CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-179

ADMINISTRATIVE DOCUMENTS

APPROVAL SUMMARY

ANDA: 75-179

DRUG PRODUCT: Nabumetone Tablets, 500 mg and 750 mg

FIRM: Copley Pharmaceutical Inc.

DOSAGE FORM: Oral Tablet

STRENGTH: 500 mg and 750 mg

cGMP STATEMENT/EIR UPDATE STATUS: acceptable EER dated 02/04/00

BIO STUDY:
Acceptable (Bio review was dated 07/21/98). The recommended disolution specifications are as follows:

> The dissolution testing should be conducted in 900 mL of 2% SLS, at 37° C using USP Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:
>
> Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

VALIDATION:
Both the drug substance and drug product are not listed in the USP 24. Method validation was conducted by Northeast Regional Laboratory. The report was dated 12/03/98. Copley's method is suitable for regulatory analysis.

STABILITY:
For the executed batches for both strengths, stability data are provided for 3-months accelerated conditions. The samples tested are those packaged in 100s and 500s. The accelerated stability test results meet the proposed specifications at the time of original ANDA submission on 08/04/97. Copley has revised their specifications for related substances since their 03/02/98 amendment(see below). Since the level of related substances for all test stations in the original ANDA submission were less than the 0.1% detection limit, Copley's stability data for related substances are considered valid.

In response to part (b) of Deficiency #2 in NA letter dated 08/04/98), Copley provided dissolution test data for Nabumetone Tablets 500 mg and 750 mg, packaged in 100s and 500s stored for three months at accelerated conditions plus additional 12 months at ambient room temperature. All dissolution data are within specifications per FDA recommended specifications.

The container/closure system used for the stability study is equivalent to the system proposed for commercial use. A 24 month expiration date is proposed.

Stability tests and specifications are as follows:

Assay: 90.0-110.0%
Dissolution: NLT in 45 min.
Appearance:
750 mg: White, modified oval shaped tablet, debossed "Copley-510" on one side, plain on the other side.
500 mg: White, modified oval shaped tablet, debossed "Copley-325" one side, plain on the other side.
Related Substances:

stances

Total related substances

LABELING:
Labeling approval summary was signed off on 05/05/00.

STERILIZATION VALIDATION: (IF APPLICABLE): N/A

SIZE OF BIO Batch:
Copley manufactured two exhibit batches: #510Z05 (750 mg tablets), and #325Z03 (500 mg tablets). The 750 mg tablet batch is the biobatch. Both batches are used for stability studies.

Drug substance used in the test batches is supplied by Napp Technologies, Inc. is adequate as of 04/13/00.

Copley will use common granulation for the two strengths in the future. The sizes for ANDA test batches and production batches are summarized as follows:

Nabumetone Tablets	Test Batch Size	Production Batch Size
500 mg (Tablet wt: 613.4 mg)		
750 mg (Tablet wt: 920.0 mg)		

Note:
Since tablets size exceeds the maximum allowable batch size increase based on the ANDA batch for the 500 mg product, Copley intends to divide the full production batch of granulation into 2 separate compression batches, one of tablets and one of tablets. Copley provided proposed granulation batch record (batch size and proposed 500 mg tablet compression batch records for batch sizes, respectively.

SIZE OF STABILITY BATCHES: See above

PROPOSED PRODUCTION BATCHES: See above. The manufacturing process for production batches is the same as that for test batches.

Review Chemist: S.H. Liu **DATE:** 05/09/00
Shing H. Liu, Ph.D.

Team Leader: DSG, for **DATE:** 5-11-00
Devinder Gill, Ph.D.

This approval summary supercedes the one dated March 2, 1998
(FIRST GENERIC)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-179 **Date of Submission: May 1, 2000**
Applicant's Name: Copley Pharmaceutical, Inc.
Established Name: Nabumetone Tablets, 750 mg
APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

1. Container Labels: 100's & 500's- Satisfactory in FPL as of 3/2/98 submission
2. Professional Package insert Labeling: Satisfactory as of May 1, 2000 submission

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Relafan®
NDA Number: 19-583
NDA Drug Name: Relafan®
NDA Firm: SmithKline Beecham Pharmaceuticals Company
Date of Approval of NDA Insert and supplement #: November 23, 1993/S-001, 002, 004 & 005)
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: Relafan®
FOR THE RECORD

1. MODEL LABELING -Relafan® (19-583/S-001, 002, 004 & 005) - SmithKline Beecham Pharmaceuticals company; approved November 23, 1993.This is **the very first generic application** for Nabumetone tablets.
2. The firm has submitted an amendment (10/24/97) to add 500 mg strength tablets to their application for 750 mg tablets. The firm was requested to delete all reference to the 500 mg strength via phone w/Jim Barlow on April 14, 2000. Similar request was made to ANDA#75-179. Teva bought Copley.
3. INACTIVE INGREDIENTS -The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of Components and Composition appearing on page 2474, Volume B. 1.1. (750 mg) and page 113, vol.2.1. (500 mg)
4. PATENTS/EXCLUSIVITIES- The patent expires December 13, 2002 without any protected exclusivity. The firm's statement is accurate. However, the firm has filed Paragraph IV Certification.
5. The package insert express the "CLINICAL TRIALS" and "INDIVIDUALIZATION OF DOSING" headings with the same prominence as other section headings, which is consistent with the innovator's labeling. We will **not** ask the firm to reduce the prominence.
6. Copley Pharmaceutical, Inc. is the sole manufacturer for this product.
7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON- NDA - Store at controlled room temperature (59°-86°F);ANDA - Store at controlled room temperature 15° - 30°C (59° - 86°F).
8. DISPENSING STATEMENT COMPARISON -NDA - Dispense in a well-closed, light-resistant.; ANDA -Dispense in a well-closed, light-resistant.
9. PACKAGING CONFIGURATIONS - NDA - 100's & 500's; ANDA -100's & 500's
10. CONTAINER/CLOSURE SYSTEM -Closure - 100's (CRC); 500's (Non-CRC) See vol.B.1.2, P.2759 (750 mg) & vol.2.2, p.329. (500 mg)
11. The debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See vol.B.1.2, p.2840 (750 mg) & vol.2.2, p.369. (500 mg)
12. SCORING: NDA – unscored ANDA - unscored

Date of Review: May 4, 2000 **Date of Submission: May 1, 2000**
Reviewer: Jim Barlow J. Barlow **Date:** 5/14/2000
Team Leader: John Grace John Grace **Date:** 5/15/2000

cc:

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
75-179

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Copley Pharmaceutical, Inc..	February 23, 2000
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
781-575-7318	781-575-7362

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
25 John Road
Canton, MA 02021

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
Nabumetone	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
4-(6-methoxy-2-naphthalenyl)-2-butanone	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablets	500 mg, 750 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Acute and chronic treatment of signs and symptoms of osteoarthritis and rheumatoid arthritis

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug	Holder of Approved Application
Relafen Tablets	SmithKline Beecham

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Patent Amendment

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at this site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

N/A

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

N/A

This application contains the following items: *(Check all that apply)*		
	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50 (c))
	4.	Chemistry section
		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7.	Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8.	Clinical data section (e.g. 314.50 (d) (5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12.	Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13.	Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306 (k)(1))
X	17.	Field copy certification (21 CFR 314.5 (k) (3))
	18.	User Fee Cover Sheet (Form FDA 3397)
X	19.	OTHER (Specify) Patent Amendment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Vincent Andolina	Vincent Andolina, RAC Sr. Manager, Product Registration	February 23, 2000

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
Copley Pharmaceutical, Inc. 25 John Road Canton, MA 02021	(781) 575-7318

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

COPLEY PHARMACEUTICAL, INC.

ANDA 75-179 / PATENT AMENDMENT

Nabumetone Tablets
500 mg and 750 mg

FIELD COPY CERTIFICATION

This is to certify that the field copy submitted in accord with 21 CFR §314.96(b) of the Code of Federal Regulations is a true copy of our Patent Amendment submitted on February 23, 2000 for Nabumetone Tablets, 500 mg and 750 mg.

Gail Shamsi
Gail Shamsi, RAC
Sr. Regulatory Associate

February 23, 2000
Date

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(617) 821-6111
Mailroom Fax: (617) 821-4068

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

October 29, 1997

Mr. Jan Leschly
Chief Executive Officer
Smithkline Beecham Pharmaceuticals
P. O. Box 1539
Route 23 Woodmont Avenue
King of Prussia, PA 19406

Re: Copley Pharmaceutical, Inc.'s ANDA

Dear Sir:

Further to our letter of September 11, 1997, Copley Pharmaceutical, Inc. ("Copley") hereby gives you notice that its ANDA, No. 75-179, now contains data which establishes that Copley's 500 mg nabumetone tablets are the generic equivalent to the corresponding dose of Relafen®. Copley's ANDA already contains a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) that United States Patent 4,420,639 ("the '639 patent") is invalid and unenforceable.

Copley continues to rely on the previously submitted detailed statement of the factual and legal basis of Copley's opinion that the '639 patent is invalid and unenforceable.

Sincerely,
Copley Pharmaceutical, Inc.

By: 
William E. Brochu
Director, Regulatory Affairs

WEB/esc

is your RETURN ADDRESS completed on the reverse side?

SENDER:

- Complete items 1 and/or 2 for additional services.
- Complete items 3, and 4a & b.
- Print your name and address on the reverse of this form so that we can return this card to you.
- Attach this form to the front of the mailpiece, or on the back if space does not permit.
- Write "Return Receipt Requested" on the mailpiece [illegible]
- The Return Receipt will show to whom the article was delivered and the date delivered.

[illegible] Consult postmaster for fee.

3. Article Addressed to:
MR JAN LESCHLY, CEO
SMITHKLINE Beecham Pharmaceuticals
P.O. BOX 1539
ROUTE 23 WOODMONT AVENUE
KING OF PRUSSIA PA 19406

4a. Article Number [illegible]92

4b. Service Type
☐ Registered ☐ Insured
☑ Certified ☐ COD
☐ Express Mail ☐ Return Receipt for Merchandise

7. Date of Delivery
11-3-97

5. Signature (Addressee)
[signature]

6. Signature (Agent)

8. Addressee's Address (Only if requested and fee is paid)

PS Form 3811, December 1991 U.S. GPO: 199[illegible]-714 DOMESTIC RETURN RECEIPT

RECORD OF TELEPHONE CONVERSATION

The t-con was initiated by the FDA regarding Stability of Finished Dosage Form: Post Approval Commitment.

Currently, the commitment states, "Any lots that fall outside of specifications, will be reported to the Food and Drug Administration in accordance to 21 CFR, **and if deemed appropriate**, withdrawn promptly from the marketplace." However, the phrase "if deemed appropriate" should be deleted in order to comply with the guideline for stability commitment, which should constitute a an agreement to "Withdrawn from the market any lots found to fall outside the approved specifications for the drug product."

The firm agreed and will provide the specifications as a telephone amendment faxed to Ruby Yu and followed by a fax and hard copy to the document.

V:\firmsam\Copley\telecon\75179.tc2.doc

DATE
September 22, 1999

ANDA NUMBER
75-179

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Nabumetone Tablets

FIRM NAME
Copley

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Vincent Andoliano, senior manager of regulatory affairs (I. Nudleman not available)

TELEPHONE NUMBER
781-575-7318

SIGNATURE
Ruby Yu
9/24/99

CC:

RECORD OF TELEPHONE CONVERSATION

The t-con was initiated by the FDA regarding drug substance specs.

The firm was asked to provide the acceptance criteria for residual solvents. The information may be obtained from the DMF Holder (NAPP).

The firm agreed and will provide the specifications as a telephone amendment faxed to Ruby Yu and followed by a fax and hard copy to the document.

V:\firmsam\Copley\telecon\75179.tc.doc

DATE
August 20, 1999

ANDA NUMBER
75-179

IND NUMBER

TELECON

INITIATED BY: FDA

PRODUCT NAME
Nabumetone Tablets

FIRM NAME
Copley

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Vincent Andoliano, senior manager of regulatory affairs (I. Nudleman not available)

TELEPHONE NUMBER
981-575-7318

SIGNATURE D Gill
Dave Gill
Shing H. Liu S.H. Liu
Ruby Yu Ruby 8/20/99

CC:

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

ANDA Number: 75-179 Date of Submission: August 4, 1997 & October 24, 1997

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Nabumetone Tablets, 500 mg & 750 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   We acknowlege your amendment to add 500 mg tablet strength.

2. CONTAINER - 100's & 500's

   a. Revise the storage temperature statement to read "Store at controlled room temperature 15° - 30°C (59° - 86°F)". [rather than "15° and 30°C (59° and 86°F)"]

   b. Revise to read "USUAL DOSAGE:" rather than "DoSAGE:".

3. INSERT

   a. GENERAL COMMENTS:

      Please delete italicization from the drug name "Nabumetone" throughout the text. This is unnecessary and rather distracting, if anything.

   b. DESCRIPTION

      i. Revise the third paragraph to read as follows:

         Each tablet, for oral administration, contains 500 mg or 750 mg of nabumetone. In addition, each tablet contains the following inactive ingredients: hydroxypropyl ...

ii. You may delete "water purified" from the list of the inactive ingredients.

c. INDICATIONS AND DOSAGE

- Nabumetone tablets are indicated ...

d. ADVERSE REACTIONS (Incidence <1%--Probably Causally Related) - Genitourinary:

Delete "*nephrotic syndrome*" from the list.

e. DOSAGE AND ADMINISTRATION - Third sentence:

Nabumetone tablets can be ...

f. HOW SUPPLIED

i. Please include the term "unscored" if your product is not scored. If scored, include the scoring information in the description of your drug product.

ii. See the comment (a) under CONTAINER.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed container labels and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

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

(Supersedes the review prepared on 10/8/97)

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

ANDA Number: 75-179 Date of Submission: August 4, 1997 & October 24, 1997

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Nabumetone Tablets, 500 mg & 750 mg

Labeling Deficiencies:

1. GENERAL COMMENT

   We acknowlege your amendment to add 500 mg tablet strength.

2. CONTAINER - 100's & 500's

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   b. Revise to read "USUAL DOSAGE:" rather than "DoSAGE:".

3. INSERT

   a. GENERAL COMMENTS:

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inactive ingredients: hydroxypropyl ...

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	

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

Relafan® (19-583/S-001, 002, 004 & 005) - SmithKline Beecham Pharmaceuticals company; issued February, 1993, and approved November 23, 1993.

2. This is **the very first generic application** for Nebumetone tablets.

3. The firm has submitted an amendment (10/24/97) to add 500 mg strength tablets to their application for 750 mg tablets.

4. INACTIVE INGREDIENTS

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of Components and Composition appearing on page 2474, Volume-B. 1.1. (750 mg) and page 113, vol.2.1. (500 mg)

5. PATENTS/EXCLUSIVITIES

The patent expires December 13, 2002 without any protected exclusivity. The firm's statement is accurate. However, the firm intends to challenge the innovator's patent and has filed Paragraph IV Certification.

6. The package insert express the "CLINICAL TRIALS" and "INDIVIDUALIZATION OF DOSING" headings with the same prominence as other section headings, which is consistent with the innovator's labeling. We will **not** ask the firm to reduce the prominence.

7. Copley Pharmaceutical, Inc. is the sole manufacturer for this product.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

NDA - Store at controlled room temperature (59°-86°F).

ANDA - Store at controlled room temperature 15° and 30°C (59° and 86°F).

We will ask the firm to revise the statement. See comment (a) under CONTAINER.

9. DISPENSING STATEMENT COMPARISON

NDA - Dispense in a well-closed, light-resistant.

ANDA -Dispense in a well-closed, light-resistant.

10. PACKAGING CONFIGURATIONS

NDA - 100's & 500's
ANDA -100's & 500's

11. CONTAINER/CLOSURE SYSTEM

Closure - 100's (CRC)
- 500's (Non-CRC) See vol.B.1.2, P.2759 (750 mg) & vol.2.2, p.329. (500 mg)

12. The debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95). See vol.B.1.2, p.2840 (750 mg) & vol.2.2, p.369. (500 mg)

13. SCORING

NDA - Not specified

ANDA - Not specified. We will ask the firm to include the scoring information.

Date of Review: October 30, 1997

Date of Submission: August 4, 1997 & October 24, 1997

Cycle # 1 (DRAFT)

Primary Reviewer: Chan Park Chan Park **Date:** 10/30/97

Team Leader: John Grace John Grace **Date:** 10/31/97

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cc:

Superseded by the Review dated 10/30/97. C. Park

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

ANDA Number: 75-179 Date of Submission: August 4, 1997

Applicant's Name: Copley Pharmaceutical, Inc.

Established Name: Nabumetone Tablets, 750 mg

Labeling Deficiencies:

1. CONTAINER - 100's & 500's

   a. Revise the storage temperature statement to read "Store at controlled room temperature 15° - 30°C (59° - 86°F)". [rather than "15° and 30°C (59° and 86°F)"]

   b. Revise to read "USUAL DOSAGE:" rather than "DoSAGE:".

2. INSERT

   a. GENERAL COMMENTS:

      Please delete the underline and italicization from the drug name "Nabumetone" throughout the text. These are unnecessary and rather distracting, if anything.

   b. DESCRIPTION

      i. Revise the third paragraph to read as follows:

         Each tablet, for oral administration, contains 750 mg of nabumetone. In addition, each tablet contains the following inactive ingredients: hydroxypropyl ...

      ii. You may delete "water purified" from the list of the inactive ingredients.

c. INDICATIONS AND DOSAGE

Nabumetone tablets are indicated ...

d. ADVERSE REACTIONS (Incidence <1%--Probably Causally Related) - Genitourinary:

Delete "*nephrotic syndrome*" from the list.

e. DOSAGE AND ADMINISTRATION - Third sentence:

Nabumetone tablets can be ...

f. HOW SUPPLIED

i. Please include the term "unscored" if your product is not scored. If scored, include the scoring information in the description of your drug product.

ii. See the comment (b) under CONTAINER.

Please revise your container labels and package insert labeling, as instructed above, and submit final printed container labels and insert labeling.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

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

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		x	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			x
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	x		
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
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12. SCORING

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ANDA - Not specified. We will ask the firm to include the scoring information.

Date of Review: October 8, 1997

Date of Submission: August 4, 1997

Cycle # 1 (DRAFT)

Primary Reviewer: Chan Park

Date:

Team Leader: John Grace

Date: 10/14/97

cc:

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