

Knoll Pharmaceutical Company



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Docket Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

**Re: Supplement to Citizen Petition 96P-0243
Bioequivalence Requirements for Propafenone Tablets**

Dear Sir/Madam:

Knoll Pharmaceutical Company submits herewith, in duplicate, a second supplement to the subject petition originally submitted on June 28, 1996. This first supplement was filed to the subject petition on September 24, 1999.

The enclosed supplement contains information received by Knoll concerning a submission to the Drug Utilization Review Council of New Jersey for an application for inclusion of a generic propafenone product on the state formulary. Based on this information Knoll believes that this product has not been shown to be bioequivalent to Rythmol[®] Tablets under existing FDA protocol recommendations for propafenone, or the proposed guidance, as listed in the Citizen Petition for Propafenone.

To facilitate your review, a complete reference list and attachments have been included in this submission.

Copies of this supplement have also been forwarded to Dr. Dale Conner, Director Division of Bioequivalence at the Office of Generic Drugs and Dr. Raymond Lipicky Director of Cardio-Renal Drug Products at the Center for Drug Evaluation and Research, for their review and information.

In view of the importance of these issues to patient safety, we appreciate your prompt consideration of this matter.

Sincerely,


Doreen V. Morgan, Pharm.D.

Associate Director, Regulatory Affairs

96P-0243

SUP 2

**A SUPPLEMENT TO
PROPAFENONE CITIZEN'S PETITION**

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1 INTRODUCTION

Knoll Pharmaceutical Company ("Knoll") submits this supplement to its Citizen Petition (96P-0243 submitted on June 28, 1996; hereinafter called "The Petition") concerning bioequivalence requirements for propafenone tablets. Knoll holds an NDA (#19,151) for Rythmol® (propafenone hydrochloride) tablets. Knoll believes that one or more Abbreviated New Drug Applications may be pending which specify Rythmol as the reference listed drug. Knoll submitted a first supplement to The Petition on September 24, 1999.

In The Petition, Knoll requested FDA to promulgate an amendment to the bioequivalence requirements for propafenone HCl as per the FDA regulation [21 CFR 320.32(c)]. The supplement submitted on September 24, 1999 referred to the recent bioavailability/bioequivalence guidances issued by the FDA and others that reinforced the need for specific bioequivalence tests, given the unique pharmacokinetic properties of propafenone. Knoll specifically requested FDA not to approve any ANDA for products not meeting the proposed guidelines. To date, Knoll has not received any response from the FDA.

Recently, Knoll received information on a submission to the Drug Utilization Review Council of New Jersey that included an Application for Product Registration in New Jersey of a generic propafenone product (**Attachment 1**). Knoll believes that this product has not been shown to be bioequivalent to Rythmol under existing FDA protocol recommendations for propafenone, or the proposed guidance as recommended by Knoll in The Petition. Accordingly, Knoll reiterates the request that FDA not approve any ANDA not shown to be bioequivalent under general conditions of use. Specifically, and as relevant to the apparent submission by Watson, Knoll strongly urges the FDA to consider the following during the review and approval process of generic propafenone products:

- Propafenone generic products that do not meet BE criteria under both fed and fasting conditions should not be approved.

For example, Watson's 225 mg propafenone tablets and Rythmol 225 mg tablets are not shown to be bioequivalent under fed conditions and therefore, should not be considered interchangeable under fed conditions. The differences between these two products are expected to be even higher at 300 mg based on nonlinear pharmacokinetic principles.

- If propafenone tablet dosage forms are ingredient-proportional, BE data at the highest strength (300 mg) should be required. If dosage forms are not ingredient-proportional, firms should be required to provide BE data for all strengths.

Watson Laboratories did not provide any data on a 300 mg tablet to the New Jersey State Drug Utilization Review Council. If this is also true with the ANDA, bioequivalence data should be required prior to approval of the Watson 300 mg propafenone tablet.

Once again, this is to emphasize to the Agency why the scientific rationale provided by Knoll in The Petition and subsequent supplement should be considered in the evaluation of the BE criteria for propafenone tablets prior to any ANDA approvals.

2 STATEMENT OF GROUNDS

a) Clinical Consequences

Propafenone is a drug with a complex pharmacokinetic profile (i.e. non-linear pharmacokinetics, active metabolites contributing to safety and efficacy, and high variability in metabolism)(References # 1 and 2). Propafenone is a class 1C antiarrhythmic drug approved for the treatment of **life-threatening documented ventricular arrhythmia**. The therapeutic effect of propafenone (safety and efficacy) has been related to its plasma concentrations (page 12 of The Petition). Therefore, **lack of bioequivalence under all general conditions pertinent to its clinical use may have serious consequences**. According to the Dosage and Administration section of the current labeling for Rythmol:

"The dose of Rythmol (propafenone HCl) must be individually titrated on the basis of response and tolerance. It is recommended that therapy be initiated with 150 mg propafenone given every eight hours (450 mg/day). Dosage may be increased at a minimum of 3 to 4 day intervals to 225 mg every 8 hours (675 mg/day) and, if necessary, to 300 mg every eight hours (900 mg/day). The usefulness and safety of dosages exceeding 900 mg/day have not been established. In those patients in whom significant widening of the QRS complex or second or third degree AV block occurs, dose reduction should be considered."

Titration and stabilization of the dose is a lengthy procedure, which involves careful patient monitoring. Once a patient is stabilized on one propafenone drug product, any product switching will require careful monitoring if products are not bioequivalent under all conditions of administration, including fasting and fed conditions. This is especially true at the 300 mg t.i.d. dosing level. Due to the higher incidence of adverse events and lower tolerability at 300 mg t.i.d., it becomes imperative that, for patients stabilized at 300 mg t.i.d., switching propafenone products without safety monitoring should be done only if products are bioequivalent under all general conditions of administration (both fasting and fed). The adverse reactions reported in the package insert include proarrhythmia, CHF, ventricular tachycardia, palpitations, first degree AV block, increased QRS duration, and bundle branch block. The incidence of these adverse events increases in the 450 mg to ≥ 900 mg daily dosing range (Reference # 3). It is noteworthy that the incidence of these adverse events also increases over the narrower daily dosing range of 600 mg to ≥ 900 mg.

In addition to the above safety concerns, the FDA also provided support for this position by commenting on a protocol for a generic propafenone 300 mg tablet (*Reference # 4*), indicating a need for conducting a BE study under fed conditions.

b) Existing Propafenone ANDAs

Recently, Knoll learned that Watson Laboratories has submitted an Application for Drug Product Registration of their propafenone HCl 150 mg, 225 mg, and 300 mg tablets to the New Jersey State Drug Utilization Review Council for approval to be added as an interchangeable product for Rythmol (**Attachment 1**). Watson has included results of two single dose bioequivalence studies (Study Nos. 96043 and 98091) using 225 mg tablets to support their request for approval of all 3 strengths (150, 225 and 300 mg tablets). It was not indicated whether or not the three dosage forms are ingredient-proportional. The package also included bioequivalency comments provided to Watson on their ANDA (ANDA # 75-203) from the Division of Bioequivalence. In these comments, FDA indicated that "The Division has completed the review and has no further comments at this time".

Knoll is committed to the safety of patients who are stabilized on a propafenone product after careful titration and monitoring by a physician. Knoll is also aware of the nonlinear increase in plasma levels with dose in the 150 to 300 mg range and that adverse events are dose/concentration-related. Based upon the information submitted to the State of New Jersey, Knoll believes that Watson's product has not been shown to be bioequivalent to Rythmol® in at least the following respects.

- **Bioequivalence Under Fed Conditions:** In Study No. 96043, Watson's product clearly was not shown to be bioequivalent to Rythmol under fed conditions. It not only failed the 90 % confidence limits required by BE guidelines, but also the ratio of the means for Cmax and AUC was approximately 115%, indicating that mean exposure to propafenone is 15% higher for the Watson product compared to Rythmol. The actual reported values are presented below:

Summary of Results from Watson's Study # 96043, ANDA # 75-203

Watson's (test) propafenone 225 mg tablet vs. Rythmol 225 mg tablet			
Parameter	Ratio	90% Confidence Limits	
		Lower	Upper
Cmax (ng/mL)	114.3	80.7	161.8
AUC0-t (ng.h/mL)	114.6	85.3	154.0
AUC0-inf (ng.h/mL)	115.9	87.2	153.9

It is important to note that the product differences (ie. ratio of means and confidence intervals) between Watson's propafenone tablets and Rythmol

tablets would be expected to be even higher at the 300 mg dose due to the nonlinear pharmacokinetic properties of the drug. Thus, the 225 mg Watson propafenone product is not bioequivalent to Rythmol under Fed conditions. Furthermore, the 300 mg tablet product would not be expected to meet the BE criteria even if the 225 mg and 300 mg tablet formulations are ingredient-proportional.

- **Bioequivalence at the Highest Dose:** There was no bioequivalence data in the New Jersey Watson submission using the 300 mg tablets under any conditions. Even though there is no official guidance for nonlinear drugs issued by FDA at this time, as noted in our September 1999 supplement, the Drug Directorate of Canada issued such guidelines (Reference # 5) on January, 1997. Based on sound scientific rationale, the Directorate stated the following in the guideline:

“For drugs with nonlinear pharmacokinetics in the single dose range of approved strengths resulting in **greater than proportional increases in AUC** with increasing dose, the comparative bioavailability studies must be conducted on at least the **highest** strength, provided that the range of products is proportionally formulated. If the range is not proportionally formulated, all strengths may have to be studied.”

At a minimum, generic products must demonstrate bioequivalence at the highest strength (300 mg tablet) even if the dosage forms are ingredient-proportional. The approval of Watson's 300 mg tablets without BE data is unsound based upon the scientific and regulatory rationale provided so far for nonlinear drugs. Moreover, given the 15% difference in the mean bioavailability seen at the 225 mg dose under fed conditions, serious safety concerns exist when considering 300 mg t.i.d. dosing. Thus, to alleviate these safety concerns, BE data on the 300 mg generic product under fasting and fed conditions are warranted.

- **Bioequivalence following multiple dosing:** In the New Jersey submission, Watson did not include any multiple dose bioequivalence data. Propafenone has complex non-linear pharmacokinetics and the adverse events are dose-dependent. Therefore, in order to ensure the safety of a generic propafenone following multiple doses, and especially at the highest dose, bioequivalence must be shown under both fasting and fed conditions at steady-state. Knoll strongly reiterates the importance of multiple dose BE studies included in the Petition and the September 24, 1999 supplement.

SUMMARY

In conclusion, Knoll reiterates its request that FDA not approve ANDAs that fail to meet appropriate BE guidelines as set forth in our Petition, the supplement to The Petition, and FDA's own protocol recommendations for propafenone. Specifically, and as relevant to the apparent submission by Watson, Knoll strongly urges the FDA to consider the following during the review and approval process of generic propafenone products:

- Propafenone generic products that do not meet BE criteria under both fed and fasting conditions should not be approved.
- If propafenone tablet dosage forms are ingredient-proportional, BE data at the highest strength (300 mg) should be required. If dosage forms are not ingredient-proportional, firms should be required to provide BE data for all strengths.
- In order to ensure the safety of generic propafenone, BE studies must be conducted under both fasting and fed conditions following multiple dosing.

4 REFERENCES

1. Connolly SJ, Kates RE, Lebsack CS, Harrison DC, Winkle RA. Clinical pharmacology of propafenone. *Circulation* 1983; 68:589-596.
2. Hill JTY, Duff HJ, Burgess ED. Clinical pharmacokinetics of propafenone. *Clinical Pharmacokinetics* 1991; 21:1-10.
3. Package insert for Rythmol, PDR 1999; p. 1483.
4. Protocol review package (PRP) for propafenone HCl tablets, 300 mg, CDER, FDA, January 31, 1996.
5. Bioequivalence requirements: Drugs exhibiting non-linear pharmacokinetics, drug directorate, Ontario, Canada, January 13, 1997.