission: July 16, 1998 and August 20, 1998

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Naproxen Sodium Extended-release Tablets, 500 mg base.

Labeling Deficiencies:

1. GENERAL COMMENT

   The established name for this product is Naprosyn Sodium Extended-release Tablets. Revise all labels and labeling accordingly.

2. CONTAINER - Bottles of 75 & 1000 tablets.

   Please assure that the established name appears as the most prominent statement on the principal display panel.

3. INSERT

   a. DESCRIPTION

      Fourth paragraph, second sentence; revise to read as follows:

      In addition, each tablet contains the following inactive ingredients: colloidal.....

   b. CLINICAL PHARMACOLOGY

      Pharmacokinetics: Revise to include the graph entitled: **Plasma Naproxen Concentrations Mean of 24 Subjects (+/-2SD) (Steady State, Day 5)**

   c. PRECAUTIONS

      Information For Patients; first sentence; revise to read as follows:

      ....tablets, like other drugs of its class, are

not free of side effects.[replace "is' with "are"]

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

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.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

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.		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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	
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?			
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 (p. #) 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 p. # 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 ½ 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.			

NOTES/QUESTIONS TO THE CHEMIST:

1. I found a discrepancy in the description of the tablet between the HOW SUPPLIED section and the Controls for Finished Dosage Form on page 3589 vol. A1.10. Do you concur?

FOR THE RECORD:

1. MODEL LABELING

   The model used was for Naprelan, NDA 20-353/S-001 approved March 28, 1996, revised February 15, 1998. (The labeling used was from an annual report and seems to incorporate the changes requested in supplement 001 in its' labeling.)

2. Went to Corporate building file room to obtain appropriate labeling, however, they did not have a copy of this labeling and could not locate a copy that was stamped with the above listed approval date. Therefore, I was forced to use copy of the insert labeling from an annual report. *(The file room is supposed to update me on this search for this labeling request.)*

3. INACTIVE INGREDIENTS

   Consistent with Components and Composition statements [VOLUME A. 1.10 PAGES 3049]

4. PATENTS/EXCLUSIVITIES

   The firm is filing a paragraph IV against patent # 5637320 which is due to expire June 10, 2014. An exclusivity (NDF) is also mentioned and is due to expire January 5, 1999.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

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

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

6. DISPENSING STATEMENTS COMPARISON

NDA: Dispense in a well-closed container.

ANDA: Dispense in a well-closed container.

7. PACKAGING CONFIGURATIONS

NDA: 375 mg tablets in bottles of 100 & 500 mg tablets in bottles of 75.

ANDA: 500 mg tablets in bottles of 75 and 1000.

8. The tablet imprintings have NOT been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.10. (see vol A 1.10 pages 3589 and notes to the chemist).

9. CLOSURE

500 mg bottles of 75 will be packaged in (b)(4) containers with a CRC closure.
500 mg bottles of 1000 will be packaged in (b)(4) containers with a non-CRC closure.
(See pages 3438 in vol. A 1.10)

Date of Review: 11/20/98 Date of Submission: July 16, 1998

Primary Reviewer: Jim Barlow Date: 12/2/98

Team Leader: John Grace Date:

John J. Grace 12/2/98

---

cc:

ANDA: 75-416
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
X:\NEW\FIRMSAM\ANDRX\LTRS&REV\75416NA1.L2
Review

(~~Tentative~~ Approval Summary)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-416 Date of Submission: April 6, 1999 & May 14, 1999.

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Naproxen Sodium Extended-release Tablets, 500 mg base.

APPROVAL SUMMARY

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels - Bottles of 75 and 1000 tablets

Satisfactory in **final print** as of May 14, 1999 submission.

Professional Package Insert Labeling:

Satisfactory in **final ~~print~~** as of April 6, 1999 submission.

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: Naprelan®

NDA Number: 20-353

NDA Drug Name: Naprelan®

NDA Firm: Elan Pharmaceutical Research Corporation

Date of Approval of NDA Insert and supplement #: 20-353/S-001, approved March 26, 1996.

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: Most recently approved container labels for the reference listed drug.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

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.		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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		x	

package insert accompany the product?			
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	
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 (p. #) 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 p. # 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 ½ 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.			

FOR THE RECORD:

1. MODEL LABELING

   The model used was for Naprelan, NDA 20-353/S-001 approved March 28, 1996, revised February 15, 1998. (The labeling used was from an annual report and seems to incorporate the changes requested in supplement 001 in its' labeling.)

2. Went to Corporate building file room to obtain appropriate labeling, however, they did not have a copy of this labeling and could not locate a copy that was stamped with the above listed ~~approval date. Therefore~~, ~~I was forced to use~~ copy of the insert labeling from an annual report. (*The file room is supposed to update me on this search for this labeling request.)* *(This has been done as of 5/5/99 review)*

3. ~~INACTIVE~~ INGREDIENTS

   Consistent with Components and Composition statements [VOLUME A. 1.10 PAGES 3049]

4. PATENTS/EXCLUSIVITIES

   The firm is filing a paragraph IV against patent # 5637320 which is due to expire June 10, 2014. An exclusivity (NDF) is also mentioned and is due to expire January 5, 1999.

5. STORAGE TEMPERATURE ~~RECOMMENDATIONS~~ COMPARISON

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

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

6. DISPENSING STATEMENTS COMPARISON

   NDA: Dispense in a well-closed container.

   ANDA:Dispense in a well-closed container.

7. PACKAGING CONFIGURATIONS

   NDA: 375 mg tablets in bottles of 100 & 500 mg tablets in bottles of 75.

   ANDA: 500 mg tablets in bottles of 75 and 1000.

8. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.10. ~~(Note comment to chemist on last review) deemed ok.~~

9. CLOSURE

500 mg bottles of 75 will be packaged in [redacted] containers with a CRC closure.
500 mg bottles of 1000 will be packaged in [redacted] containers with a non-CRC ~~closure~~.
(See pages 3438 in vol. A 1.10)

Date of Review: 5/24/99 Date of Submission: 4/6/99 & 5/14/99

Primary Reviewer: Jim Barlow J Date: 5/24/99

Team Leader: John Grace John Grace Date: 5/24/1999

---

cc:
ANDA: 75-416
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\ANDRX\LTRS&REV\75416tap.s
~~Review~~

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

ANDA Number:	75-416
Date of Submission:	May 11, 2000
Applicant's Name:	Andrx Pharmaceuticals, Inc.
Established Name:	Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

Labeling Deficiencies:

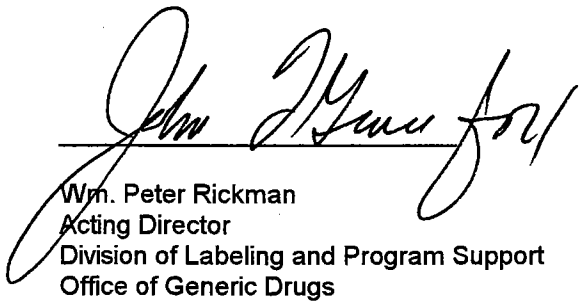
1. **CONTAINER** – bottles of 75 and 1000 tablets **(500mg tablet)**
   Satisfactory in **final print** as of the May 14, 1999 submission.

2. **CONTAINER** – bottles of 100 and 1000 tablets **(375mg tablet)**
   Satisfactory in **draft** as of the May 11, 2000 submission.

3. **PROFESSIONAL PACKAGE INSERT**
   How Supplied
   We note that you list a 100 count bottle for your 500mg strength tablet as well as your 375mg tablet. No container labeling for the 100 count bottle of 500 mg tablets has yet to be received by the Agency. Please revise and/or comment.

Please revise and prepare 12 copies of your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

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.		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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	
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			x

3. **INACTIVE INGREDIENTS**
   Consistent with Components and Composition statements
   [VOLUME A. 1.10 PAGES 3049 VOLUME B. 3.1 pg 000072]

4. **PATENTS/EXCLUSIVITIES**
   The firm is filing a paragraph IV against patent # 5637320
   which is due to expire June 10, 2014. An exclusivity (NDF) is also mentioned and is due to expire January 5, 1999.

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   NDA: Store at controlled room temperature, 20-25°C(68-77°F).
   ANDA:Store at controlled room temperature, 20-25°C(68-77°F).

6. **DISPENSING STATEMENTS COMPARISON**
   NDA: Dispense in a well-closed container.
   ANDA:Dispense in a well-closed container.

7. **PACKAGING CONFIGURATIONS**
   NDA: 375 mg tablets in bottles of 100 & 500 mg tablets in bottles of 75.

   ANDA: 500 mg tablets in bottles of 75 and 1000. (Maybe 100; see comments above)
   375mg tablets in bottles of 100 and 1000.

8. **The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.10.** (see pg 473A in vol. A. 3.2)

9. **CLOSURE**
   500 mg bottles of 75 will be packaged in (b) (4) containers with a CRC closure.
   500 mg bottles of 1000 will be packaged in (b) (4) containers with a non-CRC closure.
   375mg bottles of 100 will be packaged in (b) (4) containers with a CRC closure.
   375mg bottles of 1000 will be packaged in (b) (4) containers with a non-CRC closure.
   (See pages 3438 in vol. A 1.10 and pg. 000423 in vol. A. 3.1)

Date of Review: 10/19/00 Date of Submission: 5/11/00

Primary Reviewer: Jim Barlow Date: 11/17/..

Team Leader: John Grace Date: 11/16/2000

---

cc:

ANDA: 75-416
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\ANDRX\LTRS&REV\75416na2.l
Review

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

ANDA Number: 75-416 Date of Submission: January 9, 2001
Applicant's Name: Andrx Pharmaceuticals, Inc.
Established Name: Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

APPROVAL SUMMARY Do you have 12 Final Printed Labels and Labeling? Yes

1. **CONTAINER** – bottles of 75, 100 and 1000 tablets **(500mg tablet)**
   Satisfactory in **final print** as of the January 9, 2001 submission.

2. **CONTAINER** – bottles of 100 and 1000 tablets **(375mg tablet)**
   Satisfactory in **final print** as of the January 9, 2001 submission.

3. **PROFESSIONAL PACKAGE INSERT**
   Satisfactory in **final print** as of the January 9, 2001 submission.

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: Naprelan®
NDA Number: 20-353
NDA Drug Name: Naprelan®
NDA Firm: Elan Pharmaceutical Research Corporation
Date of Approval of NDA Insert and supplement #: 20-353/S-001: approved March 26, 1996.
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: Most recently approved container labels for the reference listed drug.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

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.		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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	
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 (p. #) 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 p. # 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 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.			

FOR THE RECORD:

1. **MODEL LABELING**
   The model used was for Naprelan, NDA 20-353/S-001 approved March 28, 1996, revised February 15, 1998. (The labeling used was from an annual report and seems to incorporate the changes requested in supplement 001 in its' labeling.)

2. **Went to Corporate building file room to obtain appropriate labeling, however, they did not have a copy of this labeling and could not locate a copy that was stamped with the above listed approval date. Therefore, I was forced to use copy of the insert labeling from an annual report. (*The file room is supposed to update me on this search for this labeling request.)*** *(This has been done as of 5/5/99 review)*

3. **INACTIVE INGREDIENTS**
   Consistent with Components and Composition statements
   [VOLUME A. 1.10 PAGES 3049 VOLUME B. 3.1 pg 000072]

4. **PATENTS/EXCLUSIVITIES (from previous FTR)**
   The firm is filing a paragraph IV against patent # 5637320
   which is due to expire June 10, 2014. An exclusivity (NDF) is also mentioned expired January 5, 1999.

5. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   NDA: Store at controlled room temperature, 20-25°C(68-77°F).
   ANDA:Store at controlled room temperature, 20-25°C(68-77°F).

6. **DISPENSING STATEMENTS COMPARISON**
   NDA: Dispense in a well-closed container.
   ANDA:Dispense in a well-closed container.

7. **PACKAGING CONFIGURATIONS**
   NDA: 375 mg tablets in bottles of 100 & 500 mg tablets in bottles of 75.

   ANDA: 500 mg tablets in bottles of 75, 100 and 1000.
   375mg tablets in bottles of 100 and 1000.

8. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.10. (see pg 473A in vol. A. 3.2)

9. **CLOSURE**
500 mg bottles of 75 will be packaged in (b) (4) containers with a CRC closure.
500mg bottles of 100 will be packaged in (b) (4) containers w/ a CRC closure (as of 1/9/01 submission)
9see pg 0077 in vol. B. 3.1)
500 mg bottles of 1000 will be packaged in (b) (4) containers with a non-CRC closure.
375mg bottles of 100 will be packaged in (b) (4) containers with a CRC closure.
375mg bottles of 1000 will be packaged in (b) (4) containers with a non-CRC closure.
(See pages 3438 in vol. A 1.10 and pg. 000423 in vol. A. 3.1)

Date of Review: 1/26/01 Date of Submission: 1/9/01
Primary Reviewer: Jim Barlow Date: 1/26/01

Team Leader: John Grace Date: 1/30/2001

---

cc:
ANDA: 75-416
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\ANDRX\LTRS&REV\75416ap.s
Review

APPROVAL SUMMARY

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

ANDA Number: 75-416
Date of Submission: August 14, 2002 and August 16, 2002
Applicant's Name: Andrx Pharmaceuticals, Inc.
Established Name: Naproxen Sodium Extended-release Tablets, 500 mg (base)

APPROVAL SUMMARY

1. **Do you have 12 Final Printed Labels and Labeling? Yes**

2. **CONTAINER** – bottles of 75, 100 and 1000 tablets **(500mg tablet)**
   Satisfactory in **final print** as of the January 9, 2001 submission.
   (See blue jacket volume 3.1)

3. **PROFESSIONAL PACKAGE INSERT**
   Satisfactory in **final print** as of the August 16, 2002 submission.
   (See blue jacket volume 4.1)

4. **Revisions needed post-approval:** None

5. **Patent Issues**
   Patent Data – NDA 20-353

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5637320	***June 10, 2014***	None		Paragraph IV	None

Exclusivity Data– NDA 20-353

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Naprelan®
NDA Number: 20-353
NDA Drug Name: Naprelan®
NDA Firm: Elan Pharmaceutical Research Corporation
Date of Approval of NDA Insert and supplement #: 20-353/S-008: approved February 4, 2002.
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: Most recently approved container labels for the reference listed drug.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

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.		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			
PROPRIETARY NAME			
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 -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? 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	
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 (p. #) 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 p. # 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 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.			

FOR THE RECORD:

1. **MODEL LABELING**
   The model used was for Naprelan, NDA 20-353/S-008 approved Feb 4, 2002.

   Note: The firm also has 375mg dose pening 30 month exclusivity
2. **INACTIVE INGREDIENTS**
   Consistent with Components and Composition statements
   [VOLUME A. 1.10 PAGES 3049 VOLUME B. 3.1 pg 000072]

3. **PATENTS/EXCLUSIVITIES (from previous FTR)**
   Patent Data – NDA 20-353

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5637320	***June 10, 2014***	None		Paragraph IV	None

   Exclusivity Data– NDA 20-353

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

4. **STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON**
   NDA: Store at controlled room temperature, 20-25°C(68-77°F).
   ANDA:Store at controlled room temperature, 20-25°C(68-77°F).

5. **DISPENSING STATEMENTS COMPARISON**
   NDA: Dispense in a well-closed container.
   ANDA:Dispense in a well-closed container.

6. **PACKAGING CONFIGURATIONS**
   NDA: 375 mg tablets in bottles of 100 & 500 mg tablets in bottles of 75.

   ANDA: 500 mg tablets in bottles of 75, 100 and 1000.

7. The tablet imprintings have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al.10. (see pg 473A in vol. A. 3.2)

8. **CLOSURE**
   500 mg bottles of 75 will be packaged in (b) (4) containers with a CRC closure.
   500mg bottles of 100 will be packaged in (b) (4) containers w/ a CRC closure (as of 1/9/01 submission) 9see pg 0077 in vol. B. 3.1)
   500 mg bottles of 1000 will be packaged in (b) (4) containers with a non-CRC closure.

Date of Review: 8/19/02 Date of Submission: 8/16/02
Primary Reviewer: Jim Barlow Date: 8/24/02

Team Leader: John Grace Date: 8/23/2002

---

cc:
ANDA: 75-416
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSAM\ANDRX\LTRS&REV\75416ap.sb
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 1 (one)

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

   Andrx Pharmaceuticals, Inc.
   Attention: David A. Gardner
   4001 S.W. 47th Street
   Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

   NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) (Elan Pharma, Ltd.)

   This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) is also stated and is due to expire January 5, 1999.

5. SUPPLEMENT(s):

   Not applicable.

6. NAME OF DRUG:

   Naproxen Sodium Extended-release Tablets, 500 mg (base)

7. NONPROPRIETARY NAME:

   None

8. SUPPLEMENT(s) PROVIDE(s) FOR:

   Not applicable.

9. AMENDMENTS AND OTHER DATES:

   7-16-98 Date of Original Submission
   8-20-98 Amendment to Application
   9-30-98 Patent Amendment

10. PHARMACOLOGICAL CATEGORY:

Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED:

℞

12. RELATED IND/NDA/DMF(s):

DMF (b) (4)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM:

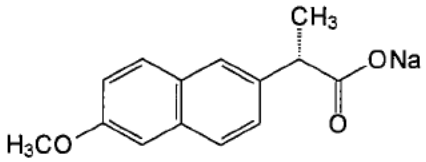
Tablets

14. POTENCY:

500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS:

None

17. COMMENTS:

None.

18. CONCLUSIONS AND RECOMMENDATIONS:

Not approvable - MINOR Amendment

19. REVIEWER: A.J. Mueller, Ph.D.

19A. DATE COMPLETED: December 17, 1998

Following this page, 20 pages withheld in full (b)(4)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Controlled Release Tablets, 550 mg (eq. 500 mg base)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (b) (4) for Naproxen Sodium, has been found deficient and the holder has been notified.

2. (b) (4)

3.

4.

5.

6.

7.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

2. We will request the appropriate FDA district laboratory to obtain samples of the new drug substance and the finished dosage form for methods validation at the appropriate time.

Sincerely yours,

1/31/95

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

cc:

ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-623/A.Mueller, Ph.D./1-7-99
HFD-623/V.Sayeed, Ph.D./1-11-99
HFD-617/M.Anderson, PM/1-26-99
X:\NEW\FIRMSAM\ANDRX\LTRS&REV\75416N00.R01
F/T by: bc/1-27-99

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 2 (two)

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

   Andrx Pharmaceuticals, Inc.
   Attention: David A. Gardner
   4001 S.W. 47th Street
   Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

   NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) (Elan Pharma, Ltd.)

   This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) is also stated and is due to expire January 5, 1999.

5. SUPPLEMENT(s):

   Not applicable.

6. NAME OF DRUG:

   Naproxen Sodium Extended-release Tablets, 500 mg (base)

7. NONPROPRIETARY NAME:

   None

8. SUPPLEMENT(s) PROVIDE(s) FOR:

   Not applicable.

9. AMENDMENTS AND OTHER DATES:

   7-16-98 Date of Original Submission
   8-20-98 Amendment to Application
   9-30-98 Patent Amendment
   4-06-99 Minor Amendment

10. PHARMACOLOGICAL CATEGORY:

Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

DMF (b) (4)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM:

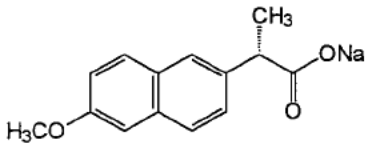
Tablets

14. POTENCY:

500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS:

None

17. COMMENTS:

None.

18. CONCLUSIONS AND RECOMMENDATIONS:

Deficient- Facsimile minor

19. REVIEWER: A.J. Mueller, Ph.D.

19A. DATE COMPLETED: April 30, 1999

Following this page, 15 pages withheld in full (b)(4)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended Release Tablets, 550 mg

The deficiencies presented below represent Minor deficiencies:

A. Deficiencies:

1. [redacted] (b) (4)

2. [redacted]

3. The **Drug Master File** [redacted] (b) (4) **has been reviewed and remains deficient and holder has been notified.**

Sincerely yours,

6/4/99

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

cc:

ANDA 75-416 ORIG
ANDA 75-416 DUP
DIV FILE
Field Copy

Endorsements:

HFD-623/A.Mueller, Ph.D./4/30/99 A.J.Mueller 6-1-99
HFD-623/V.Sayeed, Ph.D./5/5/99 Vilard Sayeed 6/2/99
HFD-617/B.McNeal, PM/6/1/99 B. McNeal 6/4/99
F/t by: gp/6/1/99
File: v:\firmsam\andrx\ltrs&rev\75416n00.r02.doc
Date: April 30, 1999

CHEMISTRY REVIEW - NOT APPROVABLE - FACSIMILE

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 3

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Street
Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) (Elan Pharma, Ltd.)

This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) is also stated and is due to expire January 5, 1999.

5. SUPPLEMENT(s): Not applicable

6. NAME OF DRUG:

Naproxen Sodium Extended-release Tablets, 500 mg (base)

7. NONPROPRIETARY NAME: None

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

7-16-98 Date of Original Submission
8-20-98 Amendment to Application
9-30-98 Patent Amendment
4-06-99 Minor Amendment
5/14/99 Amendment (Labeling)
6/21/99 Amendment (Response to 6/9/99 NA letter)
7/28/99 New corr.
8/16/99 New corr.
9/27/99 FAX (Tel) amendment
10/12/99 Tel.amendment
11/4/99 FAX correspondence
11/19/99 Tel.amendment
12/14/99 Tel.amendment

12/21/99 Minor amendment

10. PHARMACOLOGICAL CATEGORY:

Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

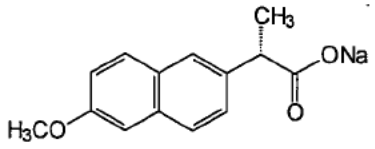
DMF (b) (4)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM: Tablets

14. POTENCY: 500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS: Reviews # 1 and 2 were performed by A. Mueller.

18. CONCLUSIONS AND RECOMMENDATIONS:
NA/Minor

This application is filed under a Paragraph IV Certification.

19. REVIEWER: J.Fan DATE COMPLETED: 7/27/99, 12/30/99 (Rev.)

Following this page, 18 pages withheld in full (b)(4)

JAN 12 2000

38. Chemistry Comment to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 550 mg

The deficiency presented below represents a MINOR deficiency:

A. Deficiency:

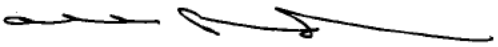
(b)(4)

B.

(b) (4)

[redacted]

Sincerely yours,



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

cc: ANDA 75-416 ORIG
ANDA 75-416 DUP
DIV FILE
Field Copy

Endorsements:
HFD-623/A.Mueller, Ph.D./1-11-00 A. Mueller 1-11-00
HFD-623/J.Fan/1-11-00 J. Fan 1/11/00
HFD-617/B.McNeal/1-11-00 B. McNeal 1/11/00

F/t by: gp/1-11-00
V:\firmsam\andrx\ltrs&rev\75416n3.d.doc

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 4

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Street
Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) (Elan Pharma, Ltd.)

This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) is also stated and is due to expire January 5, 1999.

5. SUPPLEMENT(s): Not applicable

6. NAME OF DRUG:

Naproxen Sodium Extended-release Tablets, 500 mg (base)

7. NONPROPRIETARY NAME: None

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

7-16-98 Date of Original Submission
8-20-98 Amendment to Application
9-30-98 Patent Amendment
4-06-99 Minor Amendment
5/14/99 Amendment (Labeling)
6/21/99 Amendment (Response to 6/9/99 NA letter)
7/28/99 New corr.
8/16/99 New corr.
9/27/99 FAX (Tel) amendment
10/12/99 Tel.amendment
11/4/99 FAX correspondence
11/19/99 Tel.amendment
12/14/99 Tel.amendment

12/21/99 Minor amendment
1/14/00 Minor amendment

10. PHARMACOLOGICAL CATEGORY:

Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

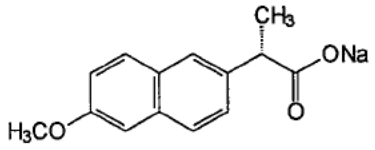
DMF [redacted] (b)(4)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM: Tablets

14. POTENCY: 500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS: Reviews # 1 and 2 were performed by A. Mueller.

18. CONCLUSIONS AND RECOMMENDATIONS:
Tentative approval

This application is filed under a Paragraph IV Certification.

19. REVIEWER: J.Fan DATE COMPLETED: 7/27/99, 1/28/00 (Rev.)

cc: ANDA 75-416 ORIG
ANDA 75-416 DUP
DIV FILE
Field Copy

Endorsements:
HFD-623/A.Mueller, Ph.D. A. Mueller 1-28-00
HFD-623/J.Fan/ 1/28/00
V:\firmsam\andrx\ltrs&rev\75416n4.d.doc

F/t by:

Following this page, 19 pages withheld in full (b)(4)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 5 (Addition of the 375 mg strength)

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

   Andrx Pharmaceuticals, Inc.
   Attention: David A. Gardner
   4001 S.W. 47th Street
   Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

   NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) and 412.5 mg (eq.375 mg) (Elan Pharma, Ltd.)

   This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) expired on January 5, 1999.

5. SUPPLEMENT(s): Not applicable

6. NAME OF DRUG:

   Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

7. NONPROPRIETARY NAME: None

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
   FDA: 3/17/00 TA letter issued.

   Firm:

7/16/98	Date of Original Submission (500 mg, base)
2/7/00	FAX amendment
5/11/00	Amendment (Submission of the additional 375 mg (base) strength
6/29/00	New corr. (Patent amendment)

10. PHARMACOLOGICAL CATEGORY:

    Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

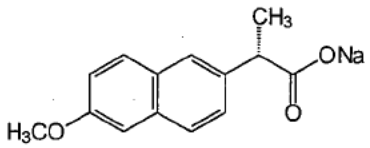
DMF (b) (4)
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF
DMF

13. DOSAGE FORM: Tablets

14. POTENCY: 375 mg, 500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS: Reviews # 1 and 2 were performed by A. Mueller.

18. CONCLUSIONS AND RECOMMENDATIONS:
NA/FAX

19. REVIEWER: J.Fan DATE COMPLETED: 11/8/00

Following this page, 21 pages withheld in full (b)(4)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5. [redacted] (b) (4)

Sincerely yours,

11/1/00

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

cc: ANDA 75-416
DUP
DIV FILE
Field Copy

Endorsements:
HFD-623/J.Fan/11/8/00 11/29/00
HFD-623/A.Mueller, Ph.D./11/10/00 11-29-00
HFD-617/TAmes/11/21/00 11/30/00
V:\firmsam\andrx\ltrs&rev\75416n5.d.doc

F/T by: gp/11/24/00

CHEMISTRY REVIEW - NOT APPROVABLE - FAX

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 6

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) and 412.5 mg (eq.375 mg) (Elan Pharma, Ltd.)

This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) expired on January 5, 1999.

5. SUPPLEMENT(s): Not applicable

6. NAME OF DRUG:

Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

7. NONPROPRIETARY NAME: None

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
FDA: 12/4/00 NA letter issued.

Firm:

7/16/98	Date of Original Submission (500 mg, base)
12/15/00	New corr.(Change of administrative address)
1/3/01	New corr.(Response to 12/4/00 NA letter)
1/9/01	Amendment (CMC update and Labeling)
1/12/01	Amendment (Legal)

10. PHARMACOLOGICAL CATEGORY:

Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

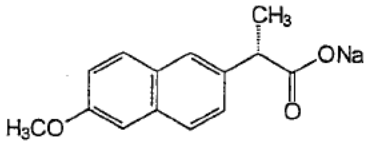
See item #37 DMF checklist.

13. DOSAGE FORM: Tablets

14. POTENCY: 375 mg, 500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS: Reviews # 1 and 2 were performed by A. Mueller.

18. CONCLUSIONS AND RECOMMENDATIONS:
NA/FAX

19. REVIEWER: J. Fan

DATE COMPLETED: 1/24/01

Following this page, 19 pages withheld in full (b)(4)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 375 mg (Base) and 500 mg (base)

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1.

2.

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

Labeling information you have provided for the Naproxen Sodium Extended-release Tablets is under review by our Division of Labeling. After the review is complete, any deficiencies found will be communicated to you under separate cover.

Sincerely yours,

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

cc: ANDA 75-416
DUP
DIV FILE
Field Copy

Endorsements:
HFD-623/J.Fan/1/24/01
HFD-623/A.Mueller, Ph.D./1/26/01
HFD-617/TAmes/1/31/01
V:\firmsam\andrx\ltrs&rev\75416n6.d.doc
F/T by: DJ 2/1/01

CHEMISTRY REVIEW - NOT APPROVABLE - FAX

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 7

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

   Andrx Pharmaceuticals, Inc.
   Attention: Diane Servello
   4955 Orange Drive
   Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

   NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) and 412.5 mg (eq.375 mg) (Elan Pharma, Ltd.)

   This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) expired on January 5, 1999.

5. SUPPLEMENT(s): Not applicable

6. NAME OF DRUG:

   Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

7. NONPROPRIETARY NAME: None

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
   FDA: 2/2/01 NA letter issued.

   Firm:
   7/16/98 Date of Original Submission (500 mg, base)
   5/11/00 Amendment (Added the 375 mg, base)
   2/12/01 Amendment (Response to 2/2/01 NA letter)

10. PHARMACOLOGICAL CATEGORY:

    Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: ℞

12. RELATED IND/NDA/DMF(s):

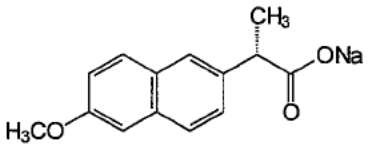
See item #37 DMF checklist.

13. DOSAGE FORM: Tablets

14. POTENCY: 375 mg, 500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS: Reviews # 1 and 2 were performed by A. Mueller.

18. CONCLUSIONS AND RECOMMENDATIONS:
Approval

19. REVIEWER: J. Fan
DATE COMPLETED: 2/22/01
3/5/01 (Revised)

cc: ANDA 75-416
DUP
DIV FILE
Field Copy
Endorsements:
HFD-623/J.Fan/3/5/01 3/9/01
HFD-623/A.Mueller, Ph.D./3/5/01 for 3/13/2001
V:\firmsam\andrx\ltrs&rev\75416n7.a.doc
F/T by: DJ 3/9/01

Following this page, 17 pages withheld in full (b)(4)

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 375 mg (Base) and 500 mg (base)

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. (b) (4)

2.

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

Labeling information you have provided for the Naproxen Sodium Extended-release Tablets is under review by our Division of Labeling. After the review is complete, any deficiencies found will be communicated to you under separate cover.

Sincerely yours,

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

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NO.: 8

2. ANDA #: 75-416

3. NAME AND ADDRESS OF APPLICANT:

Andrx Pharmaceuticals, Inc.
Attention: Diane Servello
4955 Orange Drive
Fort Lauderdale, FL 33314

4. LEGAL BASIS for ANDA SUBMISSION:

NDA 20-353 Naprelan™ Naproxen Sodium Extended-Release Tablets, 550 mg (eq. 500 mg) and 412.5 mg (eq.375 mg) (Elan Pharma, Ltd.)

This application is filed under a "paragraph IV" challenge to the patent # 5,637,320 which is due to expire June 10, 2014. An exclusivity (NDF) expired on January 5, 1999.

In a June 11, 2002 letter to FDA, Andrx declares that a final judgement (Exhibit 2) made on March 14, 2002 renders U.S. patent no. 5,637,320 to be invalid.

Andrx has entered into an agreement with [redacted] (b)(4) **whereby** [redacted] (b)(4) **has waived whatever rights it may have to market exclusively under ANDA** [redacted] (b)(4)**. A copy of the Settlement and Release Agreement is enclosed in Exhibit 3.** [redacted] (b)(4) **has provided a written statement to this effect to FDA (Exhibit B).**

5. SUPPLEMENT(s): N/A

6. NAME OF DRUG:

Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

7. NONPROPRIETARY NAME: None

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

FDA: 2/2/01 NA letter issued.
FDA: 3/17/00 Tentative Approval Letter RPL 8/12/02

Firm:
7/16/98 Date of Original Submission (500 mg, base)
5/11/00 Amendment (Added the 375 mg, base)
2/12/01 Amendment (Response to 2/2/01 NA letter)
12/1/01 Documentation of Litigation
1/22/02 Amendment - Withdrawal of API Manufacturing Site
6/11/02 Request for Final Approval

10. PHARMACOLOGICAL CATEGORY:

Anti-inflammatory, analgesic, antipyretic

11. HOW DISPENSED: Rx

12. RELATED IND/NDA/DMF(s):

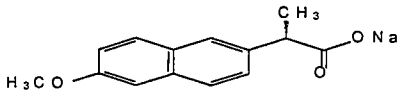
See item #37 DMF checklist. **DMF is adequate per Reviews #2.**

13. DOSAGE FORM: Tablets

14. POTENCY: 375 mg, 500 mg (base)

15. CHEMICAL NAME AND STRUCTURE:

Generic name: Naproxen Sodium
Chemical name: 2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, sodium salt, (*S*)-
Chemical formula: $C_{14}H_{13}NaO_3$
Molecular weight: 252.25
CAS number: 26159-34-2
Chemical structure:



16. RECORDS AND REPORTS: None

17. COMMENTS:

Reviews # 1 and 2 were performed by A. Mueller.
Reviews # 3-7 were performed by J. Fan.

18. CONCLUSIONS AND RECOMMENDATIONS:

Approvable

19. REVIEWER:	DATE COMPLETED:
J. Fan	2/22/01
	3/5/01 (Revised)
S. Dhanesar	6/27/02 (Final Review)

cc: ANDA 75-416
DUP
DIV FILE
Field Copy
Endorsements:
HFD-623/S. Dhanesar/6/27/02 7/31/02
HFD-623/A.Mueller, Ph.D./7/1/02 8-1-02
c:\firmsam\andrx\ltrs&rev\75416n8.d.doc
F/T by: gp/8/1/02

Following this page, 4 pages withheld in full (b)(4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

BIOEQUIVALENCE REVIEWS

Naproxen Sodium
Controlled Release
Tablet, 550 mg (500 mg Base)
ANDA # 75-416
Reviewer: James Chaney
WP #75416SDW.798

Andrx Pharmaceuticals
Ft. Lauderdale, FL
Submission Date:
July 16, 1998

Review of Three In-vivo Bioequivalence Studies and Dissolution Data

I. INTRODUCTION

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties. The sodium salt of naproxen has been developed as a more rapidly absorbed formulation of naproxen for use as an analgesic. Approximately 30% of the total naproxen sodium dose in Naprelan (reference product) is present in the dosage form as an immediate release component.

Naproxen is indicated primarily for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis.

After oral ingestion of an extended release formulation of naproxen, plasma levels of naproxen are detected within 30 minutes of dosing, with peak plasma levels occurring approximately five hours after dosing. The terminal elimination half-life is approximately 15 hours. Steady state levels of naproxen are achieved in 3 days.

The reference product is Naprelan^{Tm} 500, manufactured by Wyeth-Ayerst Laboratories.

II. PRE-STUDY ASSAY VALIDATION

Method: Samples were extracted with methylene chloride and assayed by HPLC with fluorescence detection.

Standard Curve Conc. (mcg/mL):	0.100, 0.250, 0.500, 1.00, 2.50, 5.00, 10.0, 25.0, 50.0, 100
Interday Precision (%CV):	0.826-8.62
Interday Accuracy (%Actual):	97.61-101.03
QC Conc. (mcg/mL):	0.100, 0.250, 3.00, 70.0
Intraday Precision (%CV):	0.705-9.29

Intraday Accuracy (%Actual): 95.33-104.31

Interday Precision (%CV): 1.19-8.14 (including LOQ)

Interday Accuracy (%Actual): 100.9-114.1 (including LOQ)

Stability in Plasma/Serum:

Conc. (mcg/mL): 0.250, 3.00, 70.0

a) 4 Hr @ Room Temp.: 100.872-103.44

b) Freeze-Thaw Cycles (3): 100.591-102.85

c) Long-Term Frozen (56 days) (% Actual): 91.24-102.02

Linearity (Range of r^2): 0.9988-0.9997

Linear Range (mcg/mL): 0.100-100

Sensitivity/LOQ (mcg/mL): 0.100

Recovery (Overall %): 95.4

Specificity: No endogenous peaks interfering with the quantitation of naproxen or the internal standard in the plasma blanks.

III. SINGLE DOSE FASTING STUDY

A. Study Objective:

The objective of this study was to compare the bioavailability of a test extended release formulation of naproxen sodium (Andrx Pharmaceuticals, Inc.) to an equivalent dose of the commercially available reference drug (Naprelan^{Tm} 500, Wyeth-Ayerst Laboratories), under fasting conditions.

B. Study Investigators and Facilities:

Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO

Analytical Facility: (b) (4)

Statistics:

C. Informed Consent and IRB Approval:

The protocol and the subject consent form were reviewed and approved by the St. Charles Community IRB. Prior to initial dosing, each test subject read, and signed the subject consent form acknowledging his awareness of risks and benefits from this study.

D. Study Design:

Open-label, randomized, single-dose 2-way crossover

bioavailability study.

E. Subject Selection

Eligible volunteers underwent pre-study examinations that included a physical examination, 12-lead ECG, and laboratory tests - including hematology, blood chemistries, urinalysis, infectious diseases (Hepatitis B, HIV), and drugs of abuse. Subjects meeting all entrance criteria were admitted, and sequestered, at the clinical facility for 10 hours pre-dose, and until 36 hours post-dose.

Qualifying subjects had to be in good health and physical condition as determined by medical history, complete physical examination, and laboratory tests, all obtained within four (4) weeks prior to study start. The subject could not present with a history of significant past illness expected to affect the investigation.

F. Drug Administration:

Following a supervised overnight fast, one tablet of test or reference product was administered with 240 mL of water to each subject, according to a randomization scheme.

G. Study Schedules:

Sampling times were at Hour 0 (within 60 minutes prior to dose), and at post-dosing hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48. Plasma samples were immediately frozen at -20 degrees C until shipment to the analytical facility. The frozen samples were shipped under dry ice to PPD Pharmaco for assay.

Safety Evaluations Vital signs (sitting blood pressure and pulse rate) were obtained at baseline (Hour 0), and at post-dose hours 2, 4, 24, and 36.

H. Study Dates:

Study Period 1 was initiated on February 21, 1998; Study Period 2 was initiated on February 28, 1998, and the last clinical sample was obtained on March 2, 1998. Plasma samples were shipped to (b) (4) on Monday, March 2, 1998. All plasma samples were received frozen on March 3, 1998. Analysis of subject samples began on March 17, 1998 and was completed on March 30, 1998.

I. Washout period:

There was a seven day washout period between study doses.

J. Drug Products:

A (Test): naproxen sodium 550 mg extended release tablet (Andrx Pharmaceuticals, Inc.), Lot No. 100R003A. Batch size, (b) (4)

B (Reference): naproxen sodium 550 mg extended release tablet (Naprelan 500, Wyeth-Ayerst Laboratories), Lot No. 1973033, exp. date 06/2000

Potency and Content Uniformity

	TEST	REF
Assay: mg Naproxen Na/Tab	533.2	528.3
Label Claim (%)	97.0	96.1
Uniformity of Dosage Units	96.6	95.1
Range	93.7-100.2	94.0-96.2
%RSD (n=10)	2.3	0.8

K. During Study Analytical:

LOQ 0.100 mcg/mL.

Linearity

The average correlation coefficient for the analytical runs was 0.9989.

Stability in frozen plasma (-20C): 8 weeks

Table 1. Back Calculated Calibration Data and Quality Control Sample Inter-assay Precision and Accuracy

	Back Calculated Calibration	Q.C. Samples		
Conc. (mcg/mL)	0.100, 0.250, 0.500, 1.00, 2.50, 5.00, 10.0, 25.0, 50.0, 100	0.250	3.00	70.0
Precision*	2.44% to 7.97%	5.37	2.41	2.22
Accuracy**	-1.80% to 3.80%	-5.73	-0.04	-2.30

*Precision is %CV. **Accuracy is % difference from theoretical.

L. Statistical Analyses:

The analysis of variance model included sequence, subject nested within sequence, period and drug formulation as factors. The significance of the sequence effect was tested using the subject nested within sequence as the error term. The statistical analyses were done using the SAS GLM procedure.

M. Clinical Notes:

During this clinical evaluation, there were no adverse events. Of the 28 subjects enrolled into the study, 27 subjects completed the study in its entirety. Subject #24 was unable to participate in Study Period 2 for a personal reason.

N. Results of Bioequivalence Study:

Arithmetic mean plasma concentrations versus time, arithmetic mean pharmacokinetic parameters and T/R ratios are shown in Table 2. The mean concentration versus time profiles are depicted in Fig 1. Many of the subjects had a quantifiable naproxen plasma level in their pre-dose sample for dosing period 2. These levels were generally less than 1% of the observed CMAX. Thus there was no appreciable carry-over between periods. A summary of the statistics of the pharmacokinetic parameters is shown in Table 3.

Table 2. Arithmetic Mean Plasma Concentrations (mcg/mL) Versus Time (hr), Arithmetic Mean Pharmacokinetic Parameters and T/R Ratios for Naproxen in Fasting Single Dose Study, N=27

	Test (A)		Reference (B)		
Plasma Levels					
Time	Mean	%CV	Mean	%CV	A/B
0	0.07	157	0.12	167	0.55
0.5	20.12	41	16.52	43	1.22
1	24.48	32	27.98	28	0.87
2	29.06	25	33.31	23	0.87
3	31.65	25	36.66	22	0.86
4	35.65	23	39.95	18	0.89
6	42.37	21	38.83	12	1.09
8	41.11	19	35.23	13	1.17
10	38.90	20	33.08	16	1.18
12	34.86	21	29.81	17	1.17
16	29.25	17	25.67	18	1.14
24	21.77	20	21.03	20	1.04
30	16.79	24	17.01	22	0.99
36	12.99	27	13.67	26	0.95
48	8.33	30	8.96	31	0.93
Pharmacokinetic Parameters					
Parameter	Mean	%CV	Mean	%CV	A/B
AUCT	1088.6	16	1043.6	16	1.04
AUCI	1307.2	18	1311.5	21	1.00
CMAX	45.5	15	42.4	14	1.07
THALF	17.6	16	19.6	23	0.90
TMAX	8.3	49	5.1	36	1.64

Table 3. LSMeans, Geometric LSMeans, T/R Ratios and 90% Confidence Intervals (C.I.) For Naproxen Pharmacokinetic Parameters in Fasting Single-Dose Study, N=27.				
Parameter	Test (A)	Reference (B)	A/B	90%C.I.
LSMeans				
AUCT	1088.5	1042.7	1.04	101.8-107.0
AUCI	1306.7	1309.8	1.00	97.0-102.5
CMAX	45.5	42.4	1.07	101.5-113.2
Geometric LSMeans				
AUCT	1075.8	1029.9	1.04	101.9-107.0
AUCI	1285.4	1281.4	1.00	97.6-103.1
CMAX	45.0	42.0	1.07	101.1-113.5

IV. FOOD STUDY

A. Study Objective:

The objective of this study was to compare the bioavailability of a test extended release formulation of naproxen sodium (Andrx Pharmaceuticals, Inc.) to an equivalent dose of the commercially available reference drug (Naprelan^{Tm} 500, Wyeth-Ayerst Laboratories) under fed and fasting conditions.

B. Study Investigators and Facilities:

Same as for the fasting study

C. Informed Consent and IRB Approval:

Same as for the fasting study

D. Study Design:

The study was designed as an open-label, single dose, randomized, 3-way crossover bioavailability study using 21 healthy subjects.

E. Subject Selection Criteria:

Same as for fasting study.

F. Drug Administration:

Following a supervised overnight fast and 15 minutes before their scheduled dosing times, subjects assigned to non-fasted treatments "B" and "C" received the standard high fat breakfast and were then administered one tablet of the test or reference product with 240 mL of water. Subjects assigned to the fasted treatment "A" received one tablet of the test product with 240 mL of water.

G. Study Schedules:

Sampling times were at Hour 0 (within 60 minutes prior to dose), and at post-dosing hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12,

16, 24, 36, 48, 72 and 96. Plasma samples were immediately frozen at -20C until shipment to the analytical facility. The frozen samples were shipped under dry ice to [redacted](b)(4) for assay.

Safety Evaluations Vital signs (sitting blood pressure and pulse rate) were obtained at baseline (Hour 0), and at post-dose hours 2, 4, 24, and 36.

H. Study Dates:

Study Period I was initiated on May 2, 1998; Study Period II was initiated on May 16, 1998; and Study Period III was initiated on May 30, 1998, and the last clinical sample was obtained on June 3, 1998. Analysis of subject samples began on June 16, 1998 and was completed on June 26, 1998

I. Washout Period:

Two weeks

J. Drug Products:

Same as for the fasting study

K. During Study Analytical:

LOQ 0.100 mcg/mL.

Linearity

The average correlation coefficient for the analytical runs was 0.9989.

Stability in frozen plasma (-20 degrees C): 11 weeks

Table 4. Back Calculated Calibration Data and Quality Control Sample Inter-assay Precision and Accuracy

	Back Calculated Calibration	Q.C. Samples		
Conc. (mcg/mL)	0.100, 0.250, 0.500, 1.00, 2.50, 5.00, 10.0, 25.0, 50.0, 100	0.250	3.00	70.0
Precision*	2.65% to 4.84%	3.98	2.94	2.90
Accuracy**	2.90% to 3.98%	-2.97	1.50	0.51

*Precision is %CV. **Accuracy is % difference from theoretical.

L. Statistical Analyses:

The analysis of variance model included sequence, subject nested within sequence, period and drug formulation as factors. The significance of the sequence effect was tested using the subject nested within sequence as the error term. The statistical analyses were done using the SAS GLM procedure.

M. Clinical Notes:

During this clinical evaluation, three mild adverse events occurred including headache, vomiting and an irritated right eye.

The latter two were possibly drug related. Subjects 1, 8 and 13 failed to show up for one or more dosings.

N. Results of Bioequivalence Study:

Arithmetic mean plasma concentrations versus time (hr), arithmetic mean pharmacokinetic parameters and T/R ratios are shown in Table 5. The mean concentration versus time profiles are depicted in Fig 1. A summary of the statistics of the pharmacokinetic parameters is shown in Table 6. Of the 21 subjects enrolled into the study, 18 subjects completed the study in its entirety.

Table 5. Arithmetic Mean Plasma Concentrations (mcg/mL) Versus Time (hr), Arithmetic Mean Pharmacokinetic Parameters and T/R Ratios for Naproxen in Food Study, N=18

	Test Fast (A)		Test Fed (B)		Ref. Fed ©			
Plasma Levels								
Time	Mean	%CV	Mean	%CV	Mean	%CV	A/B	B/C
0	0	-	0	-	0.25	432	.	0.00
0.5	18.51	46	3.17	110	1.46	110	5.84	2.17
1	22.99	35	8.2	91	7.4	105	2.80	1.11
2	26.41	32	14.51	54	16.78	65	1.82	0.86
3	30.37	21	19.96	42	22.06	50	1.52	0.90
4	35.71	18	21.88	44	26.72	41	1.63	0.82
6	39.35	18	36.33	44	39.75	20	1.08	0.91
8	38.81	13	35.23	35	39.61	19	1.10	0.89
10	39.22	10	34.58	35	35.81	15	1.13	0.97
12	32.61	13	31.15	34	31.62	20	1.05	0.98
16	28.11	13	24.6	32	25.69	17	1.14	0.96
24	20.68	21	24.52	36	21.13	20	0.84	1.16
36	13.04	28	14.16	38	13.13	28	0.92	1.08
48	8.1	32	9	45	8.39	31	0.90	1.07
72	3.68	47	3.61	50	3.52	43	1.02	1.03
96	1.65	59	1.6	61	1.61	58	1.03	1.00
Pharmacokinetic Parameters								
Parameter	Mean	%CV	Mean	%CV	Mean	%CV	A/B	B/C
AUCT	1255.7	16	1212.3	15	1188.3	19	1.04	1.02
AUCI	1305.7	18	1258.3	17	1236.3	21	1.04	1.02
CMAX	42.7	12	47.2	15	41.8	16	0.90	1.13
THALF	19.1	19	18.5	18	18.8	18	1.04	0.98
TMAX	7.3	30	11.3	64	7.9	56	0.65	1.44

Table 6. LSMeans and T/R Ratios For Naproxen Pharmacokinetic Parameters in Food Study, N=18					
Parameter	Test Fast (A)	Test Fed (B)	Ref Fed ©	A/B	B/C
LSMeans					
AUCT	1279.1	1231.5	1209.0	1.04	1.02
AUCI	1332.6	1280.0	1259.5	1.04	1.02
CMAX	42.8	47.3	41.9	0.91	1.13
Geometric LSMeans					
LAUCT	1264.5	1218.5	1187.6	1.04	1.03
LAUCI	1313.6	1263.3	1233.6	1.04	1.02
LCMAX	42.5	46.8	41.3	0.91	1.13

V. MULTIPLE DOSE STUDY

A. Study Objective:

The objective of this study was to compare the bioavailability of a test extended release formulation of naproxen sodium (Andrx Pharmaceuticals, Inc.) to an equivalent dose of the commercially available reference drug (Naprelan^{Tm} 500, Wyeth-Ayerst Laboratories), under fasting conditions at steady state.

B. Study Investigators and Facilities:

Same as for the fasting study.

C. Informed Consent and IRB Approval:

Same as for the fasting study

D. Study Design:

The study was designed as an open-label, randomized, 2-way crossover bioavailability study.

E. Subject Selection Criteria:

Same as for the fasting study

F. Drug Administration:

Naproxen sodium 550 mg extended release tablet was administered to subjects as a single tablet dose at hour 0 on Days 1, 2, 3, 4, and 5, with 240 mL of room temperature tap water, following a 10 hour overnight fast prior to each dose.

G. Study Schedules:

Sampling times were at Hour 0 (within 60 minutes prior to each dose) on Days 1, 2, 3, 4, and 5, and on Study Day 5 at post-dosing hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24. Samples were immediately frozen at -20C until shipment to the analytical facility.

H. Study Dates:

Study Period 1 was initiated on April 27, 1998; Study Period 2 was initiated on May 18, 1998 and the last clinical sample was

obtained on May 23, 1998. Analysis of subject samples began on May 29, 1998 and was completed on June 16, 1998

I. Washout Period:

Two weeks

J. Drug Products:

Same as for the fasting study

K. During Study Analytical:

LOQ 0.100 mcg/mL.

Linearity

The average correlation coefficient for the analytical runs was 0.9980.

Stability in frozen plasma (-20C): 10 weeks

Table 7. Back Calculated Calibration Data and Quality Control Sample Inter-assay Precision and Accuracy

	Back Calculated Calibration
Conc. (mcg/mL)	0.100, 0.250, 0.500, 1.00, 2.50, 5.00, 10.0, 25.0, 50.0, 100
Precision*	3.55% to 7.95%
Accuracy**	-3.97% to 3.92%

*Precision is %CV. **Accuracy is % difference from theoretical.

Two sets of quality controls were used. For analytical runs which contain diluted subject samples, the highest Q.C. pool was diluted and analyzed to validate the dilution of subject samples (Table 8).

Table 8. Quality Control Sample Inter-assay Precision and Accuracy

	Q.C. Samples, Run 3PLE			Q.C. Samples, Remaining Runs			QC3 Diluted 2x
Conc. (mcg/mL)	0.250	3.00	70.0	0.250	3.00	70.0	70.0
Precision*	21.0	10.8	3.69	9.59	3.76	6.19	3.55
Accuracy**	-15.1	-4.29	-4.07	-5.65	1.74	-0.72	0.304

*Precision is %CV. **Accuracy is % difference from theoretical.

L. Statistical Analyses:

The analysis of variance model included sequence, subject nested within sequence, period and drug formulation as factors.

The significance of the sequence effect was tested using the subject nested within sequence as the error term. The statistical analyses were done using the SAS GLM procedure. Steady state was judged to have been achieved if the time and time*formulation interactions were not significant for either formulation.

M. Clinical Notes:

Three subjects failed to complete this program, for the following, reasons:

Subject #2, was dropped due to the unreliability of data as a result of vomiting and the lack of standardized dietary intake. Subjects #8 and 13 dropped out of for personal reasons.

The adverse events are listed on page 2053 of Volume 1.7 and include nausea, vomiting, sore throat, stiff neck, head cold and toothache. Most events were considered as unrelated or remotely related to drug treatment.

N. Results of Bioequivalence Study:

Arithmetic mean plasma concentrations versus time (hr), arithmetic mean pharmacokinetic parameters and T/R ratios are shown in Table 9. The mean concentration versus time profiles are depicted in Fig 3. A summary of the statistics of the pharmacokinetic parameters is shown in Table 10. Of the 28 subjects enrolled into the study, 25 subjects completed the study in its entirety.

Table 9. Arithmetic Mean Plasma Concentrations (mcg/mL) Versus Time (hr), Arithmetic Mean Pharmacokinetic Parameters and T/R Ratios for Naproxen in Fasting Multiple-Dose Study, N=25					
	Test (A)		Reference (B)		
Plasma Levels					
Time	Mean	%CV	Mean	%CV	A/B
-96	0.00	.	0.00	.	-
-72	19.84	29	19.47	20	1.02
-48	25.65	33	24.25	18	1.06
-24	24.99	25	26.29	23	0.95
0	26.52	22	27.96	29	0.95
0.5	43.61	26	40.04	19	1.09
1	44.53	15	46.67	21	0.95
2	49.47	17	51.28	15	0.96
3	53.62	22	54.45	19	0.98
4	54.33	18	56.74	16	0.96
6	56.26	16	54.14	16	1.04
8	53.73	18	47.24	16	1.14
10	48.68	18	44.48	18	1.09
12	44.01	17	39.68	15	1.11
16	37.64	21	34.76	16	1.08
24	28.52	24	28.90	20	0.99
Pharmacokinetic Parameters					
Parameter	Mean	%CV	Mean	%CV	A/B
AUCTAU	1035.7	15	987.8	13	1.05
CMAX	61.0	18	60.0	16	1.02
TMAX	5.1	43	3.8	40	1.35
CMIN	26.5	22	28.0	29	0.95
CAVG	43.2	15	41.2	13	1.05
%FLUCT	80.0	22	78.2	21	1.02

Table 10. LSMeans, Geometric LSMeans, T/R Ratios and 90% Confidence Intervals (C.I.) For Naproxen Pharmacokinetic Parameters in Fasting Multiple-Dose Study, N=25				
Parameter	Test (A)	Reference (B)	A/B	90%C.I.
LSMeans				
AUCTAU	1035.3	987.3	1.05	103-107
CMAX	61.0	60.0	1.02	97.8-105
TMAX	5.1	3.7	1.35	116-154
CMIN	26.5	27.9	0.95	86.2-104
CAV	43.1	41.1	1.05	103-107
%FLUCT	80.0	78.4	1.02	92.8-111
Geometric LSMeans				
AUCTAU	1024.8	979.6	1.05	102-107
CMAX	60.1	59.3	1.01	97.7-105
CAV	42.7	40.8	1.05	102;107

VI. COMPONENTS AND COMPOSITION

Ingredient	%	mg/tablet
Naproxen Sodium, USP	(b) (4)	550.0
(b) (4)		(b) (4)
Fumaric Acid, NF (b) (4)		
Hydroxypropyl Methylcellulose, USP (b) (4)		
Hydroxypropyl Cellulose, NF (b) (4)		
Microcrystalline Cellulose, NF (b) (4)		
Magnesium Stearate, NF		
Colloidal Silicon Dioxide, NF (b) (4)		
(b) (4)		
TOTAL	100.00	

VII. IN-VITRO DISSOLUTION TESTING

The dissolution results for the test and reference products using various dissolution media and USP 23 apparatus 2 (Paddle) at 50 rpm indicated that the dissolution profiles are pH dependent (solubility increasing with pH). The dissolution media were pH 7.5 phosphate buffer (0.05M), pH 6.5 phosphate buffer (0.05 M), pH 4.2 acetate buffer (0.05 M), and simulated gastric fluid (pH 1.2). The dissolution results are shown in Table 11. The pH 7.5 phosphate buffer (0.05M) was suggested by the firm as the dissolution media with a paddle stirring rate of 50 rpm for routine testing.

Table 11. In Vitro Dissolution Testing

Drug (Generic Name): Naproxen Sodium Controlled-release (CR)
Dose Strength: 550 mg Tablets
ANDA #: 75-416
Firm: Andrx Pharmaceuticals
Submission Date: July 16, 1998

I. Conditions for Dissolution Testing:

USP XXIII Basket: Paddle: X RPM: 50 No. Units Tested: 12
Media: pH 7.5 Phosphate Buffer (0.05M), pH 6.5 Phosphate Buffer (0.05 M), pH 4.2 Acetate Buffer (0.05 M), SGF
Volume: 900 mL
Firm's Proposed Specifications at pH 7.5:

Time (Hours)	%Released
0.5	(b) (4)
3	
6	
14	NLT (b) (4)

Reference Drug: Naprelan™ 500, manufactured by Wyeth-Ayerst Laboratories

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 100R003A Strength(mg) 550 MG			Reference Product Lot # 1973033 Strength(mg) 550 MG		
	Mean %	Range	%CV	Mean %	Range	%CV
pH 7.5 Phosphate Buffer						
0.5	24	(b) (4)	6.9	29	(b) (4)	11.9
1	28		6.1	54		5.8
2	36		5.3	74		3.0
3	42		4.9	84		2.6
4	49		5.0	89		2.0
6	60		4.9	92		1.7
10	79		7.0	94		1.5
14	90		4.6	95		1.4
18	95		3.4	96		1.4

(In Vitro Dissolution Testing Continued)						
pH 6.5 Phosphate Buffer						
0.5	21	(b) (4)	4.2	20	(b) (4)	7.6
1	25		3.7	38		4.8
2	31		3.0	51		4.0
3	37		3.0	59		3.8
4	42		3.7	65		4.0
6	52		4.7	74		4.3
10	68		6.9	84		4.1
14	80		5.3	89		3.5
18	88		4.7	92		3.0
pH 4.2 Acetate Buffer						
0.5	0	(b) (4)	4.9	1	(b) (4)	33.1
1	1		9.0	6		28.3
2	1		8.9	9		15.0
3	2		6.6	9		10.7
4	2		6.7	9		8.1
6	4		7.9	9		5.2
10	6		10.9	9		3.8
14	7		9.9	9		3.5
18	9		7.9	10		5.8
SGF						
0.5	0	(b) (4)	30.4	0	(b) (4)	31.9
1	1		12.7	3		18.8
2	1		18.9	4		17.9
3	2		20.7	3		31.2
4	3		20.2	3		25.7
6	3		18.6	3		25.1
10	4		20.3	3		26.4
14	3		22.1	3		27.7
18	3		19.9	4		27.0

VIII. COMMENTS

1. Approximately 30% of the total naproxen sodium dose in Naprelan (reference product) is present in the dosage form

as an immediate release component. Apparently the test product was not so designed. In spite of this the product meets the requirements of bioequivalence.

2. The pharmacokinetic parameters and statistical analysis for the fasting study were spot-checked by the reviewer using SAS and the results were in agreement with what the firm reported.
3. In the three bioequivalence studies none of the C_{max} values were the first nonzero concentrations.
4. The assayed potency and the content uniformity of the test and reference products are satisfactory.
5. The analytical data is acceptable.
6. The bioequivalence studies are acceptable.
7. The dissolution methodology and data are acceptable. Phosphate buffer pH 7.5 (0.05M) was suggested by the firm as the dissolution media with a paddle stirring rate of 50 rpm for routine testing. The firm's proposed specifications were:

Time (Hours)	%Released
0.5	(b)(4)
3	
6	
14	NLT (b)(4)

The Division of Bioequivalence recommends that the test product meet the following tentative specifications which are (b)(4) at 3 and 6 hours:

Time (Hours)	%Released
0.5	(b)(4)
3	
6	
14	NLT (b)(4)

8. The test product used for the biostudies and the dissolution studies were from the same batch.

IX. RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study, the fed/fasted bioequivalence study and the bioequivalence study under multiple dose, fasting conditions conducted by Andrx Pharmaceuticals on its test product, naproxen sodium 550 mg

extended release tablet, Lot # 100R003A, comparing it with the reference product, Naprelan^{Tm} 500, Lot # 11973033, manufactured by Wyeth-Ayerst Laboratories have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Andrx Pharmaceuticals' naproxen sodium 550 mg extended release tablet, is bioequivalent to the reference product, Wyeth-Ayerst Laboratories Naprelan^{Tm} 500.

2. From the bioequivalence point of view, the firm has met the requirements of in vivo bioequivalency and in vitro dissolution testing and the application is acceptable.

3. The dissolution testing conducted by Andrx Pharmaceuticals, on its naproxen sodium 550 mg extended release tablet has been found acceptable. The firm's proposed dissolution testing should be incorporated into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of pH 7.5 Phosphate Buffer at 37 degrees C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following tentative specifications:

   [redacted] (b)(4) at 0.5 hour, [redacted] (b)(4) at 3 hours, [redacted] (b)(4) at 6 hours and no less than [redacted] (b)(4) at 14 hours of the labeled amount of naproxen.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang

Date 12/2/98

Concur:

Date 12/3/98

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/120298
X:\NEW\FIRMSAM\ANDRX\LTRS&REV\75416SD.798

(1)

OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA# 75-416 SPONSOR: Andrx Pharmaceuticals

DRUG & DOSAGE FORM: Naproxen Sodium Controlled Release Tablets

STRENGTH(s): 550 mg (500 mg base)

TYPE OF STUDIES: Fasting SD, Fasting/Fed SD and MD bioequivalence studies, and in vitro dissolution testing

STUDY SITES:

Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO

Analytical Facility: (b) (4)

STUDY SUMMARY:

Acceptable

DISSOLUTION:

Acceptable

PRIMARY REVIEWER: James E. Chaney, Ph.D. **BRANCH:** I

INITIAL: JEC **DATE:** 12/2/98

BRANCH CHIEF: Yih Chain Huang, Ph.D. **BRANCH:** I

INITIAL: YCH **DATE:** 12/2/98

DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm.D.

INITIAL: DPC **DATE:** 12/3/98

DIRECTOR, OFFICE OF GENERIC DRUGS:

INITIAL: _____ **DATE:** _____

BIOEQUIVALENCY COMMENTS

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Naproxen Sodium Controlled Release Tablets, 550 mg

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

Based on the data submitted, the following dissolution testing is recommended for your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of pH 7.5 Phosphate Buffer at 37 degrees C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following tentative specifications which are revised from your proposed percent released at 3 and 6 hours:

[redacted] (b)(4) at 0.5 hour, [redacted] (b)(4) at 3 hours, [redacted] (b)(4) at 6 hours and no less than [redacted] (b)(4) at 14 hours of the labeled amount of naproxen.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75416
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Secretary - Bio Drug File
HFD-652/ J. Chaney
HFD-652/ Y. Huang

HFD-652/ J. Chaney
HFD-652/ Y. Huang
HFD-617/ E. Hu 12/3/98
HFD-650/ D. Conner 12/3/98

X:\NEW\FIRMSAM\ANDRX\LTRS&REV\75416SD.798

BIOEQUIVALENCY - ACCEPTABLE Submission date: July 16, 1998

1. FASTING STUDY (STF) Strengths: 550 mg
Outcome: AC

Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO

Analytical Facility: (b)(4)
Statistics:

2. FOOD STUDY (STP) Strengths: 550 mg
Outcome: AC

Facilities same as for the fasting study

3. MULTIPLE DOSE STUDY (STM) Strengths: 550 mg
Outcome: AC

Facilities same as for the fasting study

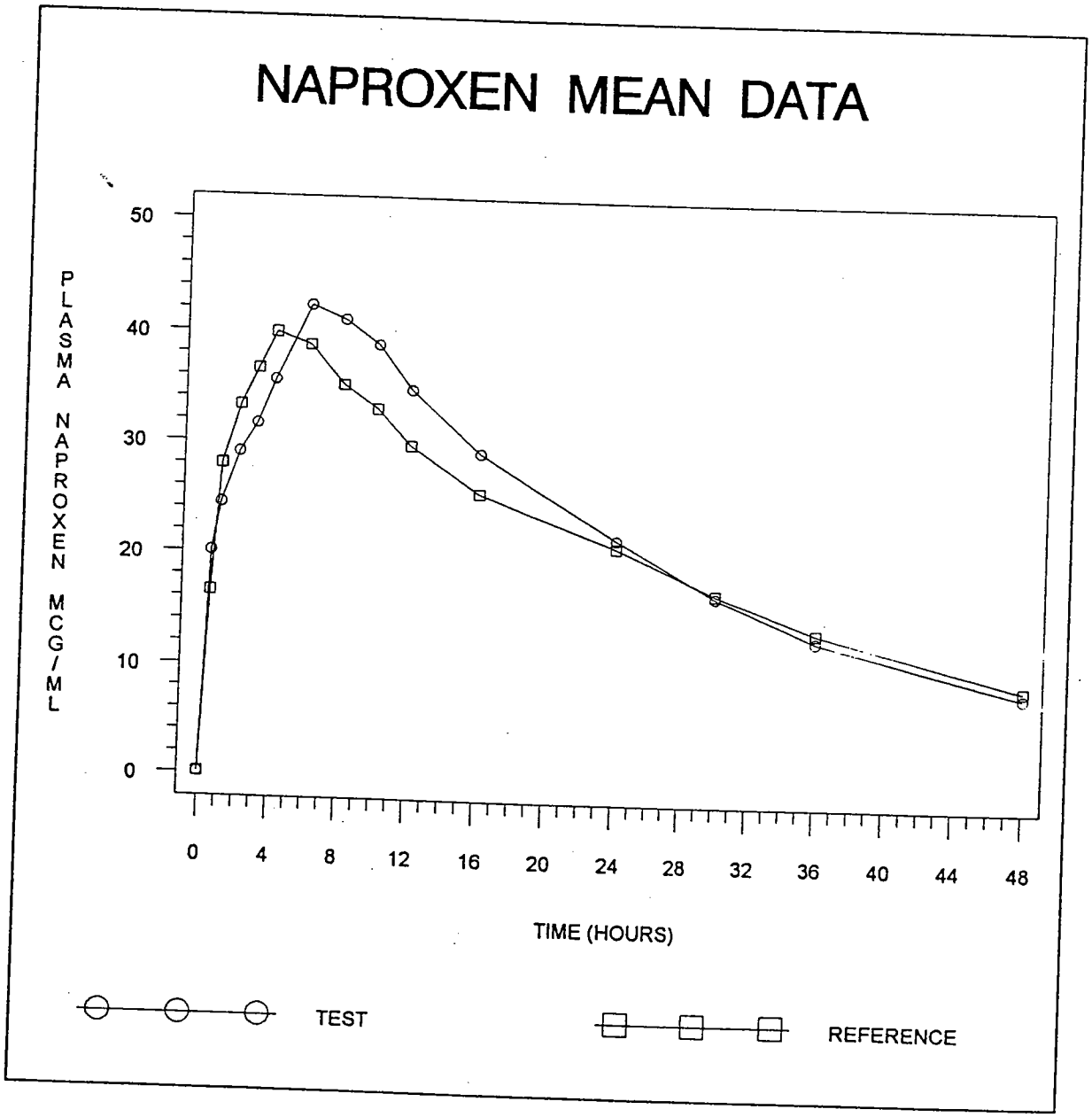
NOTE:

AC - Acceptable	UN - Unacceptable
NC - No Action	IC - Incomplete

Outcome Decision: Acceptable

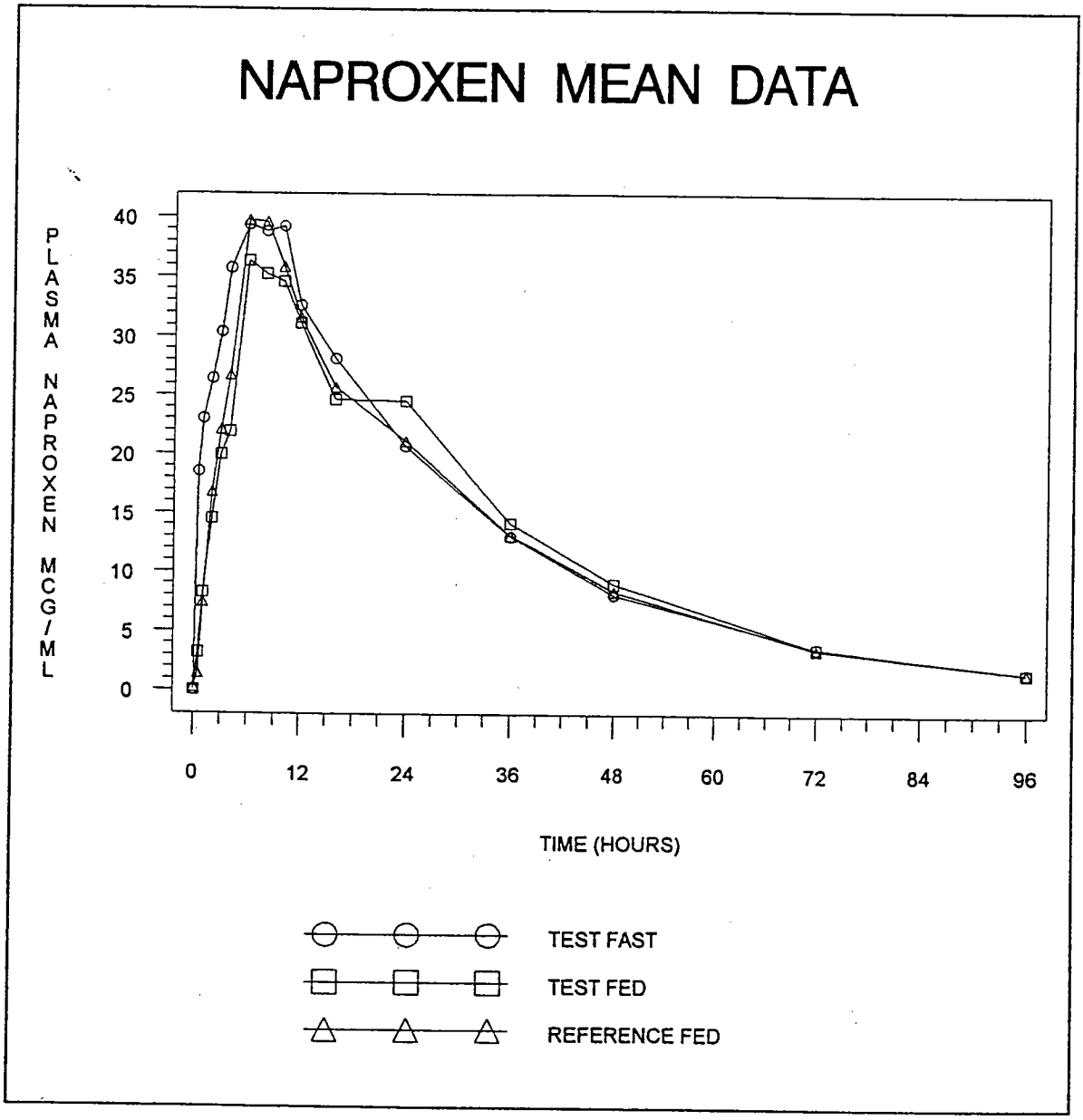
WINBIO COMMENTS:
The biostudy was found acceptable.

Figure 1 Linear Plot of Mean Plasma Naproxen Concentrations *vs* Time



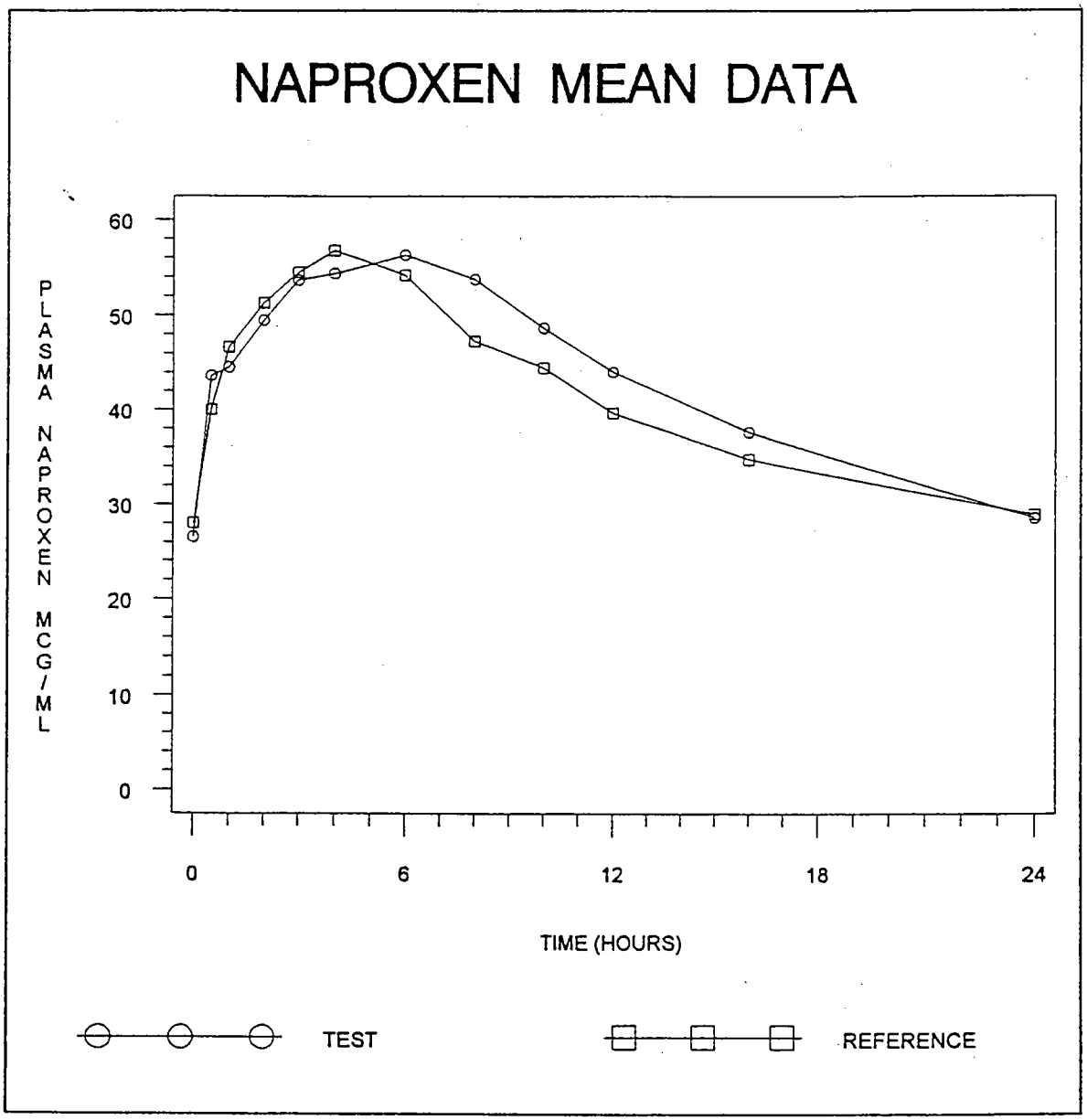
75-416

Figure 2 Linear Plot of Mean Plasma Naproxen Concentrations *vs* Time



75-416

Figure 3 Linear Plot of Mean Plasma Naproxen Concentrations *vs* Time (Day 5)



Naproxen Sodium
Controlled Release
Tablet, 412.5 mg (375 mg Base)
ANDA # 75-416
Reviewer: James Chaney
V:\FIRMSAM\ANDRX\LTRS&REV\75416SD.500

Andrx Pharmaceuticals
Ft. Lauderdale, FL
Submission Date:
May 11, 2000

Review of an Amendment - Fasting Bioequivalence Study and Dissolution Data

I. INTRODUCTION

This submission is an amendment which provides a fasting bioequivalence study in support of the firm's 412.5 mg (375 mg base) strength. The fasting, fasting/fed and multiple-dose studies on the 550 mg strength were previously found acceptable (July 16, 1998 submission reviewed by J. Chaney).

II. PRE-STUDY ASSAY VALIDATION

Method: Samples were extracted with methylene chloride and assayed by HPLC with fluorescence detection.

Standard Curve Conc. (mcg/mL):	0.100, 0.250, 0.500, 1.00, 2.50, 5.00, 10.0, 25.0, 50.0, 100
Interday Precision (%CV):	0.826-8.62
Interday Accuracy (%Actual):	97.61-101.03
QC Conc. (mcg/mL):	0.100, 0.250, 3.00, 70.0
Intraday Precision (%CV):	0.705-9.29
Intraday Accuracy (%Actual):	95.33-104.31
Interday Precision (%CV):	1.19-8.14 (including LOQ)
Interday Accuracy (%Actual):	100.9-114.1 (including LOQ)
Stability in Plasma/Serum:	
Conc. (mcg/mL):	0.250, 3.00, 70.0
a) 4 Hr @ Room Temp.:	100.872-103.44
b) Freeze-Thaw Cycles (3):	100.591-102.85
c) Long-Term Frozen (56 days) (% Actual):	91.24-102.02
Linearity (Range of r^2):	0.9988-0.9997
Linear Range (mcg/mL):	0.100-100
Sensitivity/LOQ (mcg/mL):	0.100

Recovery (Overall %): 95.4

Specificity: No endogenous peaks interfering with the quantitation of naproxen or the internal standard in the plasma blanks.

The equation was calculated for each naproxen calibration curve using a weighted ($1/C^2$) least squares linear regression analysis.

III. SINGLE DOSE FASTING STUDY

A. Study Objective:

The objective of this study was to compare the bioavailability of a test extended release formulation of naproxen sodium (Andrx Pharmaceuticals, Inc.) to an equivalent dose of the commercially available reference drug (Naprelan™ 375, Elan Pharma, Ltd.) under fasting conditions.

B. Study Investigators and Facilities:

Clinical Investigator: Daniel R. Shipley, M.D.
Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO
Analytical Investigator: (b) (6)
Analytical Facility (b) (4)
Statistics:

C. Informed Consent and IRB Approval:

The protocol and the subject consent form were reviewed and approved by the St. Charles Community IRB. Prior to initial dosing, each test subject read, and signed the subject consent form acknowledging his awareness of risks and benefits from this study.

D. Study Design:

Open-label, randomized, single-dose 2-way crossover bioavailability study.

E. Subject Selection

Eligible volunteers underwent pre-study examinations that included a physical examination, 12-lead ECG, and laboratory tests - including hematology, blood chemistries, urinalysis, infectious diseases (Hepatitis B, HIV), and drugs of abuse. Subjects meeting all entrance criteria were admitted, and sequestered, at the clinical facility for 10 hours pre-dose, and until 24 hours post-dose.

Qualifying subjects had to be in good health and physical condition as determined by medical history, complete physical examination, and laboratory tests, all obtained within four (4) weeks prior to study start. The subject could not present with a history of significant past illness expected to affect the investigation.

F. Drug Administration:

Following a supervised overnight fast, one tablet of test or reference product was administered with 240 mL of water to each subject, according to a randomization scheme.

G. Study Schedules:

Sampling times were at Hour 0 (within 60 minutes prior to dose), and at post-dosing hours 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72 and 96. Plasma samples were immediately frozen at -20 degrees C until shipment to the analytical facility. The frozen samples were shipped under dry ice to (b)(4) for assay.

Safety Evaluations Vital signs (sitting blood pressure and pulse rate) were obtained at baseline (Hour 0), and at post-dose hours 2, 4, 24, and 36.

H. Study Dates:

Study Period 1 was initiated on 8/1/99; Study Period 2 was initiated on 8/15/99, and the last clinical sample was obtained on 8/15/99. Plasma samples were shipped to (b)(4) on 8/21/99. All plasma samples were received frozen on 8/24/99. Analysis of subject samples began on 9/3/99 and ended 9/30/99. The maximum time samples were stored frozen from the first day of collection to the last day of analysis was 60 days.

I. Washout period:

There was a 14 day washout period between study doses.

J. Drug Products:

A (Test): naproxen sodium 412.5 mg extended release tablet (Andrx Pharmaceuticals, Inc.), Lot No. 825R002A. Batch size, (b)(4)

B (Reference): naproxen sodium 412.5 mg extended release tablet (Naprelan™ 375, Elan Pharma, Ltd.), Lot No. 1973040, exp. date 06/2000

Potency and Content Uniformity

	TEST	REF
Label Claim (%)	96.0	96.6
Uniformity of Dosage Units	95.3	97.5
Range	93.5-97.5	96.5-99.5
%RSD (n=10)	1.4	1.0

K. During Study Analytical:

LOQ 0.100 mcg/mL.

Linearity

The average correlation coefficient for the analytical runs was 0.9988.

Stability in frozen plasma (-20°C): 4.5 months

Table 1. Back Calculated Calibration Data and Quality Control Sample Inter-assay Precision and Accuracy				
	Back Calculated Calibration	**Q.C. Samples**		
Conc. (mcg/mL)	0.100, 0.250, 0.500, 1.00, 2.50, 5.00, 10.0, 25.0, 50.0, 100	**0.250**	**3.00**	**70.0**
Precision*	2.46% to 6.64%	6.39	3.46	3.29
Accuracy**	-3.05% to 1.69%	-2.05	4.33	2.29

*Precision is %CV. **Accuracy is % difference from theoretical.

L. Statistical Analyses:

The analysis of variance model included sequence, subject nested within sequence, period and drug formulation as factors. The statistical analyses were done using the SAS GLM procedure.

M. Clinical Notes:

During this clinical evaluation, there were no adverse events. Of the 30 subjects enrolled into the study, 29 subjects completed the study in its entirety. Subject #12 was dropped because of smoking during the study.

N. Results of Bioequivalence Study:

Arithmetic mean plasma concentrations versus time, arithmetic mean pharmacokinetic parameters and T/R ratios are shown in Table 2. The mean concentration versus time profiles are depicted in Fig 1. Only one subject (#15) had a quantifiable naproxen plasma level ((b)(4)) in his pre-dose sample for dosing period 2 which was not carry-over from period 1 in that the last sample of period 1 had a concentration of less than 21.8 mcg/mL. Also, this subject did not return to the clinic for the 72 and 96 hour blood collection for period 1. Therefore the data from this subject was not included in the statistical analysis. A summary of the statistics of the pharmacokinetic parameters is shown in Tables 3 and 4.

Table 2. Arithmetic Mean Plasma Concentrations (mcg/mL) Versus Time (hr), Arithmetic Mean Pharmacokinetic Parameters and T/R Ratios for Naproxen in Fasting Single Dose Study, N=28

	Test (A)		Reference (B)		
Plasma Levels					
Time	Mean	%CV	Mean	%CV	A/B
0	0.01	700	0	-	-
0.5	11.74	44	9.44	54	1.24
1	15.59	28	16.31	39	0.96
2	20.53	28	21.44	33	0.96
3	24.1	24	26.28	27	0.92
4	25.83	24	29.77	20	0.87
6	29.72	24	29.18	11	1.02
8	30.59	21	25.77	11	1.19
10	28.8	21	24.23	12	1.19
12	26.32	16	21.89	13	1.2
16	22.05	15	18.93	13	1.17
24	16.19	16	15.32	14	1.06
36	10.36	19	10.55	18	0.98
48	6.34	22	6.73	24	0.94
72	2.62	28	2.83	31	0.93
96	1.19	37	1.22	40	0.98
Pharmacokinetic Parameters					
Parameter	Mean	%CV	Mean	%CV	A/B
AUCI	1001.29	14	966.86	14	1.04
AUCT	966.89	13	931.68	13	1.04
CMAX	32.94	15	31.83	15	1.04
THALF	18.91	11	19.2	12	0.98
TMAX	7.36	25	4.71	28	1.56

Table 3. LSMeans, Geometric LSMeans, T/R Ratios and 90% Confidence Intervals (C.I.) For Naproxen Pharmacokinetic Parameters in Fasting Single-Dose Study, N=28.

Parameter	Test (A)	Reference (B)	A/B	90%C.I.
LSMeans				
AUCI	1001.29	966.86	1.04	101.8-105.4
AUCT	966.89	931.68	1.04	102.0-105.5
CMAX	32.94	31.83	1.04	98.1-108.9
Geometric LSMeans				
AUCI	991.61	957.60	1.04	101.6-105.5
AUCT	958.34	923.90	1.04	101.9-105.6
CMAX	32.58	31.45	1.04	98.3-109.2

Table 4. Total Standard Deviation And Root Mean Square Error, Ln-Transformed PK Data		
Parameter	**LnCmax**	**LnAUCt**
Total SD, test	0.15	0.14
Total SD, reference	0.16	0.13
Total SD, test & reference combined	0.0134276	0.00156485
Root MSE, test & reference combined	0.1158736	0.03958172

IV. FORMULATION

Table 5. Components And Composition				
Ingredient	**375 mg Tablet**		**500 mg Tablet**	
	%	**mg**	**%**	**mg**
Naproxen Sodium, USP	(b) (4)	412.5	(b) (4)	550
Microcrystalline Cellulose, NF		(b) (4)		(b) (4)
Hydroxypropyl Methylcellulose, USP (b) (4)				
Hydroxypropyl Cellulose, NF				
Fumaric Acid, NF (b) (4)				
Magnesium Stearate, NF				
Colloidal Silicon Dioxide, NF				
TOTAL	100		100	

The composition of the added lower strength 412.5 mg (375 mg base) is proportional to that of the higher strength.

V. IN-VITRO DISSOLUTION TESTING

A. Dissolution Method Used by Firm

No. Units Tested: 12 tablets

USP XXIV apparatus 2 (paddle)

Media: The dissolution media were pH 7.5 phosphate buffer, pH 6.5 phosphate buffer, pH 4.2 acetate buffer, and simulated gastric fluid (pH 1.2).

Temperature: 37°C

Volume: 900 mL
Rpm: 50
Sampling Times: 0.5, 1, 2, 3, 4, 6, 10, 14 and 18 hours
Assay Method: UV
Firm's Dissolution Specification:

0.5 hour	(b) (4)
3 hours	
6 hours	
14 hours	no less than (b) (4)

The 900 mL of pH 7.5 phosphate buffer was suggested by the firm as the dissolution medium with a paddle stirring rate of 50 rpm for routine testing.

B. **Dissolution Results:** The dissolution data are presented in Table 6.

C. Comments on Dissolution Testing:

1. The dissolution testing on the current added strength is acceptable.

2. The dissolution method and proposed specifications used for the new strength are the same as for the higher strength on which acceptable required biostudies were performed. The dissolution testing results in all the media are similar for the two strengths. The proposed specifications for the added strength are the same as the specifications recommended to the firm for its original strength.

Table 6. Results of *In Vitro* Dissolution Testing:						
Sampling Times (Hours)	Test Product Lot # 825R002 Strength(mg) 412.5 mg			Reference Product Lot # 1973040 Strength(mg) 412.5 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
PH 7.5 Phosphate Buffer						
0.5	23	(b) (4)	6	27	(b) (4)	6
1	28		5	51		5
2	36		5	74		3
3	42		4	85		3
4	47		4	89		3
6	57		4	92		2
10	77		6	94		2
14	89		5	95		1
18	94		4	96		1
pH 6.5 Phosphate Buffer						
0.5	22	(b) (4)	7	22	(b) (4)	8
1	26		7	38		6
2	32		6	53		4
3	37		6	61		4
4	42		7	68		4
6	51		7	76		4
10	69		12	87		4
14	82		12	93		3
18	87		9	96		2

(In Vitro Dissolution Testing Continued)						
pH 4.2 Acetate Buffer						
0.5	1	(b) (4)	18	1	(b) (4)	27
1	1		15	2		28
2	1		13	8		25
3	2		13	10		22
4	2		14	10		19
6	3		12	10		16
10	5		11	11		11
14	7		8	11		9
18	8		8	11		8
SGF (pH 1.2)						
0.5	1	(b) (4)	25	0	(b) (4)	23
1	1		22	2		40
2	2		21	5		26
3	3		20	7		22
4	3		18	8		19
6	4		15	9		15
10	6		10	10		16
14	6		10	10		16
18	7		8	9		15

VI. COMMENTS

1. The pharmacokinetic parameters and statistical analysis for the fasting study were spot-checked by the reviewer using SAS and the results were in agreement with what the firm reported.
2. None of the C_{max} values were the first nonzero concentrations.
3. The assayed potency and the content uniformity of the test and reference products are satisfactory.
4. The analytical data is acceptable.
5. The bioequivalence study is acceptable.
6. The test product used for the biostudies and the dissolution studies were from the same batch.

VII. RECOMMENDATIONS

1. The single-dose, fasting bioequivalence study conducted by Andrx Pharmaceuticals on its test product, naproxen sodium 412.5 mg (375 mg base) extended release tablet, Lot # 825R002, comparing it with the reference product, Naprelan™ 375, Lot # 1973040, manufactured by Elan Pharma, Ltd. has been found acceptable by the Division of Bioequivalence. The study demonstrates that the test product, Andrx Pharmaceuticals' naproxen sodium 412.5 mg extended release tablet, is bioequivalent to the reference product, Elan Pharma's Naprelan™ 375.

2. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

3. The dissolution testing conducted by Andrx Pharmaceuticals, on its naproxen sodium 412.5 mg extended release tablet has been found acceptable. The firm's proposed dissolution testing should be incorporated into its manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of pH 7.5 Phosphate Buffer at 37° C using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following interim specifications:

0.5 hour	(b) (4)
3 hours	
6 hours	
14 hours	no less than (b) (4)

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

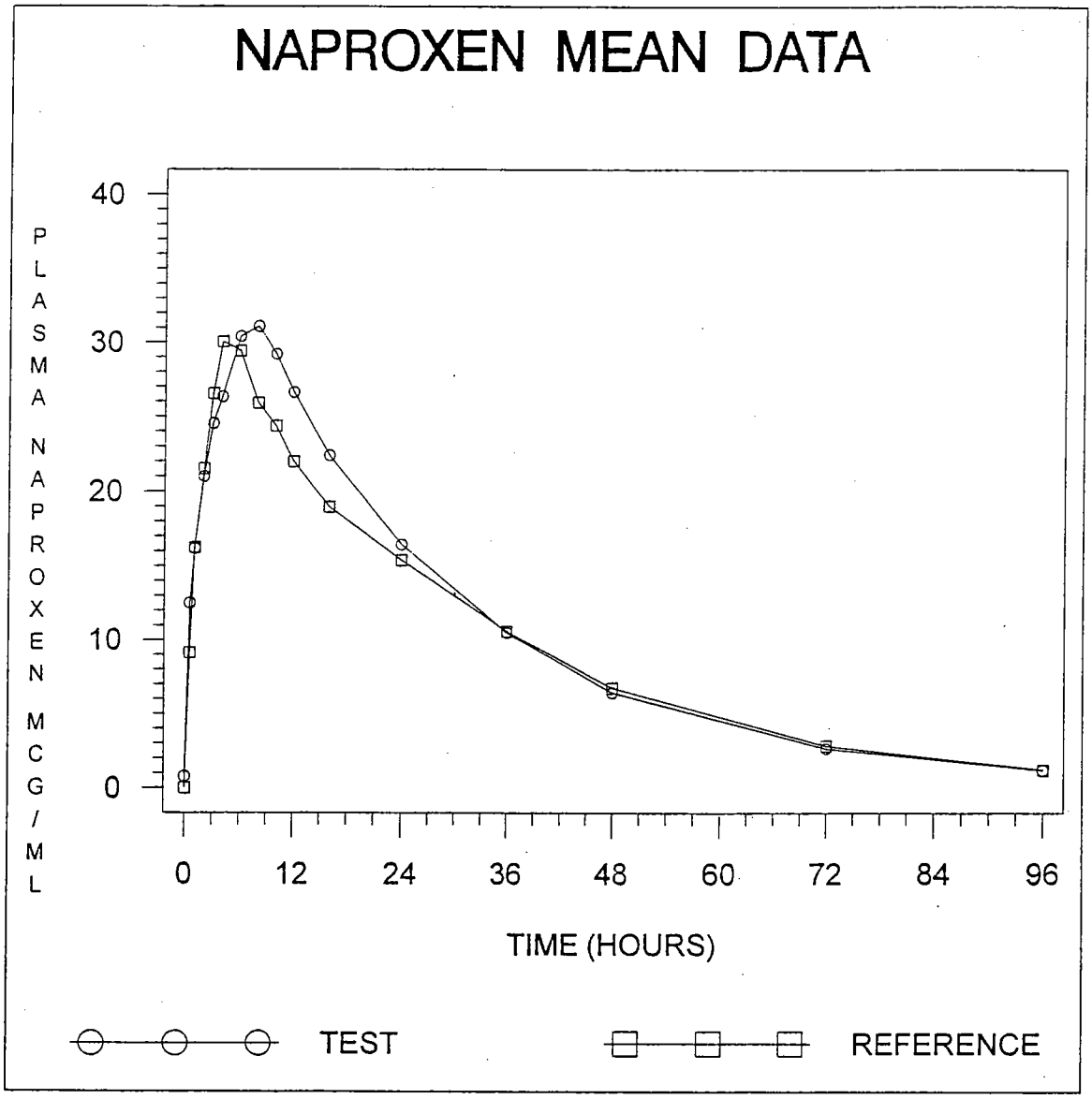
RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date 6/16/2000

Concur: _____ Date 7/12/00
Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/061600
V:\FIRMSAM\ANDRX\LTRS&REV\75416SD.500

Naproxen Sodium, Controlled Release Tablet, 412.5 mg (375 mg Base), Andrx Pharmaceuticals

Figure 1 Linear Plot of Mean Plasma Naproxen Concentrations *vs* Time



CC: ANDA 75-416
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J Chaney 6/16/00
HFD-652/ Y. Huang 6/16/2000
HFD-617/ J. ~~Fan~~ 7/12/00
HFD-650/ D. Conner 7/12/00

V:\FIRMSAM\ANDRX\LTRS&REV\75416SD.500

BIOEQUIVALENCY - ACCEPTABLE Submission date: May 11, 2000

1. **FASTING STUDY** (STF) DIC

Strengths: 412.5 mg
Outcome: AC
Clinical Facility: Gateway Medical Research, Inc., St. Charles, MO
Analytical Facility: (b) (4)
Statistics:

NOTE:

AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Acceptable

WINBIO COMMENTS:

The biostudy was found acceptable.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 75-416 SPONSOR: Andrx Pharmaceuticals
DRUG AND DOSAGE FORM: Naproxen Sodium CR Tablets
STRENGTH: 412.5 mg (375 mg Base)
TYPE OF STUDY: Fasting
CINICAL STUDY SITE: Gateway Medical Research, Inc., St. Charles, MO
ANALYTICAL SITE: (b) (4)

STUDY SUMMARY: The fasting study on the 412.5 mg (375 mg Base) is acceptable.

This submission was an amendment that provided a fasting bioequivalence study in support of the firm's added 412.5 mg (375 mg base) strength. The fasting, fasting/fed and multiple-dose studies on the 550 mg (375 mg base) strength were previously found acceptable (July 16, 1998 submission reviewed by J. Chaney).

DISSOLUTION: Acceptable.

DSI INSPECTION STATUS

Inspection needed: **NO**	Inspection status:	Inspection results:
New facility_____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James Chaney BRANCH: I
INITIAL: James Chaney DATE: 6/16/00

TEAM LEADER: Yih-Chain Huang BRANCH: I
INITIAL: YCH DATE: 6/16/2000

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.
INITIAL: DPC DATE: 7/12/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 075416Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Andrx
PHARMACEUTICALS, INC.

VIA AIRBORNE EXPRESS

July 16, 1998

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ABBREVIATED NEW DRUG APPLICATION
Naproxen Sodium Controlled-release Tablets, 550 mg

Dear Sir:

Pursuant to the requirements of Section 505(j) of the FD&C Act and 21 CFR 314.94, Andrx Pharmaceuticals, Inc. submits an original Abbreviated New Drug Application for approval to market its formulation of naproxen sodium controlled-release tablets, 550 mg (equivalent to 500 mg naproxen), which is bioequivalent to Naprelan™ (naproxen sodium) Controlled-release Tablets, 550 mg, manufactured by Elan Pharma, Ltd.

This application consists of 10 volumes containing the required information to demonstrate that Andrx's naproxen sodium controlled-release tablets are pharmaceutically equivalent and bioequivalent to the reference listed drug. Two copies are provided – an archival copy and a review copy separated into a bioequivalence review section and a chemistry review section. **NOTE: THIS APPLICATION CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA – the draft package insert has been provided in WordPerfect v.6.1 format on 3.5" diskettes. The data contained in the electronic submission is the same as in the hardcopy submission.**

Andrx Pharmaceuticals, Inc. certifies that in accordance with 21 CFR 314.94(d)(5), a field copy of this application was concurrently submitted to the Florida District Office. The field copy is a true copy of the chemistry, manufacturing, and controls technical sections contained in the archival and review copies of the application.

Please direct any questions regarding this submission to Jacqueline Davis, Regulatory Affairs Manager, at by telephone at (954) 321-5229 or by facsimile at (954) 587-1054.

Sincerely,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED
1998
GENERIC DRUGS

RECEIVED
Jul 16 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

ANDA# 75-416 **FIRM NAME** Andrx

RELATED APPLICATION(S) N/A

DRUG NAME: Naproxen Sodium

DOSAGE FORM: Extended-release Tablets 500 mg Base

FIRST GENERIC? N/A

Electronic Submission (Chem) ✓ yes for labeling only E-mail notification sent NO

Team Leader Sayeed VS

Labeling Reviewer James Barlow JBB

Random Assignment Random I

Micro Reviewer N/A

Pharmacodynamic study (Dr. Fanning) N/A

Letter Date 7-16-98 Received Date 7-16-98			
	Comments EC1 ✓ On Cards ✓ Therapeutic Code 5030300 ✓ NSAID	YES ✓	NO
	Methods Validation Package (3 copies) yes (Required for Non-USP drugs)	✓	
	Archival, and Review copies Field copy certification (original signature)	✓	
	Cover Letter	✓	
	Table of Contents	✓	

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding (Rx) OTC Status)	✓	
Sec. II	**Basis for Submission** RLD or Monograph Naprelan Firm Elan Pharma, Ltd Is an ANDA suitability petition required?_____	✓	
Sec. III	**Patent Certification** 1. Paragraph? IV 2. Expiration of Patent 6-10-2014	✓	
	Exclusivity Statement ✓ Pediatric Exclusivity?_____	✓	
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	✓	
Sec. V	**Labeling** 1. 4 copies of draft ✓ (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓	✓	
Sec. VI	**Bioavailability/Bioequivalence** 1. In Vivo Study Protocol(s) ✓ 2. In Vivo Study(ies) ✓ 3. Computer Disk Submitted NO only Labeling 26K 4. Request for Waiver of In Vivo Study(ies) N/A 5. In Vitro Dissolution Data ✓ 6. Formulation Data Same? (Comparison of all Strengths) inactives not ok (Ophthalmics, Otics, Externals, Parenterals) 7. Paragraph IV bio study acceptable for filing ✓ 8. Lot numbers of products used in Bio-study ✓ lot 100R003		
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation 2. Inactive ingredients as appropriate		

*

[redacted] (b)(4)

Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis ✓ c. Certificate(s) of analysis specifications and test results from drug substance manufacturer(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. Approved application for bulk antibiotic N/A h. CFN numbers — 2. **Inactive Ingredients** a. Source of inactive ingredients identified ✓ b. Testing specifications (including identification and characterization) ✓ c. Suppliers' certificates of analysis (specifications and test results) ✓ d. Applicant certificate of analysis ✓	✓	
Sec. IX	**Description of Manufacturing Facility** 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing ✓ 2. CGMP Certification ✓ 3. CFN numbers	✓	
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ✓ 4. CFN numbers	✓	
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with Equipment Specified ✓ 3. If sterile product: Aseptic fill — / Terminal sterilization 4. Reprocessing Statement ✓	✓	

Production [redacted] (b)(4) Tabs

exhibit [redacted] (b)(4) tabs → lot 100R003

100R003A (75's) [redacted] (b)(4) packaged

100R003B (1000's) [redacted] (b)(4) packaged

Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (AADA/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓	✓	
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and supplier's address ✓	✓	
Sec. XIV	**Controls for the Finished Dosage Form** 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. Certificate of Analysis for Finished Dosage Form ✓	✓	
ec. V	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on Stability records the same as the test batch ✓	✓	
Sec. XVI	**Samples** - Statement of Availability and Identification of: ✓ 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓	✓	
Sec. XVII	**Environmental Impact Analysis Statement**	✓	

Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) N/A 2. Debarment Certification (original signature) ✓ 3. List of Convictions statement (original signature) ✓	✓	

Reviewing CSO/CST _____ Date _____

Recommendation: FILE REFUSE to FILE

Supervisory Concurrence/Date _____

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD_____for consult

Type of consult:

Comments regarding the ANDA:

- check bio study design + lot #

- (b) (4)

Revised 6/98 - x:\wpfile\nasser\chklst

ANDA 75-416

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

AUG 11 1998

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated July 16, 1998 submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Naproxen Sodium Extended-release Tablets, 500 mg (base).

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(2)for the following reason:

> The concentration of the inactive ingredient, [redacted] (b)(4) in your proposed product exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in an oral dosage form. Please provide additional justification to demonstrate safety of [redacted] (b)(4) in the proposed concentration. The information to demonstrate safety should include, but is not limited to examples of approved drug products administered by the same route of administration which contain the same inactive ingredients and that are within the same concentration range.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act. Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the

application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Nasser Mahmud
Project Manager
(301) 827-5862

Sincerely yours,

8/7/98

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

ANDA 75-416
cc: DUP/Jacket
Division File
HFD-92
Field Copy
HFD-610/JPhillips
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief, date 8/7/98
HFD-615/NMahmud, CSO, date 8/7/98
HFD-623/VSayeed/Chem. Sup, date
WP File x:\new\firmsam\Andrx\ltrs&rev\75416.rtf
F/T mjl/8/4/98
ANDA Refuse to File!

Andrx
PHARMACEUTICALS, INC.

August 20, 1998

NDA ORIG AMENDMENT AC

Jerry Phillips
Director, Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Rm. 150
Rockville, MD 20855-2773

RE: ANDA 75-416 for Naproxen Sodium Extended-release Tablets, 550 mg

Dear Mr. Phillips:

Reference is made to our abbreviated new drug application dated July 16, 1998 for Naproxen Sodium Extended-release Tablets, 550 mg, and to the Agency's refusal to file letter dated August 11, 1998.

Andrx Pharmaceuticals is amending its application to include information to demonstrate the safety of (b) (4). Andrx's naproxen sodium product contains (b) (4) per tablet. The daily dosage is two tablets per day. Therefore, the daily intake of (b) (4) will be (b) (4) per day. Toxicological studies have been performed by the manufacturer, (b) (4) Based on the no effect levels found in these studies it is estimated that up to (b) (4) per day is safe in humans (see attached). In addition, the studies indicate that there is very little absorption and the material is almost completely excreted from the gastrointestinal tract. The full toxicology reports are contained in (b) (4) Drug Master File for (b) (4) DMF # (b) (4). A copy of the letter authorizing access to DMF # (b) (4) is also provided in this amendment.

We trust that this information is satisfactory to demonstrate the safety of this excipient and to allow filing of our application. Should you have additional questions please contact Ms. Jacqueline Davis, Regulatory Affairs Manager, Tel. (954) 321-5229/ Fax. (954) 587-1054.

Sincerely,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED
AUG 21 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

ANDA 75-416

Andrx Pharmaceuticals, Inc.
Attention: David A. Gardner
4001 S.W. 47th Avenue
Fort Lauderdale, FL 33314

SEP 2 1998

Dear Sir:

After careful review, the Office of Generic Drugs has decided to rescind our "Refuse to File" letter dated August 11, 1998. Accordingly, the application is acceptable for filing.

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: Naproxen Sodium Extended-release Tablets, 500 mg (base)

DATE OF APPLICATION: July 16, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 16, 1998

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(I)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b),provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period,

that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the District Court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Peter Rickman, Chief, Regulatory Support Branch, at (301)827-5862.

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:

Pat Beers-Block
Project Manager
(301) 827-5848

Sincerely yours,

9/1/98

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

cc: ANDA 75-416
DUP/Jacket
Field Copy
HFD-600/Reading File
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB _____ date 9/1/98
HFD-615,NMahmud, CSO _____ date 8/25/98
HFD-623,VSayeed, Sup. Chem. _____ date
WP File x:\new\firmsam\andrx\ltrs&rev\75416.ack
FT/mjl/8/25/98
ANDA Acknowledgment Letter!

9-30-98
10-1-98
1.1

1.1

Andrx
PHARMACEUTICALS, INC.

NEW CORRESP
NC

ANDA 75-416
PATENT AMENDMENT

September 30, 1998

Mr. Douglas Sporn
Director, Office of Generic Drugs (HFD-600)
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Dear Mr. Sporn:

Please refer to Andrx's ANDA 75-416, for Naproxen Sodium Controlled-release Tablets, 550 mg. In accordance with 21 CFR 314.95(b), Andrx Pharmaceuticals, Inc. certifies that: **(i)** notices of certification of noninfringement of a patent have been provided by U.S. registered mail, return receipt requested, to each person identified under section 314.95(a), and **(ii)** the notices met the content requirements under section 314.95(c). The notices were sent by James Costigan, patent counsel for Andrx.

In accordance with section 314.95(e), a letter acknowledging receipt and copies of the return receipt postcards are provided in this amendment as documentation of receipt of the notices.

This amendment consists of one volume, two copies of which are provided - an archival copy (blue binder) and review copy (black binder). Please direct any questions or comments regarding this submission to Ms. Jacqueline Davis, Regulatory Affairs Manager, Tel. (954) 321-5229 or Fax. (924) 587-1054.

Sincerely yours,

David A. Gardner

David A. Gardner
Vice President, Regulatory Affairs/QA/QC

RECEIVED
OCT 0 1 1998
GENERIC DRUGS

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

10-27-98
10-28-98

1.1

Andrx
PHARMACEUTICALS, INC.

IA AIRBORNE EXPRESS

October 27, 1998

NEW CORRESP
NC

Douglas L. Sporn
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: PATENT AMENDMENT
ANDA #75-416: Naproxen Sodium Controlled-release Tablets, 550 mg

Dear Mr. Sporn:

In accordance with 21 CFR 314.107(f)(2), Andrx Pharmaceuticals, Inc. is providing notification of legal action against it for patent infringement:

(i) ANDA No.: 75-416

(ii) Name of applicant: Andrx Pharmaceuticals, Inc.

(iii) Established name of drug product: Naproxen Sodium Controlled-release Tablets, 550 mg

(iv) Certification of action for patent infringement:
This certifies that an action for patent infringement (Case No. 98-7164, CIV-FERGUSON) has been filed by Elan Corporation, PLC, against Andrx Pharmaceuticals, Inc., alleging infringement of United States Patent No. 5,637,320 ("the '320 patent"). That Complaint was filed in the United States District Court for the Southern District of Florida, on October 23, 1998.

Should you have any questions concerning this submission I can be contacted by telephone at (954) 321-5229 or by fax at (954) 587-1054.

Sincerely,

RECEIVED
OCT 28 1998
GENERIC DRUGS

Jacqueline Davis
Regulatory Affairs Manager

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

1300 I STREET, N. W.
WASHINGTON, DC 20005-3315

202 • 408 • 4000
FACSIMILE 202 • 408 • 4400

ATLANTA
404•653•6400
PALO ALTO
650•849•6600

WRITER'S DIRECT DIAL NUMBER:

TOKYO
011•813•3431•6943
BRUSSELS
011•322•646•0353

NEW CORRESP
NC

202-408-4159

October 28, 1998

Office of Generic Drugs
HFD-600
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place
Rockville, Maryland 20855

VIA HAND-DELIVERY

Re: Notice of Action for Patent Infringement Concerning
Andrx Pharmaceuticals, Inc.'s ANDA No. 75-416 for
Naproxen Sodium Controlled Release Tablets

Dear Office of Generic Drugs:

We are writing on behalf of Elan Corporation, PLC ("Elan") to inform you that Elan filed a patent infringement action against Andrx Pharmaceuticals, Inc. on October 23, 1998, pursuant to 35 U.S.C. § 271(e)(2), which action is based on the filing of Abbreviated New Drug Application ("ANDA") No. 75-416.

Elan is the owner of United States Letters Patent No. 5,637,320 ("the '320 patent"). The '320 patent covers a controlled-release formulation having an active ingredient known by the generic name naproxen sodium. Elan sells a tabletized form of this drug in the United States under the trademark Naprelan®.

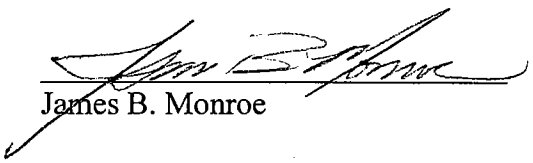
On or about September 10, 1998, Elan received from Andrx a letter informing Elan that Andrx had filed ANDA No. 75-416 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, seeking FDA approval to engage in the commercial use, manufacture and sale of naproxen sodium controlled release tablets. Andrx contended in this letter that the '320 patent will not be infringed by the manufacture, use or sale of Andrx's naproxen sodium controlled release tablets.

In accordance with 21 U.S.C. § 314.107(f)(2), and on behalf of Elan, we hereby certify that Elan filed an action for infringement of the '320 patent in the United States District Court for the Southern District of Florida on October 23, 1998, based on Andrx's filing of ANDA No. 75-416. A copy of the date-stamped complaint filed with the district court is attached. The district court has assigned this case Civil Action No. 98-7164.

Thank you for your consideration of this matter.

Sincerely,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: 
James B. Monroe

encl.

MINOR AMENDMENT

FEB 1 1999

ANDA 75-416

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Andrx Pharmaceuticals, Inc. PHONE: 954-321-5229

ATTN: ~~David Gardner~~ Jackie Davis FAX: 954-587-1054

FROM: Mark Anderson PROJECT MANAGER (301) 827–5849

Dear ~~Sir~~ Madam:

This facsimile is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naproxen Sodium Extended-release Tablets, 550 mg.

Reference is also made to your amendment dated August 20, 1998.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (5 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

Chemistry, labeling and bioequivalence comments are provided.

X:\new\ogdadmin\macros\faxmin.frm

OK mx

FEB

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Controlled Release Tablets, 550 mg (eq. 500 mg base)

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (b)(4) for Naproxen Sodium, has been found deficient and the holder has been notified.

2. (b)(4)

3.

4.

5.

6.

7.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The firms referenced in your ANDA application relative to the manufacturing and testing of the product must be in compliance with cGMP's at the time of approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

2. We will request the appropriate FDA district laboratory to obtain samples of the new drug substance and the finished dosage form for methods validation at the appropriate time.

Sincerely yours,

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

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

ANDA Number: 75-416 Date of Submission: July 16, 1998 and August 20, 1998

Applicant's Name: Andrx Pharmaceuticals, Inc.

Established Name: Naproxen Sodium Extended-release Tablets, 500 mg base.

Labeling Deficiencies:

1. GENERAL COMMENT

   The established name for this product is Naprosyn Sodium Extended-release Tablets. Revise all labels and labeling accordingly.

2. CONTAINER - Bottles of 75 & 1000 tablets.

   Please assure that the established name appears as the most prominent statement on the principal display panel.

3. INSERT

   a. DESCRIPTION

      Fourth paragraph, second sentence; revise to read as follows:

      In addition, each tablet contains the following inactive ingredients: colloidal.....

   b. CLINICAL PHARMACOLOGY

      Pharmacokinetics: Revise to include the graph entitled: **Plasma Naproxen Concentrations Mean of 24 Subjects (+/-2SD) (Steady State, Day 5)**

   c. PRECAUTIONS

      Information For Patients; first sentence; revise to read as follows:

      ....tablets, like other drugs of its class, are

not free of side effects.[replace "is' with "are"]

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

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.

John D. Kraus for/

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Naproxen Sodium Controlled Release Tablets, 550 mg

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

Based on the data submitted, the following dissolution testing is recommended for your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of pH 7.5 Phosphate Buffer at 37 degrees C using USP 23 apparatus 2 (paddle) at 50 rpm. The test product should meet the following tentative specifications which are revised from your proposed percent released at 3 and 6 hours:

[redacted] (b) (4) at 0.5 hour, [redacted] (b) (4) at 3 hours, [redacted] (b) (4) at 6 hours and no less than [redacted] (b) (4) at 14 hours of the labeled amount of naproxen.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

7-99
1.1

Andrx
PHARMACEUTICALS, INC.

April 6, 1999

NDA ORIG AMENDMENT
N/AM FPL

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

MINOR AMENDMENT

Dear Mr. Sporn:

In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is herewith submitting a minor amendment to our abbreviated new drug application for Naproxen Sodium Extended-release Tablets, 550 mg (equivalent to 500 mg base).

This amendment is being submitted in response to a Not Approvable facsimile, received on February 1, 1999. Complete responses to the chemistry and labeling deficiencies are provided. We note that the Division of Bioequivalence has completed its review and has no further questions at this time.

Andrx Pharmaceuticals, Inc. certifies that true copies of the technical sections contained in this amendment were sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 321-5229 (telephone) or (954) 587-1054 (fax).

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

RECEIVED
APR 07 1999
GENERIC DRUGS

Nadine 4-8-99

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

May 14, 1999

NDA ORIG AMENDMENT
N/AM

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to a telephone communication on May 7, 1999 between Jim Barlow of your office and Diane Servello of Andrx Pharmaceuticals, Inc. In that communication, Mr. Barlow requested several minor revisions to our container labels.

In this regard, we have prepared final printed container labels incorporating the requested revisions. The following information is enclosed in this submission:

1. Twelve final printed container labels for the 75 count and 1000 count package sizes. (Six copies are attached to the archival copy, the remaining six are attached to the review copy).
2. A side-by-side comparison of the revised and previously submitted labels. (This comparison was done for the 75 count label only, because the same revisions were made to both size labels).

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG
REC'D
MAY 17 1999
OGD
EVALUATION AND RESEARCH

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

RECORD OF TELEPHONE CONVERSATION

I initiated a call pertaining to ANDA 75-416 for Naproxen extended-release tablets CONTAINER labeling and spoke with Diane Servello.(covering for J. Davis (b)(6) (b)(6)) I informed her that the container labels had to be revised to read:

Front panel:

Naproxen Sodium
EXTENDED-RELEASE TABLETS

Rx Only
500 mg*

Side Panel:
*Each tablet contains...

She will revise the labeling as requested by the agency and will submit 12 copies of final print as soon as possible.

DATE 5/7/99

ANDA NUMBER
75-416

IND NUMBER

TELECON

INITIATED BY Jbarlow
MADE BY
APPLICANT/ SPONSOR TELE x
X FDA _ IN PERSON

PRODUCT NAME
Naproxen sodoium extended-release tablets.

FIRM NAME
Andrx. Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Diane Servello (Assistant to the head of Regulatory Affairs)

TELEPHONE NUMBER
(954)321-5229

SIGNATURE

MINOR AMENDMENT

9

ANDA 75-416

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Andrx Pharmaceuticals Inc. PHONE: 954-581-7500

ATTN: Dianne Servello FAX: 954-587-1054

FROM: Bonnie McNeal PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naproxen Sodium Extended-release Tablets, 550 mg.

Reference is also made to your amendments dated April 6 and May 14, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CMC deficiencies enclosed.

X:\new\ogdadmin\macros\faxmin.frm

B. McNeal
6/9/99

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended Release Tablets, 550 mg

The deficiencies presented below represent Minor deficiencies:

A. Deficiencies:

1. (b) (4)

2.

3. The Drug Master File (b) (4) has been reviewed and remains deficient and holder has been notified.

Sincerely yours,

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

Andrx
PHARMACEUTICALS, INC.

June 21, 1999

NDA ORIG AMENDMENT
N/A

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

MINOR AMENDMENT

Dear Mr. Sporn:

In accordance with 21 CFR 314.120, Andrx Pharmaceuticals, Inc. is herewith submitting a minor amendment to our abbreviated new drug application for Naproxen Sodium Extended-release Tablets, 550 mg (equivalent to 500 mg base).

This amendment is being submitted in response to a Not Approvable facsimile, dated June 9, 1999. Complete responses to the chemistry deficiencies are provided on the following pages.

Andrx Pharmaceuticals, Inc. certifies that true copies of the technical sections contained in this amendment were sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUN 22 1999
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

NEW CORRESP

July 28, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

GENERAL CORRESPONDENCE
ADDITIONAL COPIES OF METHOD VALIDATION SECTION

Dear Mr. Sporn:

We refer to a telephone request from Ms. Bonnie McNeal of your office on July 26, 1999, requesting two additional copies of the method validation section of our ANDA. In accordance with her request, enclosed please find two separately bound copies of the requested information.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUL 29 1999
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

1C

Andrx
PHARMACEUTICALS, INC.

NEW CORRES
NC

August 16, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

GENERAL CORRESPONDENCE
ADDITIONAL COPIES OF METHOD VALIDATION SECTION

Dear Mr. Sporn:

We refer to a telephone request from Ms. Bonnie McNeal of your office on August 13 1999, requesting two additional copies of the method validation section of our ANDA. In accordance with her request, enclosed please find two separately bound copies of the requested information.

Please note that this submission replaces the method validation copies submitted to your Office on July 28, 1999. Certain information contained in our original method validation section has been updated in response to CMC deficiencies related to this ANDA. The following items have been updated since our original submission:

1. *Methods for the Drug Substance*: A new "Standard Test Method" was issued to describe the test procedures for "[redacted (b)(4)] in Naproxen Sodium" ([redacted (b)(4)] – see item 2 for explanation)
2. *Specifications for the Drug Substance:* A test for "Residual Solvents – [redacted (b)(4)], was added, per a facsimile deficiency letter dated June 9, 1999. The updated specifications were included in our amendment dated June 21, 1999.
3. *Specifications for the Drug Product:* The dissolution specifications were updated per a facsimile deficiency dated February 1, 1999. The updated specifications were submitted in our amendment dated April 6, 1999.
4. *Update of compendial references:* References to the current compendium have been updated to reflect USP 24/NF 19.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG
REC'D
AUG 17 1999
OGD
EVALUATION AND RESEARCH

4021 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

RECORD OF TELEPHONE CONVERSATION

Called Sponsor to ask for information needed for tertiary chemistry review.

1. Asked Sponsor to provide [redacted] (b) (4)

2. Asked Sponsor to perform [redacted] (b) (4)

3. Asked Sponsor for additions to their post-approval stability commitment (page 3585 of original application):
   a. need a statement stating that the largest and smallest containers of drug product will be tested on an annual basis.
   b. In statement about …."lots found to fall outside of the approved …" "may be withdrawn", please change "may" to "will".

Filename: V:\FIRMSAM\ANDRX\TELECONS\75416.001.DOC

DATE
September 17, 1999

APPLICATION NUMBER
75-416

TELECON

INITIATED BY APPLICANT/ FDA
FDA

PRODUCT NAME
Naproxen Sodium Extended-release Tablets, 550 mg

FIRM NAME
Andrx Pharmaceutical

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Diane Servello

TELEPHONE NUMBER
954-327-4412

SIGNATURE
B. McNeal 10/4/99
B. McNeal

CC: ANDA 75-416
Division File
Chem Division T-con Notebook

Andrx
PHARMACEUTICALS, INC.

September 27, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA DRUG AMENDMENT

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

FAX AMENDMENT

Dear Mr. Sporn:

We refer to a telephone communication between Ms. Bonnie McNeal of your office and Diane Servello of Andrx Pharmaceuticals, Inc. on September 17, 1999. In order to complete the review of this ANDA, Ms. McNeal requested that we submit additional information relating to the chemistry, manufacturing and controls section of our application. In this regard, we are submitting the following:

1.

(b) (4)

2.

CENTER FOR DRUG
RECD
SEP 28 1999
OGD
EVALUATION AND RESEARCH

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

3. We have revised our Post-Approval Stability Commitment to state that (1) one production batch will be added to the stability program in the smallest and largest of each container/closure system; and (2) any lots found to fall outside of the approved specifications will be withdrawn from the market. Please see Exhibit 3 for the revised commitment.

4. We have added [redacted] (b) (4) to the finished product test requirements. Please see the revised specification in Exhibit 2, reflecting this additional test.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

NDA ORIG AMENDMENT
N/Am

October 12, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

FAX AMENDMENT

Dear Mr. Sporn:

Please refer to a telephone conversation between Allen Rudman and Diane Servello of Andrx Pharmaceuticals, Inc. on October 7, 1999. In that conversation Mr. Rudman requested two additional items be provided. Accordingly we are amending the application to provide the following:

1. (b) (4)

2.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG
OCT 13 1999

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

RECORD OF TELEPHONE CONVERSATION

Participants:
FDA:
Allen Rudman, Deputy Director Chem I
Al Mueller, Chem Team Leader
Jim Fan, Chem Reviewer
Bonnie McNeal, Project Manager
Andrx:
Chih-Ming Chen, Pres. Of Andrx
Francisco Alverez, Dir. Of Analytical Research and Development
Jacquelyn Davis, Manager of Reg. Affairs
Dianne Servello, Director of Reg. Affairs

The Sponsor asked if the Agency had reviewed the fax of November 4, sent as background information for this telecon. Most of Agency had reviewed the fax and said the data and graphs look good.

The Agency asked the Sponsor to summarize their method. Sponsor stated that they prepare samples according to their dissolution method. They use USP acceptance criteria (for capsules). The batches pass specifications with a range of (b) (4), average 103.9 and RSD of 3.9.

The Agency asked how a time of 6 minutes was picked for dissolution of the IR coat. The Sponsor referred the Agency to Exhibits 1 and 2 of the 11/4/99 fax. (b) (4) [redacted] The Sponsor stated they would like to adopt this method and submit it to the ANDA.

The Agency said Sponsor should submit it but that this would have to go through a 1st Generic Review and we did not know if the method would ultimately be acceptable.

The Agency asked if this test would be used in the future (b) (4) [redacted]

Note: Called Sponsor back after telecon and asked that information be submitted within 10 days as a telephone amendment.
Filename:
V:\FIRMSAM\ANDRX\TELECONS\75416.004.DOC

DATE
November 17, 1999

APPLICATION NUMBER
75-416

TELECON

INITIATED BY APPLICANT/ FDA
FDA

PRODUCT NAME
Naproxen Sodium Extended-release Tablets, 550 mg

FIRM NAME
Andrx Pharmaceutical

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Diane Servello

TELEPHONE NUMBER
954-327-4412

SIGNATURE

J. Fan 12/1/99
A. Mueller 12.4.99
A. Rudman
B. McNeal 12/8/99

CC: ANDA 75-416 Division File Chem Division T-con Notebook

Andrx
PHARMACEUTICALS, INC.

November 19, 1999

NEW CORRESP
NC

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

TELEPHONE AMENDMENT

Dear Mr. Sporn:

As a follow-up to a teleconference held on November 17, 1999 between Andrx and the members of the OGD's Division of Chemistry I, we are amending the above-referenced ANDA to provide information on the proposed (b) (4)

Please note that the method development work for (b) (4)

. If an adjustment is needed to the (b) (4) dissolution time, we will submit a revised test method to the ANDA with data supporting the time adjustment as a Changes Being Effected supplement.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

NOV 22 1999

...ION AND RESEARCH

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

December 14, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our pending ANDA for the above-mentioned product. We also refer to a telephone communication on December 14, 1999 from Bonnie McNeal of your office. Ms. McNeal requested that Andrx Pharmaceuticals, Inc. ("Andrx") revise our Release Specification for (b) (4) to specify that the product will meet the USP content uniformity acceptance criteria for tablets.

Accordingly, we have revised the specification as requested. A copy is enclosed.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

Andrx
PHARMACEUTICALS, INC.

NDA ORIG AMENDMENT
N/AM

December 21, 1999

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our pending ANDA for the above-mentioned product. We also refer to a telephone communication on December 21, 1999 between Bonnie McNeal and James Fan of your office and Diane Servello of Andrx Pharmaceuticals, Inc. ("Andrx"). Ms. McNeal and Dr. Fan requested that Andrx clarify two minor CMC issues concerning this application. In response, we offer the following:

1. (b) (4)

[redacted]

REC'D
DEC 22 1999
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1654

(b) (4)

2. (b) (4)

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 327-4412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

MINOR AMENDMENT

ANDA 75-416

JAN 12 2000

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Andrx Pharmaceuticals Inc. PHONE: 954-581-7500

ATTN: Dianne Servello FAX: 954-587-1054

FROM: Bonnie McNeal PROJECT MANAGER (301) 827–5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 17, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naproxen Sodium Extended-release Tablets, 550 mg.

Reference is also made to your amendments dated June 21, September 27, October 12, November 19 and December 14, 1999.
^ and Dec. 21, 1999

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

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 of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

CMC deficiencies only enclosed.

B.Mc
1/12/00

X:\new\ogdadmin\macros\faxmin.frm

JAN 12 2000

38. Chemistry Comment to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 550 mg

The deficiency presented below represents a MINOR deficiency:

A. Deficiency:

(b) (4)

B.

(b) (4)

[redacted]

Sincerely yours,

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

Andrx
PHARMACEUTICALS, INC.

January 14, 2000

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/AM

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our pending ANDA for the above-mentioned product. We also refer to your letter dated January 12, 2000. As indicated in your letter, this response is considered a minor amendment.

The following represents our response to all of the deficiencies listed in your letter:

A. [redacted] (b) (4)

Response:

[redacted] (b) (4)

RECD
JAN 18 2000
OGD
EVALUATION AND RESEARCH

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

B. [redacted] (b) (4)

Response:

[redacted] (b) (4)

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact Jacqueline Davis, Regulatory Affairs Manager at (954) 321-5229 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

MEMO TO RECORD

DATE: 2/2/00

SUBJECT: ANDA 75-416, Naproxen Sodium ER Tab

ORGANIZATION: Andryx

PARTICIPANTS: Allen Rudman
Diane Savello

I informed Diane that the DMF holder [redacted] (b) (4) now has a new site for the manufacture of the API Sodium Naproxen. She was asked to contact the DMF holder so that the location of manufacture of the API is identified on any bulk purchased and to either make a commitment to use only the bulk source from the site used in the manufacture of the bio batch or make a commitment to submit a CBE -30 supplement with 3 months accelerated data on the first batch of drug product manufactured using the bulk made at the new site of manufacture.

I asked her to respond back to me within 10 days. She said that she would contact the DMF holder immediately.

2/7/00 amendment is satisfactory QR 2/9/00

Andrx
PHARMACEUTICALS, INC.

NDA 75-416
NC

VIA FAX TO 301-827-4337

February 7, 2000

Douglas L. Sporn, Director
Office of Generic Drugs, CDER, FDA
Attention: Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416: Naproxen Sodium Extended-Release Tablets, 550 mg

FAX AMENDMENT

Dear Mr. Sporn:

We refer to a telephone conversation between Dr. Allen Rudman and Ms. Diane Servello of Andrx Pharmaceuticals, Inc. on February 2, 2000. In that conversation Dr. Rudman requested that Andrx submit additional commitments regarding the manufacturing site of the Naproxen Sodium drug substance, manufactured by (b) (4). Accordingly we are amending the application to provide the following:

1. A letter from (b) (4) is attached that makes a commitment to only supply material manufactured by their plant located at (b) (4) (b) (4). They also make a commitment to notify Andrx in advance, in the event that they ship us material manufactured at their new site in (b) (4) (b) (4).
2. A signed commitment from Andrx, stating that we will only utilize Naproxen Sodium drug substance manufactured by (b) (4) in their plant located in (b) (4). We also commit to submitting a "Changes Being Effected Supplement – 30 day", accompanied by three-month accelerated stability data if we decide in the future to use drug substance manufactured by (b) (4).

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact the undersigned at (954) 321-5229 (telephone) or (954) 587-1054 (fax).

Sincerely,

Jacqueline Davis
Regulatory Affairs Manager

CENTER FOR DRUG
RECD
FEB 08 2000
EVALUATION AND RESEARCH

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

CHECKLIST FOR APPROVAL/TENTATIVE APPROVAL LETTERS WHEN AN ANDA CONTAINS PARAGRAPH IV CERTIFICATION

ne following information should be completed and/or answered before a final or tentati approval letter can be issued to a firm. Complete the "licensing agreement" questions applicable. **Approval of the ANDA should not be granted unless all applicable questions are answered "yes" on this checklist.**

ANDA applicant	
ANDA applicant name:	Andrx Pharmaceuticals, Inc.
ANDA number:	75-416
Drug product name:	Naproxen Sodium Controlled Release Tablets, 550 mg (500 mg base)
Did the ANDA applicant give P.IV notice[1] to each PO and AH (if different)? If the PO and AH do not live or work in the U.S., was a copy provided to the U.S. designee of the PO and AH[2]?	YES
Did the ANDA applicant send the P.IV notice after it received OGD's acknowledgement letter [314.95(b)]?	YES
es OGD have copies of the signed return receipts from the PO and AH (if different) or a letter from PO and AH acknowledging receipt [314.95(e)]?	YES
In the absence of a signed return receipt or letter, did the applicant receive OGD permission to submit another form of documentation in advance?	N/A
Does OGD have a copy of the other form of documentation of receipt of notice from the PO and AH [314.95(e)]?	N/A
Did the ANDA applicant submit an amendment that the notice was sent and met the content requirements under 314.95(b)&(c)?	YES
Was the ANDA applicant sued on the patent challenge?	YES
Name of person(s) that sued the applicant:	Elan Pharmaceuticals.
Date of lawsuit:	10/23/98

[1] 314.95(e) states that a "copy of the notice itself need not be submitted to the agency". Also, page 50350, #60, preamble states that agency does not have the expertise to become involved in issues concerning sufficiency of notice. Therefore, OGD will not read the notice to determine if the notice met the content requirements.

[2] See 314.52, 314.53, 314.95(a)(2), and by implication, 314.95(a)(1).

Did ANDA applicant or the PO/AH notify OGD of the filing of legal action within 45 days of receipt of P.IV notification [314.107(f)(2)]?

YES

If ANDA applicant is a licensee, did it submit a statement that it has been granted a license [314.94(a)(12)(v)]?

N/A

Patent Owner (PO)

Name and address (state and country) of each PO:

Elan Corporation, PLC

Name and address of U.S. agent if PO is foreign:

Athlone, Ireland

Specific number and expiration date of each patent that claims the drug product:	US 5637320 exp. 6/10/2014

If OGD intends to approve the ANDA within 45 days of notification, did each PO and the send OGD a statement that it waives its right to sue within the 45 days after it received the P.IV notice[3] [314.107(f)(3)]?

N/A

Does the statement (above) follow the format in the proposed rule [314.107(f)(3)]?

N/A

NDA applicant/Application holder (AH) (if different from PO)

Name of AH: Elan Pharmaceuticals

Name of U.S. agent if AH is foreign: Marla Church, Esq.
1300 Gould Drive, Gainesville, GA 30504

Was the patent timely filed?

If the AH is either the PO or an exclusive licensee of the PO and, if OGD intends to approve the ANDA within 45 days of notification, did the AH send OGD a statement that it waives its right to sue within the 45 days after it received the P.IV notice [314.107(f)(3)]?

N/A

[3] Although a patent owner doesn't have to consent to final ANDA approval (see preamble, page 50351, #67) for a licensee, it does have to submit a waiver to OGD in the 45 day period.

Does the written statement (above) follow the format in the proposed rule (p.50368) [314.107(f)(3)]?

N/A

Licensing agreement/licensee (complete this section if ANDA applicant is a licensee) 314.94(a)(12)(v)

Names of the parties in the licensing agreement:
Licensor: _____

Licensee: _____

Is the licensor the PO, AH/PO, or a designated representative of the PO [314.53(c)(1)(iv) and 314.95(a)(1)]?

Do we have a copy of the signed licensing agreement?

Name of the person who provided us a copy of the agreement:

Date of the agreement:

N/A

Has GC authorized approval if there are provisions in the agreement that appear to preclude granting immediate effective approval, such as a date before which approval ...uld be granted, etc.?

If OGD has written evidence that the PO assigned its rights or is a name other than the person originally issued the patent, has GC authorized approval?

When the licensing agreement was sent to OGD, was the transmittal on the ANDA applicant's letterhead with an original signature (or if faxed, is it signed)?

In the case of patent litigation, has OGD received a copy of the following?

1. Stipulation signed by the parties to the agreement to dismiss the case because of the licensing agreement.
2. Stipulation free of any obstacles to final approval.
3. Signed court order dismissing the case.

Drug product

If the ANDA refers to a listed drug that is itself a licensed generic of a patented pioneer drug, is there a P.IV certificate as to the patent on the pioneer [314.94(a)(12)(i)(B)]?

N/A

Approval/Tentative approval letter

Does the approval letter include:

1. All patents and their expiration dates? YES
2. References to relevant court rulings, if any, that impacted on the decision to issue a tentative or final approval. YES
3. The reason why OGD is issuing final approval, if that is the case, of the ANDA before the expiration of the patent? N/A

If the ANDA applicant is a licensee, does the letter: N/A

1. Disclose the patent owner's identity[4]? On 1/17/96, PTO confirmed that once patent is issued, it is public information.
2. Omit the details of the licensing agreement (details are not allowed in the letter per C. A. Hooton 9/28/95)?

Signatures

Regulatory Counsel (re: GC referrals) Date

3/13/05

Regulatory Support Branch Date

V:\division\regsupp\pivappchklst

ANDA filed 7/16/98, Andrx notified AH + PO (same) - Return Receipt dated 9/14/98. Elan filed a Lawsuit against Andrx on 10/23/98 in Dist. Court (Southern District of Florida). Litigation ongoing. Per conversation with Dianne Servello of Andrx on 3/13/05. Applicant will amend application with changes in litigation status, if any.

OGD should have GC advice if it is evident that the current PO is different from the original PO. The existence of an agreement between the assignee of the PO and the ANDA holder may not mean the current PO's name is public.

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-416 Applicant Andrx Pharmaceuticals, Inc.
Drug Naproxen Sodium Extended-release Tablets Strength 550 mg (base)

FINAL ☐ TENTATIVE APPROVAL ☑ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Project Manager Bonnie McWard
   Review Support Br I

DRAFT RECEIPT
Date _____
Initials _____

FINAL ACTION
Date _____
Initials _____

Application Summary:
Original Rec'd date July 16, 1998
Date Acceptable for Filing July 16, 1998
Patent Certification (type) Para III
Date of Office Bio Review Dec. 3, 1998
Methods Val. Samples Pending Yes ☑ No ☐
30 Day Clock Start NA End _____
Commitment Rcd. from Firm Yes ☐ No ☑
First Generic Yes ☑ No ☐
Needs First Generic Review - However is not first application filed.

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status August 30, 1999 Feb 8, 2000
Date Patent/Exclus.expires June 10, 2014
Citizens Petition/Legal Case Yes ☑ No ☐
(If YES, attach email from PM to Pet. Coord. notifying of pending approval) C. Parise notified in person 8/30/99
Pediatric Exclusivity Tracking System
Date checked _____
Nothing Submitted ☐
Written request issued ☐
Study Submitted ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def./N/A Minor issued ☐ Date _____
Comments:

No longer pend. 1/21/10 JMC

2. Div. Dir./Deputy Dir. Date 3/7/00 Initials _____ Date 3/8/00 Initials _____
   Chemistry Div. I or II
   Comments:

Satisfactory pending 1st Generic approval only

3. Office Level Chem Review **(1st Generic Only)** Date _____ Initials _____ Date 3/3/00 Initials _____
   Chemistry ~~Div. I or II~~
   Comments:

Satisfactory

4. Pat Beers Block
   Supv., Review Support Branch Date 3/7/00 Initials _____ Date 3/9/00 Initials _____
   RLD = 20-353 / 002
   EER Status: Acceptable for all facilities as of 2/8/2000 (from OMI)
   Bioequivalence sites:
   Clinical site: Gateway Medical Research Inc, St Charles MO
   Inspection needed: ☐ yes ☑ no
   Status: ☑ acceptable ☐ unacceptable ☐ pending
   Date of status: based on DSI inspection history
   Analytical site: [redacted] (b) (4)
   Inspection needed: ☐ yes ☑ no
   Status: ☑ acceptable ☐ unacceptable ☐ pending
   Date of status: based on DSI inspection history

Labeling Status: Acceptable P.I. submitted for bottles of 75 and 1000. Approval memo prepared and signed 5/24/99
Bioequivalence office level sign off: Fasting, fed and multiple dose BE studies; and in vitro testing were found acceptable for approval on 12/13/98
Microbiology status: N/A
Patent Certification: Para IV; Lawsuit for exclusivity for RLD expired 1/5/99.
Controlled Correspondence/Cit. Pet:
Comments:

→ Civil action filed by Elan on 10/23/98. Tentative approval for this (2nd) para IV filed with OGD (this is not first filed para IV). No deficiencies (since amendment Dtd. 1/14/00) adequately resolved.

REVIEWER: | **DRAFT RECEIPT** | **FINAL ACTION**

5. Nasser Mahmud
Supv., Reg. Support Branch

Date 3/13/00 Initials NM | Date 3/13/00 Initials NM

Contains certification: Yes ☑ No ☐
(required by the GDEA if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☑ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder in a
Timely manner: Yes ☑ No ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐
Has case been settled: Yes ☐ No ☑
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity: Yes ☐ No ☑

Determ. of Involvement? Yes ☐ No ☑
Pediatric Exclusivity System
Date Checked 3/13/00
Nothing Submitted ☑
Written request issued ☐
Study Submitted ☐

Not first generic - (b) (4) work 1st w/ PIV challenge

Bio acceptable 12/3/98
Labeling acceptable 5/24/99
EER acceptable 2/8/00

Comments: Andrx notified AH + PO (same) - Return receipt dated 9/14/98. Elan (AH/PO) filed a lawsuit against Andrx on 10/23/98. Litigation is ongoing per my conversation w/ Andrx on 3/3/00. 30 mos. will expire 3/14/01

6. Peter Rickman
Acting Director, DLPS

Date 3/14/00 Initials [illegible] | Date 3/14/00 Initials [illegible] for

Comments: Acceptable ltr dated 2/8/00 (verified 3/14/00). No O.A.I. alerts noted. Bioequivalence review (3 studies) found acceptable 12/6/98, office level bio endorsed 12/3/98. Labeling acceptable for tentative approval 5/24/99 (endorsed 1/24/2000). CMC acceptable 1/28/00. Methods validation completed. First-generic CMC audit completed. Recommend tentative Approval.
Note: Andrx was not the first to file a PIV challenge.

7. Robert L. West
Acting Deputy Director, OGD

Date 3/14/00 Initials [illegible] | Date 3/14/00 Initials [illegible]

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☒

Comments: Citizens Petition submitted by Elan was responded to on 10/28/99. Andrx has made a PIV patent certification to the '330 patent held by Elan. Elan has sued Andrx. Litigation is ongoing. OK to issue a tentative approval letter to Andrx. No pediatric study request issued to Elan. DSI status-satisfactory.

8. ~~Gary Buehler~~
Acting Director, OGD
Comments:

Date _____ Initials _____ | Date _____ Initials _____

Janet Woodcock, M.D.
Director
Center for Drug Evaluation
And Research
First Generic Approval ☒

First Generic Tentative Approval

Date _____ Initials _____ | Date 3-10-00 Initials MAR 17 2000

PD or Clinical for BE ☐ Special Scientific or Reg. Issue ☐

9. Project Manager Bonnie McNeal
Review Support Branch

Date _____ Initials _____ | Date _____ Initials _____

3/14/00 Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification: 3/17/00
4:30 PM Time notified of approval by phone 4:40 PM Time approval letter faxed

FDA Notification:
3/17/00 Date e-mail message sent to "OGD approvals" account
3/17/00 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

Andrx
PHARMACEUTICALS, INC.

VIA FEDERAL EXPRESS

May 11, 2000

Gary Buehler
Acting Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AC

RE: MAJOR AMENDMENT - ANDA 75-416
Naproxen Sodium Extended-release Tablets

Dear Sir:

In accordance with 21 CFR 314.96, Andrx Pharmaceuticals is submitting an amendment to the above-referenced application to provide for an additional strength of the drug product. This new strength contains 412.5 mg of naproxen sodium per tablet (equivalent to 375 mg naproxen). The reference listed drug is Naprelan™375 (naproxen sodium) Controlled Release Tablets, manufactured by Elan Pharma, Ltd.

This application consists of five (5) volumes and contains the required chemistry, manufacturing and controls information as well as the results of a completed *in vivo* bioequivalence study. Two copies are provided - an archival copy and a review copy that is divided into a bioequivalence review section and chemistry review section. A copy of this amendment was submitted to the Florida District Office as a Field Copy. An executive summary of this amendment is located after the Table of Contents.

Andrx Pharmaceuticals, Inc. commits to cooperate with the FDA to resolve any methods validation issues that may be revealed to the Office of Generic Drugs when the method validation work is completed.

THIS APPLICATION CONTAINS AN ELECTRONIC SUBMISSION OF LABELING DATA - The proposed package insert is provided in Microsoft Word 97 format on a 3.5" diskette located with the four copies of the draft labeling in the Chemistry Review Copy. The data contained in the electronic submission is the same as in the hardcopy submission.

Please direct any questions regarding this application to Jacqueline Davis, Regulatory Affairs Manager, at (954) 321-5229 (tel.) or (954) 587-1054 (fax).

Sincerely,

Diane Servello

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 12 2000
OGD

4001 S.W. 47TH AVENUE, SUITE 201, FORT LAUDERDALE, FLORIDA 33314 • 954-581-7500 • FAX: 954-587-1054

FAX AMENDMENT

DEC 4 2000

ANDA 75-416

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Andrx Pharmaceuticals, Inc. TEL: 954-581-7500

ATTN: Diane Servello FAX: 954-587-1054

FROM: Timothy Ames PROJECT MANAGER (301) 827–5765

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naproxen Sodium Extended-release Tablets, 500 mg (base) and 375 mg (base).

Reference is also made to your amendment(s) dated May 11, 22000.

Attached are 3 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS: Bioequivalence and CMC comments included.

X:\new\ogdadmin\macros\faxfax.frm

DEC 4 2000

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. (b) (4)

2.

3.

4.

5. [redacted] (b) (4)

Sincerely yours,

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

3.1

BIOEQUIVALENCY COMMENTS

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals

DRUG PRODUCT: Naproxen Sodium Controlled Release Tablets, 412.5 mg (375 mg Base)

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

Based on the data submitted, the following dissolution testing is recommended for your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of pH 7.5 Phosphate Buffer at 37° C using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following interim specifications:

0.5 hour	(b) (4)
3 hours	
6 hours	
14 hours	no less than (b) (4)

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS (HFD-600)
7500 STANDISH PLACE, ROCKVILLE, MD 20855

DATE: 12/5/00

TO: Janet Vaughn

PHONE: 954-327-4412

FAX: 954-587-1054

FROM Tim Ames

PHONE: 301-827-5848

FAX: 301-594-0180

TOTAL NUMBER OF PAGES: 1
(EXCLUDING COVER SHEET)

SPECIAL INSTRUCTIONS: ANDA 75-416 labeling comments

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

ANDA Number:	75-416
Date of Submission:	May 11, 2000
Applicant's Name:	Andrx Pharmaceuticals, Inc.
Established Name:	Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)

Labeling Deficiencies:

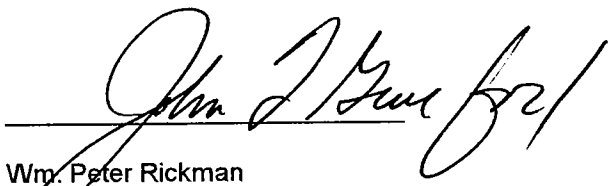
1. **CONTAINER** – bottles of 75 and 1000 tablets **(500mg tablet)**
   Satisfactory in **final print** as of the May 14, 1999 submission.

2. **CONTAINER** – bottles of 100 and 1000 tablets **(375mg tablet)**
   Satisfactory in **draft** as of the May 11, 2000 submission.

3. **PROFESSIONAL PACKAGE INSERT**
   How Supplied
   We note that you list a 100 count bottle for your 500mg strength tablet as well as your 375mg tablet. No container labeling for the 100 count bottle of 500 mg tablets has yet to be received by the Agency. Please revise and/or comment.

Please revise and prepare 12 copies of your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html



Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Andrx
PHARMACEUTICALS, INC.

ANDA #: 75-416, Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg

December 15, 2000

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: General Correspondence

Dear Sir:

This letter is to inform you that the administrative offices of Andrx Pharmaceuticals, Inc. have relocated to a new address. Please direct all future correspondences pertaining to the above referenced ANDA to the following address and/or contact persons:

Andrx Pharmaceuticals, Inc.
4955 Orange Drive
Fort Lauderdale, Florida 33314

Diane Servello, *Director of Regulatory Affairs*
Telephone: (954) 585-1412

Janet Vaughn, *Manager of Regulatory Affairs*
Telephone: (954) 585-1665

Facsimile: (954) 587-1054

Please note that the manufacturing site for the drug product has not changed. The new address for the administrative offices is contiguous with the manufacturing site.

Should you have any questions or comments concerning these changes, please contact Janet Vaughn at the above telephone number.

Sincerely,

Janet Vaughn for
Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 18 2000
OGD

Andrx
PHARMACEUTICALS, INC.

ANDA 75-416
Naproxen Sodium Extended-Release Tablets
375 mg and 500 mg (base)

Via fax to 301-827-4337

January 3, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: FAX AMENDMENT: CMC & BIOEQUIVALENCY

Dear Mr. Buehler:

Please refer to our abbreviated new drug application for Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg, ANDA 75-416. Reference is also made to the Agency's facsimile (copy attached) dated December 4, 2000 providing chemistry and bioequivalency comments for the 375 mg strength of this product. We are amending the application to provide the following responses to all the deficiencies listed in the facsimile.

Response to Chemistry, Manufacturing and Controls Deficiencies (December 4, 2000 facsimile)

A. Deficiencies:

1. (b) (4)

Response

(b) (4)

Following this page, 1 page withheld in full (b)(4)

(b) (4)

[redacted]

Response to Bioequivalency Comments (December 4, 2000 facsimile)

We note that the Division of Bioequivalence has completed its review and has no further questions at this time.

Based on the data provided, the following dissolution testing was recommended and has been incorporated by Andrx into our stability and quality control programs:

The dissolution testing is conducted in 900 mL of pH 7.5 Phosphate Buffer at 37° C using USP 24 apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

0.5 hour	(b) (4)
3 hours	
6 hours	
14 hours	no less than (b) (4)

We also note that the bioequivalency comments provided in the facsimile are preliminary and that the comments are subject to revision after review of the entire application.

ANDA 75-416
Naproxen Sodium ER Tablets, 375 mg & 500 mg (base)
Fax Amendment – 01/01

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Andrx is in receipt of your facsimile date December 5, 2000 providing labeling comments for this ANDA. We are preparing final printed labeling, and expect to submit an amendment with the revised labeling during the week of January 8, 2001. This amendment will also notify the agency of our eligibility for final approval of the 500 mg (base) strength of this product.

Please note that a list of the attachments included in this amendment is provided after the FDA Form 356h (page 0002(a)). Should you have any questions concerning this submission, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

ANDA 75-416
Naproxen Sodium Extended-Release Tablets
375 mg and 500 mg (base)

January 9, 2001

ORIG AMENDMENT
N/FA

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: MINOR AMENDMENT
Notification of Eligibility for Final Approval/ Final Printed Labeling/CMC Update

Dear Mr. Buehler:

Please refer to our abbreviated new drug application for Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg, ANDA 75-416. Reference is also made to the Agency's tentative approval letter dated March 17, 2000 for the 500 mg (base) strength of the drug product and the labeling comments contained in a facsimile dated December 5, 2000.

Notification of eligibility for final approval:
As instructed in the tentative aproval letter, we are notifying the agency that we believe the 500 mg (base) strength of this product will be eligible for final approval on March 11, 2001.

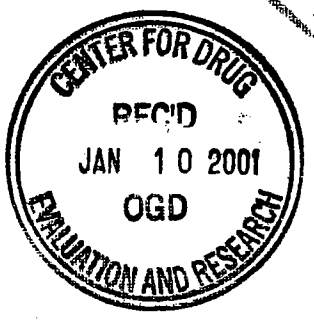
Final Printed Labeling:
In accordance with the Agency's December 5, 2000 facsimile providing labeling comments, we are submitting final printed labeling as follows:

- Twelve (12) copies of final printed container labels for the 375 mg tablet (100 and 1000 counts) identical in content to the draft labels submitted on May 11, 2000 (Tab 1).

- Twelve (12) copies of final printed container labels for the 500 mg tablets (75 and 1000 counts) identical in content to the draft labels submitted on May 14, 1999. Please note that twelve copies of final printed labels for the 100 count are also provided -- please see explanation under "CMC Update" below. (Tab 2).

- Twelve (12) copies of final printed package outserts (Tab 3).

Please note that the final printed labeling included in this amendment is the same as the previously submitted draft labeling. Therefore, a side-by-side comparison is not necessary.



4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

CMC Update:
We are reporting one minor change in the conditions under which this drug product was tentatively approved. Our marketing department has requested a new 100s package size for the 500 mg strength of this product. Since this new size is bracketed by the existing 75 count and 1000 count package size, it was our original intent to submit the new size in the first post-approval annual report. However, for the sake of completeness, we are providing information on the 100 count packaging size of the 500 mg strength in this amendment. The information on the (b) (4) child-resistant closure (Andrx code (b) (4)), has already been submitted, as the same closure is also used 75 count configuration of the 500 mg strength of the drug product. Thus, this amendment only includes information on the (b) (4) bottle used for the 100 count package (Andrx code (b) (4)) (Tab 4)

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

A copy of the Agency's December 5, 2000 facsimile is attached. Should you have any questions concerning this submission, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

FAX AMENDMENT

ANDA 75-416

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB 12 2001

TO: APPLICANT: Andrx Pharmaceuticals, Inc. TEL: 954-581-7500

ATTN: Diane Servello FAX: 954-587-1054

FROM: Timothy Ames PROJECT MANAGER (301) 827–5765

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated July 16, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Naproxen Sodium Extended-release Tablets, 500 mg (base) and 375 mg (base).

Reference is also made to your amendment(s) dated January 3, and 9, 2001. 1/12/01

Attached are 1 pages of minor deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FAX AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. Further if a major deficiency is cited in the bioequivalence review, the subsequent Not Approvable letter will request that the reply be declared a MAJOR AMENDMENT.

SPECIAL INSTRUCTIONS: CMC .

X:\new\ogdadmin\macros\faxfax.frm

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-416 APPLICANT: Andrx Pharmaceuticals, Inc.

DRUG PRODUCT: Naproxen Sodium Extended-release Tablets, 375 mg (Base) and 500 mg (base)

The deficiencies presented below represent FAX deficiencies.

A. Deficiencies:

1. (b) (4)

2.

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

Labeling information you have provided for the Naproxen Sodium Extended-release Tablets is under review by our Division of Labeling. After the review is complete, any deficiencies found will be communicated to you under separate cover.

Sincerely yours,

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

Andrx
PHARMACEUTICALS, INC.

VIA FEDERAL EXPRESS

January 12, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

FA
NDA ORIG AMENDMENT

RE: ANDA 75-416 – Naproxen Sodium Extended-release Tablets, 375 mg (base)
DOCUMENTATION OF LITIGATION

Dear Mr. Buehler:

On May 11, 2000 Andrx Pharmaceuticals amended the above referenced ANDA to include an additional strength of the drug product, Naproxen Sodium Extended-release Tablets, 375 mg (base). As that amendment contained a Paragraph IV certification the notices of certification required under 21 CFR 314.95(b) were sent to the patent holder and NDA holder at the same time that the amendment was submitted to FDA.

As previously indicated in our June 29, 2000 patent amendment, the notices were received on June 16, 2000.

The purpose of this letter is to certify that an action for patent infringement (Case No. 98-7164) was filed by Elan Corporation, PLC against Andrx alleging infringement of patent 5,637,320. The complaint was filed on July 3, 2000, in the United States District Court for the Southern District of Florida. A copy of the complaint is included in this amendment.

Should you have any questions regarding this amendment, please do not hesitate to contact Janet Vaughn at (954) 585-1665 (Telephone) or (954) 585-1858 (Fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 16 2001
OGD

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

2/15/01
FA noted, to CMC reviewer for review.

Andrx
PHARMACEUTICALS, INC.

ANDA 75-416
Naproxen Sodium Extended-Release Tablets
375 mg and 500 mg (base)

Via fax to 301-827-4337
(Hard copy to follow by Federal Express

February 12, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

N/FA
VIA OGD AMENDMENT

RE: FAX AMENDMENT: CMC

Dear Mr. Buehler:

Please refer to our abbreviated new drug application for Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg, ANDA 75-416. Reference is also made to the Agency's facsimile (copy attached) dated February 2, 2001 providing chemistry comments for this product. We are amending the application to provide the following responses to the deficiencies listed in the facsimile.

Response to Chemistry, Manufacturing and Controls Deficiencies

A. Deficiencies:

1. [redacted] (b) (4)

Response

[redacted] (b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB 12 2001
OGD

ANDA 75-416
Naproxen Sodium ER Tablets, 375 mg & 500 mg (base)
Fax Amendment – February 12, 2001

2. (b) (4) [redacted]

Response

(b) (4) [redacted]

Notes and acknowledgements

Andrx notes and acknowledges that the labeling information we submitted on January 9, 2001 is under review by your Division of Labeling. After their review is complete, any deficiencies found will be communicated to us under separate cover.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please contact Janet Vaughn, Manager Regulatory Affairs, at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

Andrx
PHARMACEUTICALS, INC.

February 16, 2001

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: GENERAL CORRESPONDENCE - ANDA 75-416 - Eligibility for Final Approval - Naproxen Sodium Extended-Release Tablets, 375 mg and 500 mg (base)

Dear Mr. Buehler:

On March 17, 2000, the Agency granted tentative approval of ANDA 75-416 for Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base), ANDA 75-416, and on January 9, 2001, Andrx Pharmaceuticals, Inc. (Andrx) advised your office that we believe that such ANDA was eligible for final approval on March 11, 2001. This letter shall explain the reasons why we believe the referenced ANDA is eligibility for final approval on March 11, 2001, when the 30-month stay of approval provided for in section 505 (j) (5) (B) (iii) expires.

In a letter dated September 18, 1998 (attached), Elan Corporation, plc and its subsidiaries (Elan), the holder of the approved application for the reference listed drug and the listed patent owner, acknowledged receipt of the Paragraph IV notification sent by Andrx on September 10, 1998. Elan then initiated litigation against Andrx, claiming that the Andrx product infringed one of the patents listed in the Orange Book for the reference listed drug, thereby imposing the 30 month stay of approval provided for in section 505 (j) (5) (B) (iii). That litigation is ongoing, and since the court has not extended the 30-month period, our ANDA will be eligible for approval on March 11, 2001, when that the 30-month stay of approval expires.

Andrx knows that [redacted] (b) (4) submitted an earlier ANDA application, containing a Paragraph IV certification, for a Naproxen Sodium Extended-release Tablet. While [redacted] (b) (4) first to file application might have originally been afforded a 180-day period of exclusivity, we believe that such exclusivity period is no longer warranted in this instance, for various reasons.

CENTER FOR DRUG
RECD
FEB 20 2001
OGD
EVALUATION AND RESEARCH

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 · 954 [illegible] · FAX: 954 587-1054

First, under the Agency's February 6, 2001 response to a Citizen Petition filed by Teva Pharmaceuticals with respect to nifedipine extended release tablets (the Agency Response), the Agency determined that the first Paragraph IV ANDA applicant is no longer eligible for the 180-day period of exclusivity if it effectively changed its paragraph IV certification to a paragraph III certification. On [redacted], while Andrx does not know whether [redacted] formally amended its certification, as required by FDA regulations, the Agency Response clearly indicates that "FDA must determine the effect of this settlement on [the first to file's] patent certification." As clearly evidenced by [redacted] has admitted that its original certification was erroneous, and has agreed not to market its ANDA product. Andrx believes this admission and agreement is a clear indication that [redacted] "effectively changed its patent certification from a paragraph IV certification to a paragraph III certification", much the same as Mylan did in the case referred to in the Agency Response, thereby causing it to lose its exclusivity rights.

Second, if [redacted] has not withdrawn or amended its ANDA, the Agency should conclude that [redacted] is not actively pursuing approval of the application, in accordance with 21 CFR §314.107 (c) (3). Pursuant to this regulation, the Agency can make the approval of subsequent abbreviated applications immediately effective if they are otherwise eligible for immediate effective approval.

Finally, with our January 9, 2001 letter responding to the Agency's last minor amendment, all of remaining requirements of the March 17, 2000 tentative approval letter (a CMC update and submission of final printed labeling as requested by the Agency's December 5, 2000 labeling comments facsimile) have been completed. Therefore, Andrx requests that our Naproxen Sodium Extended Release Tablets, 500 mg (base) strength be granted final approval on March 11, 2001.

Should you have any questions concerning this submission, please contact Diane Servello (954) 585-1412 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director, Regulatory Affairs

OGD APPROVAL ROUTING SUMMARY

NDA # 75-416 Applicant ANDRX Pharmaceuticals

Drug Naproxen Sodium Extended-Release Tablets Strength 375mg (base) + 500mg (base)

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: DRAFT RECEIPT FINAL ACTION

1. Tim Ames, Project Manager, Team 1 Date 3/7/01 Date _____
Review Support Br Initials [illegible] Initials _____

Application Summary:

Original Rec'd date 16-JUL-1998 ✓ EER Status Pending ☐ Acceptable ☒ OAI ☐

Date Acceptable for Filing Same Date of EER Status 08-FEB-2000

Patent Certification (type) PIV Date of Office Bio Review 03-DEC-1998

Date Patent/Exclus.expires 10-JUN-2014 Date of Labeling Approv. Sum 30-JAN-2001

Citizens Petition/Legal Case Yes ☒ No ☐ Date of Sterility Assur. App. NA

(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒

First Generic ?? Yes ☒ No ☐ 30 Day Clock Start _____ End _____

(If YES, check PETS) Commitment Rcd. from Firm Yes ☐ No ☐

Pediatric Exclusivity Tracking System(PETS) Modified-release dosage form: Yes ☒ No ☐

Date checked _____ NDA# 20553 Interim Dissol. Specs in AP Ltr: Yes ☒

Nothing Submitted ☒

Written request issued ☐

Study Submitted ☐

MV Acceptable 04-JAN-2000

Office Bio Signoff (375mg) 7/12/00.

Previously reviewed and tentatively approved ☐ Date _____

Previously reviewed and CGMP def./N/A Minor issued ☒ Date 3/17/01

Comments:

2. Div. Dir./~~Deputy Dir.~~ Date 3/14/01 Date 3/14/01
Chemistry Div. I ~~or II~~ Initials PAS Initials PAS

Comments:

The CMC section is satisfactory for approval. Updated EER on Celsis lab however is needed.

3. Frank Holcombe Date _____ Date 3/16/01
Assoc. Dir. For Chemistry Initials _____ Initials [illegible]
Comments: (First generic drug review)

Site is Facility

4. Pat Beers Block Date 3/19/01 Date 3/20/01
Supv., Review Support Branch Initials [illegible] Initials [illegible]

EER Status: Acceptable for all facilities as of 2/8/2000 (none OAI)

Bioequivalence sites: Eastern Research Analytical site: (b) (4)

Clinical site: St Charles, Missouri Inspection needed: ☐ yes ☐ no Richmond VA

Inspection needed: ☐ yes ☐ no Status: ☒ acceptable

Status: ☒ acceptable ☐ unacceptable ☐ pending

☐ unacceptable ☐ pending Date of status: _____

Date of status: _____ Reason: Based on DSI inspection history 7/12/00

Reason: Based on DSI history

Bioequivalence office level sign off: Acceptable 12/3/98 (see previous memo + Tentative approval letter/reviews)

Labeling Status: Acceptable 1/30/01

Microbiology status: N/A

Patent Certification: Para IV ; 30 months has expired. 3/31/01

Controlled Correspondence/Cit.Pet:

Comments: RLD = 20-353 M.V acceptable 1/4/2000.

Interim Dissol. specs same for both strengths

First Para IV applicant lost lawsuit ∴ all 180 day exclusivity lost (for subsequent ANDA)

REVIEWER: | **DRAFT RECEIPT** | **FINAL ACTION**

Gregory Davis
Supv., Reg. Support Branch

Date 4/11/01 | Date 7/5/2001
Initials RW | Initials RW for

Contains GDEA certification: Yes ☐ No ☐ Determ. of Involvement? Yes ☐ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☐ No ☐ Pediatric Exclusivity System
If Para. IV Certification- did applicant Date Checked 7/5/01
Notify patent holder/NDA holder Yes ☒ No ☐ Nothing Submitted ☒
Was applicant sued w/in 45 days: Yes ☒ No ☐ Written request issued ☐
Has case been settled: Yes ☐ No ☐ Study Submitted ☐
Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☐

RLD = Naprelan Extended-release Tablets; Elan Pharmaceutical Research Corp; NDA 20-353

Comments: Andrx made a "paragraph 4" certification to the '320 patent upon submission of notification. Andrx made a "paragraph 4" cert. with respect to the '315 mg (base) strength on 2/11/00. for the 550 mg strengths only. There are no unexpired exclusivity. Andrx was sued by Elan within 45 days

6. Peter Rickman
Acting Director, DLPS

Date 4/11/01 | Date 7/5/2001
Initials RW | Initials for

Comments: RLD 20-353 NAPRELAN ELAN. Bioequivalence studies on 550 mg strength (fasting, fed, multi-dose) found acceptable 12/98. Study conducted by Gateway Medical Research; analytical facility was [redacted] (b)(4). Office level bio endorsed 12/3/98. This ANDA received tentative approval on 9/7/00 for the 550 mg (base) strength only. Bio found acceptable for 315 mg (base) strength on 6/16/00. Office level bio endorsed 7/12/00. (DSI-OK). FPL found acceptable 1/30/01. Note: package insert includes both strengths. CMC acceptable 3/30/01. Methods validation completed + acceptable. Acceptable GES dated 2/8/00 (Verified 4/18/01). No ORA-Quest noted.

7. Robert L. West
Acting Deputy Director, OGD

Date 7/5/01 | Date 7/5/01
Initials RW | Initials Robert L. West

Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☐ No ☒

Comments: [redacted] (b)(4) continues to hold the "first in" exclusivity seat on this drug product. We cannot approve the Andrx ANDA. Elan issue Andrx a second tentative approval letter (this time including the 315 mg strength) [redacted] (b)(4) must be approved before Andrx can be. ([redacted] (b)(4) is currently on [redacted] (b)(4) status)

8. Gary Buehler
Acting Director, OGD
Comments:

Date 7/5/01 | Date 7/5/01
Initials GB | Initials GB

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

9. Tim Ames, Project Manager, Team 8
Review Support Branch

Date _____ | Date 7/9/01
Initials _____ | Initials

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
10A Time notified of approval by phone 10:12a Time approval letter faxed

FDA Notification:
7/9/01 Date e-mail message sent to "OGD approvals" account
7/9/01 Date Approval letter copied to "//cder/drugapp" directory

v:\reports\approval\approvrou

Andrx
PHARMACEUTICALS, INC.

ANDA 75-416
Naproxen Sodium Extended-Release Tablets, 375 mg and 500 mg (base)

January 22, 2002

NC

NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

RE: AMENDMENT - WITHDRAWAL OF API MANUFACTURING SITE

Dear Mr. Buehler:

We refer to a telephone conversation between Tim Ames and Janet Vaughn of Andrx Pharmaceuticals, Inc. on January 17, 2002, regarding [redacted] (b) (4) manufacturing site in [redacted] (b) (4).

Andrx Pharmaceuticals, Inc. would like to withdraw the manufacturing site in [redacted] (b) (4) from ANDA 75-416, Naproxen Sodium Extended-Release Tablets, 375 mg and 500 mg (base). Please note that as of today's date we have never received material from this site.

Andrx Pharmaceuticals, Inc. certifies that a true copy of this amendment was sent to the Florida District Office as a Field Copy.

Should you have any questions concerning this submission, please do not hesitate to contact Janet Vaughn at (954) 585-1665 (telephone) or (954) 587-1054 (fax).

Sincerely,

Diane Servello
Director of Regulatory Affairs

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS INC.

N/Am

June 11, 2002

ORIG AMENDMENT

Gary Buehler,
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-416 – Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)
REQUEST FOR FINAL APPROVAL

Dear Mr. Buehler:

Reference is made to your tentative approval letter dated July 5, 2001 (copy attached as Exhibit 1), which discusses the requirements for final approval of this ANDA. The purpose of this letter is to inform your office of two new developments with respect to this ANDA:

- On March 14, 2002, a final judgment was entered in the favor of Andrx Pharmaceuticals, Inc., declaring U.S. patent no. 5,637,320 to be invalid. A copy of the Final Judgment is enclosed as Exhibit 2.

- Andrx has entered into a settlement with [redacted] (b) (4) whereby [redacted] (b) (4) has waived whatever rights it may have to market exclusivity under ANDA [redacted] (b) (4) A copy of the Settlement and Release Agreement is enclosed as Exhibit 3. As indicated in the settlement, [redacted] (b) (4) will be providing a written notice to the Office of Generic Drugs waiving their rights to market exclusivity.

With these new developments, we have satisfied the requirements set forth in your tentative approval letter and believe this ANDA is now eligible for final approval.

Please note that no significant changes in the conditions outlined in our application have been made. Final printed labeling was submitted to this application with an amendment dated January 9, 2001.

Should you have any questions, please do not hesitate to contact me at (954) 358-6125 (Telephone) or (954) 358-6350 (Fax).

Sincerely,

Diane Servello

Diane Servello
Sr. Director, Regulatory Affairs

RECEIVED
JUN 12 2002
OGD / CDER

21-528
amd

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS INC.

June 17, 2002

Gary Buehler,
Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: ANDA 75-416 – Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg (base)
NOTICE OF SUBMISSION OF CONFIDENTIAL DOCUMENT

Dear Mr. Buehler:

Reference is made to our letter dated June 11, 2002, which requested final approval of this ANDA. That letter included a copy of an agreement between (b) (4) and Andrx.

Please be advised that the Agreement between (b) (4) and Andrx is confidential, (b) (4) (b) (4). Accordingly, we are requesting that this document be maintained as confidential in your files.

Should you have any questions, please do not hesitate to contact me at (954) 358-6114 (Telephone) or (954) 358-6350 (Fax).

Sincerely,

Diane Servello
Sr. Director, Regulatory Affairs

RECEIVED
JUN 1 8 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

Andrx™
PHARMACEUTICALS, INC.

ANDA 75-416
Naproxen Sodium Extended-release Tablets, 375 mg and 500 mg

July 22, 2002

Via facsimile to (301) 594-1174

NEW CORRESP
NC

Gary Buehler,
Acting-Director, Office of Generic Drugs, HFD-600
CDER, Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: Patent Amendment
Elan's Motion for Reconsideration

Dear Mr. Buehler:

Please refer to the above referenced Abbreviated New Drug Application (ANDA). Reference is also made to the telephone conversation between Greg Davis of your office and Janet Vaughn, Andrx Pharmaceuticals. In response to Mr. Davis' request for further documentation regarding the final outcome of the litigation initiated by Elan Corporation (manufacturer of the reference drug, Naprelan™) against Andrx, we are providing a copy of Elan's "motion, and incorporated memorandum, for reconsideration, to alter the judgement, and to amend and supplement the court's findings of fact and conclusions of law" (attached).

A copy of the March 14, 2002 final judgement declaring U.S. patent no. 5,637,320 to be invalid, was previously submitted to your office in our June 11, 2002 correspondence. To date, this judgement has not been appealed. In addition, the 30 month stay of approval for this ANDA expired on March 15, 2001.

Should you have any questions, please do not hesitate to contact me at (954) 358-6114 (Telephone) or (954) 358-6350 (Fax).

Sincerely,

Diane Servello
Sr. Director, Regulatory Affairs

RECEIVED
JUL 23 2002
OGD / CDER

Cc: Greg Davis
Branch Chief
Regulatory Support Branch
OGD

Andrx™
PHARMACEUTICALS INC.

August 16, 2002

ORIG AMENDMENT
N/AF

Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA #75-416; NAPROXEN SODIUM EXTENDED-RELEASE TABLETS LABELING AMENDMENT

Dear Mr. Buehler:

Reference is made to our labeling amendment dated August 14, 2002 responding to the August 13, 2002 facsimile from James Barlow of your labeling review team. Reference is also made to a telephone communication from Mr. Barlow's on August 16, 2002 advising Andrx that references to the 375 mg strength must be removed from our labeling until this strength is eligible for approval at a later data. In accordance with Mr. Barlow's request, Andrx Pharmaceuticals, Inc. has revised our labeling to remove references to the 375 mg strength.

In this regard, we have enclosed the following:

1. Twelve copies of final printed inserts. (Six copies are included with the archival copy and six copies are included with the review copy.)
2. A side-by-side comparison, annotating the revisions to our labeling.

Should you have any questions or comments concerning this submission, please contact the undersigned at (954) 358-6114.

Sincerely,
ANDRX PHARMACEUTICALS, INC.

Diane Mw

Diane Servello
Sr. Director Regulatory Affairs

RECEIVED
AUG 19 2002
OGD / CDER

4955 ORANGE DRIVE, FORT LAUDERDALE, FLORIDA 33314 • 954 581-7500 • FAX: 954 587-1054

OGD APPROVAL ROUTING SUMMARY

ANDA # 75-416 Applicant Andrx Pharmaceuticals
Drug Naproxen Sodium ER tablets Strength 375 mg, 500 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:

1. Project Manager, Team 1 Craig Kuester
Review Support Br

DRAFT Package
Date 7/10/02
Initials CK

FINAL Package
Date 8/27/02
Initials CK

Application Summary:

Original Rec'd date July 16, 1998
Date Acceptable for Filing July 16 1998 J
Patent Certification (type) PIV
Date Patent/Exclus.expires 6/10/14
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
(If YES, Pediatric Exclusivity Tracking System (PETS)
RLD =
Date checked 7/15/02 NDA# 20353
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status July 10, 2002
Date of Office Bio Review 7/12/00
Date of Labeling Approv. Sum 1/30/2001
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒
MV acceptable 1/4/02

Previously reviewed and tentatively approved ☒ Date 3/17/00
Previously reviewed and CGMP def./N/A Minor issued ☐ Date
Comments:

2. Gregg Davis PPIV ANDAs Only
Supv., Reg. Support Branch

Date 19-JUL-2002
Initials

Date 19-JUL-2002
Initials

Contains GDEA certification: Yes ☒ No ☐
(required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☒ No ☐
Date settled: 3/14/02
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Comments:

Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
Date Checked 7/31/02
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐

NDA 20-353

RLD = Naprelan Extended-Release Tablets Elan Pharmaceutical Research Corp 375mg (base) + 500mg (base)

(b)(4) was 1st w/ PIV for all strengths but relinquished their 180 d - no seat for exclusivity is left - for the 500mg, 30 exp. but 375mg does not expire until 12/03 - d/c court finding '320 invalid - appeal?

3. Div. Dir./~~Deputy~~ Dir.
Chemistry Div. I ~~or~~ II
Comments:

Date 8/21/02
Initials RRS

Conc section for the 500mg strength is satisfactory for approval

CMC acceptable 8/1/02. FPL acceptable for 500mg strength 8/23/02.

REVIEWER:

FINAL ACTION

4. Frank Holcombe
Assoc. Dir. For Chemistry
Comments: (First generic drug review)
N/A. Completed at the time of the first T/A on March 17, 2000.

Date _____
Initials _____

5. Peter Rickman
Acting Director, DLPS
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition:Yes☐ No☐
Comments: Acceptable EES dated 7/10/02 (verified 7/31/02) No O.A.I. Objects noted. Refer to the administrative section of the memo completed at the time of the second tentative approval on July 5, 2001. [redacted] (b)(4) eligibility for 180-day generic exclusivity, presented approval of Andex 500mg strength at that time. Andex June 11, 2002 submission informing us of an agreement between [redacted] (b)(4) waived its eligibility for 180-day exclusivity. [redacted] (b)(4)

Andex has also requested final approval both the 500mg and the 375mg (base) strengths. G. Davis has concluded that the 500mg (base) strength may be approved on the basis of the expiration of the 30-month litigation period (3/14/01). However because the first ANDA [redacted] (b)(4) was received by the agency prior to the March 27, 2000 Hylan decision, the court decision referenced by Andex in its 6/10/02 submission is not considered to be a "final decision". Furthermore, the 30-month period for the 375mg strength has not expired. This will not occur until 12/16/02.

Date 7/31/02
Initials Robert West

5. Robert L. West
Acting Deputy Director, OGD
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☒ No☐; Petition:Yes☐ No☐
Comments:

Plan: Issue approval letter for the 500mg (base) strength. The 375mg (base) strength will remain tentatively approved until the expiration of its 30-month period (or a final court decision).

6. Gary Buehler
Director, OGD
Comments:

Date 8/27/02
Initials GB

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

7. Project Manager, Team Review Support Branch Craig Kiester

Date _____
Initials _____

N/A Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
3:45 Time notified of approval by phone 3:45 Time approval letter faxed

FDA Notification:
8/27 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
8/27 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

V :orts\approval\approvrou2.doc