

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75203

ADMINISTRATIVE DOCUMENTS

MINUTES

Meeting type: Telephone conference

Date: March 2, 2000

Drug Name: Propafenone tablets/ANDA 75-203

OGD Representatives:

Gary Buehler, Deputy Director, OGD

Dale Conner, Director, DBE

Lizzie Sanchez, Special Assistant to Director, DBE

Watson Laboratories Representatives:

Neil Parekh, VP, Research & Development

Ernie Lengle, Director, Regulatory Affairs

Phillip Sanvordeckr, Director, Biopharmaceutics

Margaret Choy, Regulatory Affairs

Discussion:

1. The purpose of this meeting is to discuss bioequivalence (BE) issues regarding the propafenone 300 mg tablet. Dr. Conner recounted the history of the application. Initially, Watson submitted a fasting study on the 300mg tablet, and a fed study on the 225mg. The fed study on the lower strength was based on correspondence submitted by Watson stating safety concerns. The fasting study conducted on the 300 mg strength failed to demonstrate BE. Watson submitted another request for consideration of safety issues before conducting another study on the 300mg strength. Dr. Sanvordeckr stated that Watson's concern was to limit exposure of healthy subjects to propafenone in a replicate design.
2. The Division has reevaluated the safety issue. Dr. Mary Fanning, Associate Director for Medical Affairs, OGD, and Dr. Lipicky, Director, Division of CardioRenal Drug Products agree that it is safe to conduct bioequivalence studies on the 300mg strength. Dr. Fanning evaluated the safety data included in the original study, in addition to other Division data. Due to the pharmacokinetics of propafenone, the Division is concerned that the 300mg strength may not be BE to the RLD.
3. Watson has two options. Watson was advised to either withdraw the 300mg strength and seek approval of the 225mg and 150mg tablets, since the data submitted in the ANDA supports the approval for these two strengths or Watson can conduct a new BE fasting study on the 300mg strength. A fed study is not necessary, since Watson has conducted a fed study on the 225mg strength, which was found acceptable. Ernie Lengle asked whether a pilot study with fewer subjects would be acceptable. Dr. Conner explained that a new acceptable pivotal fasting BE study will be necessary to obtain approval of the 300mg strength. It is Watson's responsibility to enroll a sufficient number of subjects to power their study appropriately to meet the current BE criteria. A pilot study is not acceptable. If a replicate design is used, less subjects would be needed, but more treatments would have to be administered to the subjects. If a 2-way crossover study, more subjects would be needed, but less treatments. According to the medical opinion, it is safe to conduct BE studies using the 300mg strength.

4. Watson will discuss internally their options and inform the agency accordingly.

Action Items:

1. The Division will follow up in writing.

Prepared by: L. Sanchez, March 2, 2000

V:\FIRMSAM\watson\TELECONS\75203b.doc

MEMORANDUM

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

Date: February 3, 2000

To: Drug File, ANDA 75-203

From: Barbara M. Davit, Ph.D. *BMD*
Team Leader, Branch III *2/13/00*
Division of Bioequivalence
Office of Generic Drugs

Through: Dale P. Conner, Pharm.D. *DP*
Director *3/7/00*
Division of Bioequivalence
Office of Generic Drugs

Subject: Recommendation for studies necessary to support approval of Propafenone HCl Tablets, 300 mg strength.

The following presents a chronology of written communications regarding ANDA 75-203, for Watson's Propafenone HCl Tablets, 300 mg. Unless otherwise noted, all dates are letter dates. Following is a recommendation for regulatory action.

(1) October 10, 1995: Watson submitted to DBE two protocols for evaluation of bioequivalence of Propafenone HCl tablets. One protocol described a single-dose fasting bioequivalence study, the other described a single-dose postprandial bioequivalence study. Both proposed use of a single 300 mg dose.

(2) December 4, 1996: Watson asked OGD if the postprandial bioequivalence study could be conducted using a single 225 mg dose (cc #96292), based upon adverse events observed in the recently completed 300 mg single-dose fasting study #96040. Watson made the following statements to support this request: (1) several subjects experienced electrocardiographic T-wave changes; and (2) the Principal Investigator, Robert Scott, M.D., expressed concern that pro-arrhythmic events might occur in subjects receiving 300 mg doses with food, since food increases propafenone bioavailability. Data from study #96040 were not submitted.

(3) August 18, 1997: DBE informed Watson that it is acceptable to conduct a postprandial BE study with 225 mg.

(4) September 11, 1997: Watson submitted results of Study #96040, the single-dose fasting bioequivalence study of 300 mg, and Study #96043, a single-dose postprandial bioequivalence study of 225 mg.

(5) March 13, 1998: DBE informed Watson that the postprandial study #96043 with 225 mg was acceptable but the single-dose fasting study #96040 with 300 mg was unacceptable.

(6) April 29, 1998: Watson asked DBE in writing if the fasting BE study could be conducted with 225 mg due to safety reasons.

(7) August 19, 1998: The DBE informed the firm in writing that it is acceptable to conduct the fasting BE study using a 225 mg tablet.

(8) December 28, 1998: The firm submitted a single-dose fasting BE study with the 225 mg tablet.

(9) May 17, 1999: DBE found acceptable the single-dose fasting BE study with 225 mg and recommended that Watson be granted a waiver of bioequivalence testing for their 300 mg strength tablet.

(10) January 21, 2000: Dr. Mary Fanning completed a review of clinical data from the 300-mg single-dose fasting study #96040 and noted no evidence of electrocardiographic T-wave changes. This reviewer confirmed her observations.

Conclusion: OGD reviewed all data submitted to ANDA 75-203 and found no evidence of electrocardiographic T-wave changes in subjects participating in Study #96040, a single-dose fasting bioequivalence study of 300 mg Propafenone HCl tablets. This is in contrast to a description of Study #96040 adverse events presented by Watson laboratories in a letter to OGD dated 12/4/96.

Recommendation: (The waiver of in vivo bioequivalence study requirements for Watson's Propafenone HCl Tablets, 300 mg, should be denied.) The FDA Orange Book lists Rhymol® 300 mg as the reference listed drug (RLD) for Propafenone HCl Tablets. Thus, in support of Abbreviated New Drug Applications to market generic Propafenone HCl Tablet strengths of 300, 225, and 150 mg, in vivo bioequivalence should be assessed with the 300 mg dose. Review of clinical data from Study #96040 revealed no safety concerns which would preclude use of the 300 mg dose as the RLD. The firm should submit acceptable bioequivalence studies of Propafenone HCl, 300 mg, under fasting and fed conditions to support marketing approval of this strength.

cc: ANDA 75-203
ANDA Duplicate
Division File
HFD-651/Bio Drug File
HFD-658/Davit

See 175
Labeled 2/11/99

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

ANDA Number: 75-203 Date of Submission: June 16, 1999

Applicant's Name: Watson Laboratories, Inc.

Established Name: Propafenone Hydrochloride Tablets,
150 mg, 225 mg and 300 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

Container Labels: 150 mg, 225 mg and 300 mg - 100s and 500s
Satisfactory in FPL as of the October 16, 1998 submission.

Professional Package Insert Labeling:
Satisfactory in FPL as of the June 16, 1999 submission.

Revisions needed post-approval: INSERT - CLINICAL PHARMACOLOGY, Hemodynamics, second paragraph "C.I." rather than "C.1"; WARNINGS, Hematologic Disturbances, last sentence "sore" (spelling); PRECAUTIONS, Desipramine "demethylation" (spelling)

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-151

NDA Drug Name: Rythmol® Tablets

NDA Firm: Knoll Pharmaceutical Company

Date of Approval of NDA Insert and supplement #: 12/23/97 (S-002)

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:

Rythmol® container labels submitted for side-by-side comparison.

[Note, a copy of the approved RLD container label from Drug Information requested on 2/17/99].

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?			
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an AMD or NDA? If yes, describe in FTR. FIRST GENERIC.	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	
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 (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 dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/AND 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 AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

NOTE TO THE PROJECT MANAGER:

The firm's exclusivity statement is not accurate. There is an exclusivity for a new indication (I-209), paroxysmal supraventricular tachycardia (PSVT). The exclusivity is scheduled to expire on December 23, 2000.

Is this an issue that you call the firm and request them to update the exclusivity statement?

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of the listed drug (RYTHMOL®; Knoll Pharmaceutical Company; 19-151/S-2; Approved December 23, 1997 (acknowledged and retain April 7, 1998), revised January 1998).
2. Patent/Exclusivities:

There is an exclusivity for a new indication (I-209), paroxysmal supraventricular tachycardia (PSVT). The exclusivity is scheduled to expire on December 23, 2000.

3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container as defined in the USP.

ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container as defined in the USP. Container label does not state "controlled room temperature. I have requested the firm include.

USP: Not a monograph in the USP and not listed in the PF. (per previous reviewer) However, the drug substance Propafenone Hydrochloride is a monographed in the USP. Preserve in tight, light-resistance containers.

4. Scoring:

NDA: ALL strengths SCORED.

ANDA: ALL strengths SCORED.

5. Product Line:

The innovator markets their product in bottles of 100s and unit-dose cartons of 100.

The applicant proposes to market their product in bottles of 100s and 500s.

6. The tablet imprintings have 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). [Vol. p. 1041, 1043 & 1045].

7. 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 pages 372 and 477. [Vol. B1.1].

8. All manufacturing will be performed by Watson Laboratories, Corona, CA. [Vol. B1.2, p. 496]

9. Container/Closure:

This product will be packaged in HDPE bottles with both the 100s and 500s having CRC caps. See pages 771-776. [Vol. B1.2]

10. The bio was found satisfactory on 5-17-99.

Date of Review: 6/29/99

Date of Submission: 6/16/99

Reviewer: Adolph Vezza

Date:

/S/

7/2/99

Team Leader: Charlie Hoppes

Date:

7-2-99

cc:

/S/

corum: jo /S/

7/6/99

ANDA 75-203

DUP/DIVISION FILE

HFD-613/AVezza/CHoppes (no cc)

aev/6/29/99|V:\FIRMSNZ\WATSON\LTRS&REV\75203.APL

Review

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

ANDA Number: 75-203

Date of Submission: October 16, 1998

Applicant's Name: Watson Laboratories, Inc.

Established Name: Propafenone Hydrochloride Tablets,
150 mg, 225 mg and 300 mg

Labeling Deficiencies:

1. INSERT

a. General Comments

- i. We encourage you to improve the readability of your insert by increasing the print size.
- ii. We encourage you to relocate "R only" to appear immediately following the Title/Established name. We refer you to A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements", which was revised July 1998 and posted at Internet site:
<http://www.fda.gov/cder/guidance/index.htm>. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.
- iii. Due to recent changes in the approved labeling of the reference listed drug, Rythmol® (propafenone HCl) Tablets, approved December 23, 1997 (acknowledged and retained April 7, 1998) and revised January 1998), please revise your package insert labeling to be in accord with the attached mocked-up insert labeling.

- iv. The reference listed drug, Rythmol® (propafenone HCl) Tablets has exclusivity for a new indication (I-209), paroxysmal supraventricular tachycardia (PSVT). The exclusivity is scheduled to expire on December 23, 2000. We refer you to the Approved Drug Product Book, 18th edition. Please update your exclusivity statement.

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

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

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

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

Attachment: Rythmol® mocked-up insert labeling

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

Do you have 12 Final Printed Labels and Labeling? Yes _ No_

Container Labels: 150 mg, 225 mg and 300 mg - 100s and 500s
Satisfactory in final print as of the October 16, 1998
submission.

Professional Package Insert Labeling:
Satisfactory in final print as of the --- submission.

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

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

NDA Number: 19-151

NDA Drug Name: Rythmol® Tablets

NDA Firm: Knoll Pharmaceutical Company

Date of Approval of NDA Insert and supplement #:S-004

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:

Rythmol® container labels submitted for side-by-side
comparison.

[Note, I requested a copy of the approved RLD container
label from Drug Information on 2/17/99].

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?			
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 AND or NDA? If yes, describe in FTR. FIRST GENERIC.	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/AND 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 AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND 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 C _{max} , T _{max} , 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.		X	

NOTE TO THE PROJECT MANAGER:

The firm's exclusivity statement is not accurate. There is an exclusivity for a new indication (I-209), paroxysmal supraventricular tachycardia (PSVT). The exclusivity is scheduled to expire on December 23, 2000.

See GENERAL COMMENT 1(a)(iv).

FOR THE RECORD:

1. Review based on the labeling of the listed drug (RYTHMOL®; Knoll Pharmaceutical Company; 19-151/S-2; Approved December 23, 1997 (acknowledged and retain April 7, 1998), revised January 1998).

2. Patent/Exclusivities:

There is an exclusivity for a new indication (I-209), paroxysmal supraventricular tachycardia (PSVT). The exclusivity is scheduled to expire on December 23, 2000.

3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container as defined in the USP.

ANDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container as defined in the USP. Container label does not state "controlled room temperature. I have requested the firm include.

USP: Not a monograph in the USP and not listed in the PF. (per previous reviewer) However, the drug substance Propafenone Hydrochloride is a monographed in the USP. Preserve in tight, light-resistance containers.

4. Scoring:

NDA: ALL strengths SCORED.
AND: ALL strengths SCORED.

5. Product Line:

The innovator markets their product in bottles of 100s and unit-dose cartons of 100.

The applicant proposes to market their product in bottles of 100s and 500s.

6. The tablet imprintings have 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). [Vol. p. 1041, 1043 & 1045].

7. 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 pages 372 and 477. [Vol. B1.1].

8. All manufacturing will be performed by Watson Laboratories, Corona, CA.
[Vol. B1.2, p. 496]

9. Container/Closure:

This product will be packaged in HDPE bottles with both the 100s and 500s having CRC caps. See pages 771-776.
[Vol. B1.2]

Date of Review: 2/17/99

Date of Submission: 10/16/98

Reviewer:

Jacqueline White, Pharm.D.

Date:

Jacqueline White, Pharm.D.
3-5-99

Team Leader:

Date:

MS
10
cc:

ANDA 75-203

DUP/DIVISION FILE

HFD-613/J White/C Hoppes (no cc)

2/99-V:\...75203na2.1

Review

3/5/99

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

ANDA Number: **75-203** Date of Submission: **September 11, 1997**

Applicant's Name: **Watson Laboratories, Inc.**

Established Name: **Propafenone Hydrochloride Tablets,
150 mg, 225 mg and 300 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

Revise the temperature storage recommendations to read as follows:

Store at controlled room temperature 15...

2. INSERT

- a. TITLE

Do not abbreviate "Hydrochloride" in the title.

- b. DESCRIPTION

- i. Revise paragraph one to read as follows:

...antiarrhythmic drug. Propafenone has...

- ii. Revise the molecular weight to read "377.91" rather than to be in accord with USP 23.

- iii. Insert the following text to appear as the third sentence of the last paragraph:

Each tablet, for oral administration, contains 150 mg, 225 mg or 300 mg of propafenone hydrochloride.

- c. CLINICAL PHARMACOLOGY

- i. Electrophysiology, chart - Change and

percent...values for each treatment group.

[Note: "for" rather than "to"]

ii. Pharmacokinetics and Metabolism, Paragraph one

A) Line 1 - Propafenone hydrochloride is nearly...

B) Penultimate sentence - Insert a space between "7" and "mL/min".

d. INDICATIONS AND USAGE

Delete the space between the "hyphen" and "threatening" in the first sentence.

e. WARNINGS

Boxed Warning

i. Revise paragraph one to read as follows:

...multi-center, randomized...non-life-threatening ventricular arrhythmias who had a myocardial infarction more...cardiac arrest rate (7.7%) was seen...flecainide compared...assigned to fully matched placebo-treated groups (3.0%). The average...

ii. Delete "italics" and add "bold" to the text in paragraph two and revise to read as follows:

The applicability of the CAST results...infarction) is uncertain.

f. PRECAUTIONS

i. Renal Dysfunction - Delete "tablets" from the first sentence of the second paragraph.

ii. Drug Interactions, Beta-antagonists - Delete the space between the "hyphen" and "blockers" in the penultimate sentence.

g. ADVERSE REACTIONS

i. Paragraph one, first sentence -

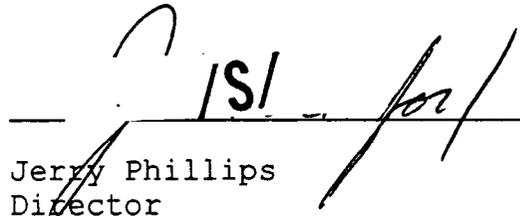
...propafenone hydrochloride occur...

- ii. Revise to read "> 1%" rather than in paragraph one, paragraph two and both titles of the tables.
- iii. Table one
 - A) "First Degree AV Block" appears twice. Delete the second reference to it.
 - B) Revise to read "Constipation" rather than
 - C) Revise to read "Intraventricular Conduction Delay" rather than "Conduction Delay".
 - D) Dry Mouth, last column - Revise to read "5.8%" rather than
 - E) Dyspnea, third column - Revise to read "3.8%" rather than
 - F) Angina, last column - Revise to read "3.8%" rather than
 - G) Diarrhea, last column - Revise to read "38.5" rather than
- iv. Italicize "(adverse events for marketing experience are given in italics)" appearing in the first sentence of paragraph three.
- v. Nervous System - Italicize "apnea" and "coma".
- vi. Hematologic - Italicize "increased bleeding time".
- vii. Other - Italicize "hyponatremia/inappropriate ADH secretion", "kidney failure", and "lupus erythematosus".
- h. HOW SUPPLIED
 - Revise to read "Dispense in a tight..." rather than "Dispense in tight...".

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

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

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

A handwritten signature in black ink, appearing to read "J. Phillips", is written over a horizontal line. The signature is stylized and includes a large initial "J" and a flourish at the end.

Jerry Phillips
Director
Division of Labeling and Program Support
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: **75-203** Date of Submission: **September 11, 1997**

Applicant's Name: **Watson Laboratories, Inc.**

Established Name: **Propafenone Hydrochloride Tablets,
150 mg, 225 mg and 300 mg**

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

Revise the temperature storage recommendations to read as follows:

Store at controlled room temperature 15...

2. INSERT

- a. TITLE

Do not abbreviate "Hydrochloride" in the title.

- b. DESCRIPTION

- i. Revise paragraph one to read as follows:

...antiarrhythmic drug. Propafenone has...

- ii. Revise the molecular weight to read "377.91" rather than to be in accord with USP 23.

- iii. Insert the following text to appear as the third sentence of the last paragraph:

Each tablet, for oral administration, contains 150 mg, 225 mg or 300 mg of propafenone hydrochloride.

- c. CLINICAL PHARMACOLOGY

- i. Electrophysiology, chart - Change and

percent...values for each treatment group.

[Note: "for" rather than "to"]

ii. Pharmacokinetics and Metabolism, Paragraph one

A) Line 1 - Propafenone hydrochloride is nearly...

B) Penultimate sentence - Insert a space between "7" and "mL/min".

d. INDICATIONS AND USAGE

Delete the space between the "hyphen" and "threatening" in the first sentence.

e. WARNINGS

Boxed Warning

i. Revise paragraph one to read as follows:

...multi-center, randomized...non-life-threatening ventricular arrhythmias who had a myocardial infarction more...cardiac arrest rate (7.7%) was seen...flecainide compared...assigned to fully matched placebo-treated groups (3.0%). The average...

ii. Delete "italics" and add "bold" to the text in paragraph two and revise to read as follows:

The applicability of the CAST results...infarction) is uncertain.

f. PRECAUTIONS

i. Renal Dysfunction - Delete "tablets" from the first sentence of the second paragraph.

ii. Drug Interactions, Beta-antagonists - Delete the space between the "hyphen" and "blockers" in the penultimate sentence.

g. ADVERSE REACTIONS

i. Paragraph one, first sentence -

...propafenone hydrochloride occur...

- ii. Revise to read "> 1%" rather than "> 1%" in paragraph one, paragraph two and both titles of the tables.
- iii. Table one
 - A) "First Degree AV Block" appears twice. Delete the second reference to it.
 - B) Revise to read "Constipation" rather than "Constipation Intraventricular".
 - C) Revise to read "Intraventricular Conduction Delay" rather than "Conduction Delay".
 - D) Dry Mouth, last column - Revise to read "5.8%" rather than
 - E) Dyspnea, third column - Revise to read "3.8%" rather than
 - F) Angina, last column - Revise to read "3.8%" rather than
 - G) Diarrhea, last column - Revise to read "38.5" rather than
- iv. Italicize "(adverse events for marketing experience are given in italics)" appearing in the first sentence of paragraph three.
- v. Nervous System - Italicize "apnea" and "coma".
- vi. Hematologic - Italicize "increased bleeding time".
- vii. Other - Italicize "hyponatremia/inappropriate ADH secretion", "kidney failure", and "lupus erythematosus".
- h. HOW SUPPLIED
 - Revise to read "Dispense in a tight..." rather than "Dispense in tight...".

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Office of Generic Drugs
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**REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH**

ANDA Number: 75-203 Date of Submission: September 11, 1997

Applicant's Name: Watson Laboratories, Inc.

Established Name: Propafenone Hydrochloride Tablets,
150 mg, 225 mg and 300 mg

Labeling Deficiencies:

1. CONTAINER (100s and 500s)

Revise the temperature storage recommendations to read as follows:

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Each tablet, for oral administration, contains 150 mg, 225 mg or 300 mg of propafenone hydrochloride.

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i. Electrophysiology, chart - Change and

percent...values for each treatment group.

[Note: "for" rather than "to"]

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B) Penultimate sentence - Insert a space between "7" and "mL/min".

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Delete the space between the "hyphen" and "threatening" in the first sentence.

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Boxed Warning

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A handwritten signature in black ink, appearing to read "J Phillips", is written over a horizontal line.

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

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

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

Container Labels:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form:
No name listed just firm. Rythmol®

NDA Number: 19-151

NDA Drug Name: Rythmol® Tablets

NDA Firm: Knoll Laboratories

Date of Approval of NDA Insert and supplement #:
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:
Labels submitted for side-by-side review in jacket.

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 AND or NDA? If yes, describe in FTR. FIRST GENERIC.	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/AND 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 AND meet them?			X
Is the product light sensitive? If so, is NDA and/or AND 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 C_{max}, T_{max}, T_{1/2} and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

FOR THE RECORD:

1. Review based on the labeling of the listed drug (RYTHMOL®; Knoll Pharmaceutical Company; 19-151/S-004; Approved March 19, 1997, Revised January 1997).
2. Patent/ Exclusivities:

There are no patents or exclusivities that pertain to this drug product.
3. Storage/Dispensing Conditions:

NDA: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container as defined in the USP.

AND: Store at controlled room temperature 15° to 30°C (59° to 86°F). Dispense in a tight, light-resistant container as defined in the USP. Container label does not state "controlled room temperature". I have requested the firm include.

USP: Not a monograph in the USP and not listed in the PF. However, the drug substance Propafenone Hydrochloride is a monographed in the USP.
4. Scoring:

NDA: ALL strengths SCORED.
AND: ALL strengths SCORED.
5. Product Line:

The innovator markets their product in bottles of 100s and unit-dose cartons of 100.

The applicant proposes to market their product in bottles of 100s and 500s.
6. The tablet imprintings have 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 pages 849, 858 and 867, Vol. 1.2.
7. 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

pages 374-376 and 477, Vol. 1.1.

8. All manufacturing will be performed by Watson Laboratories. All outside firms are utilized for testing. See pages 496 and 499, Vol. 1.2.
9. Container/Closure:

This product will be packaged in HDPE bottles with both the 100s and 500s having CRC caps. See pages 771-776, Vol. 1.2.

Date of Review: November 3, 1997

Date of Submission: September 11, 1997

Reviewer:

IS/

Date: 11/13/97

Team Leader:

IS/

Date:

11/17/97

cc:

ANDA 75-203
DUP/DIVISION FILE
HFD-613/CHolquist/JGrace (no cc)
11/3/97/X:\NEW\FIRMSNZ\WATSON\LTRS&REV\75203NA1.L
Review

Telecon

Date: 092697

Time: 1000

ANDA: 75-203

Firm: Watson Laboratories

Participants: Gregg Davis, FDA and Monica Taccione, Watson

Agenda:

I called David Hsia in regards to ANDA 75-203, Watson's application for Propafenone Hydrochloride Tablets, 150 mg, 225 mg and 300 mg. David Hsia was away on vacation and Monica Taccione was filling in. I told her I had some loose ends to tie up in regards to their recent submission. First, the 356h needed revision. Watson mentioned the RLD company but never listed the name of the RLD. Specifically, they left out Rythmol but listed Knoll as the innovator. Secondly, in their in vivo biowaiver request, they mention a study done on their 200 mg strength. I asked them to revise the waiver request to include the 225 mg strength not a 200 mg strength. She thanked me and said she would fax the revisions and follow with a hard copy.

*no date -
submit to
9/26/97*