

Knoll Pharmaceutical Company



BASF Pharma

January 12, 2000

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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 third supplement to the subject petition originally submitted on June 28, 1996. The last supplement was filed to the subject petition on December 10, 1999.

Knoll submits this supplement to highlight to the Office of Regulatory Policy that in the *Orange Book* FDA has designated the 300mg dose of propafenone to be the reference listed drug for any bioequivalence studies. As previously noted in Knoll's supplement (submitted on December 10, 1996), the Division of Bioequivalence, Office of Generic Drugs, supported this position in their comments (January 31, 1996) to a sponsor of a generic propafenone HCl protocol. The division stated, that to demonstrate bioequivalence, the 300mg dose of propafenone should be used, especially under fed and fast conditions.

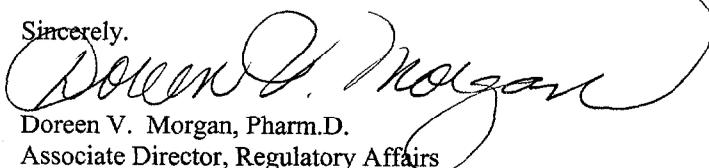
Knoll is aware that an application has been submitted to the Drug Utilization Review Council of New Jersey for inclusion of a generic propafenone product on the state formulary. Watson Labs Inc. submitted data in this application that **did not** use the reference listed 300mg dose in conducting their BE studies (fed and fasted). Knoll is interested in understanding the agency's rationale in allowing generic BE studies to be conducted using propafenone strengths other than the reference listed dose of 300 mg. It is our understanding that waivers may be granted permitting a BE study to be conducted without using the reference listed strength, particularly if the upper dose poses safety concerns in healthy volunteers. Based on healthy volunteer data at the 300 mg dose submitted in Knoll's NDA 19-151 for Rythmol® tablets, there were no safety concerns noted [Axelson et. al; Br. J.Clin.Pharmacol (1987), 23:735-741].

As stated in the December 10, 1999 supplement to the petition, a difference in the mean bioavailability seen at the 225 mg dose under fed conditions with the generic product raises significant safety concerns for the use of propafenone in the patient population. Due to nonlinearity of propafenone, bioequivalence, as well as, the effect of food at 300 mg, **cannot** be assured based on BE data at a lower strength. Knoll is in agreement with the *Orange Book* that lists propafenone 300 mg tablets as the reference standard for generic approvals. Knoll considers that an approval of a generic propafenone based on BE studies conducted using a reference standard other than Rythmol 300 mg is inconsistent with FDA guidelines.

A copy of this supplement has also been sent to Dr. Dale Conner of the Office of Generic Drugs and to the Cardio-Renal Drug Product Division for their review and information.

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

Sincerely,



Doreen V. Morgan, Pharm.D.  
Associate Director, Regulatory Affairs

96P-0243

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