CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-416

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: **21,416 SE5 029 N000 (BB, IN,BC)**

Submission Dates: January 31, 2003

Drug Name: Rythmol SR (propafenone hydrochloride) extended release capsules

Applicant: Abbott Laboratories

Submission: Original NDA

Reviewer: Elena V. Mishina, Ph.D.

1 BACKGROUND

Reference is made to the teleconference with the sponsor held on January 27, 2003 for the discussion of an Approvable Letter and proposed labeling for NDA 21-416, Rythmol SR (propafenone hydrochloride) extended release capsules. During this teleconference, the sponsor requested that the Division reassess the proposed changes to the dissolution method and specifications outlined in the approval letter. The sponsor submitted additional information to the Division to support their proposal.

In this submission, the sponsor clarified the nature of the 'pH independence' of drug release for Rythmol ER capsules, which was claimed in the original NDA. All experiments describing the release profiles for capsules were conducted initially in — — with a pH change — — The change of pH — imitates the physiologic conditions in which the capsule dissolves. In Figure 1 below the curves are smooth, the drug release was not affected by pH changes —

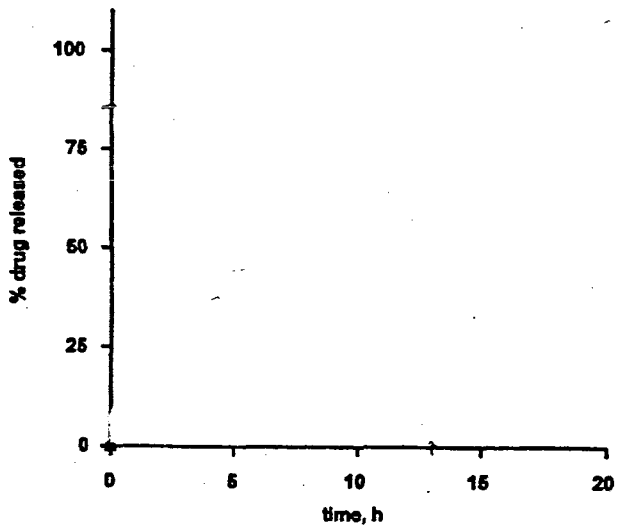
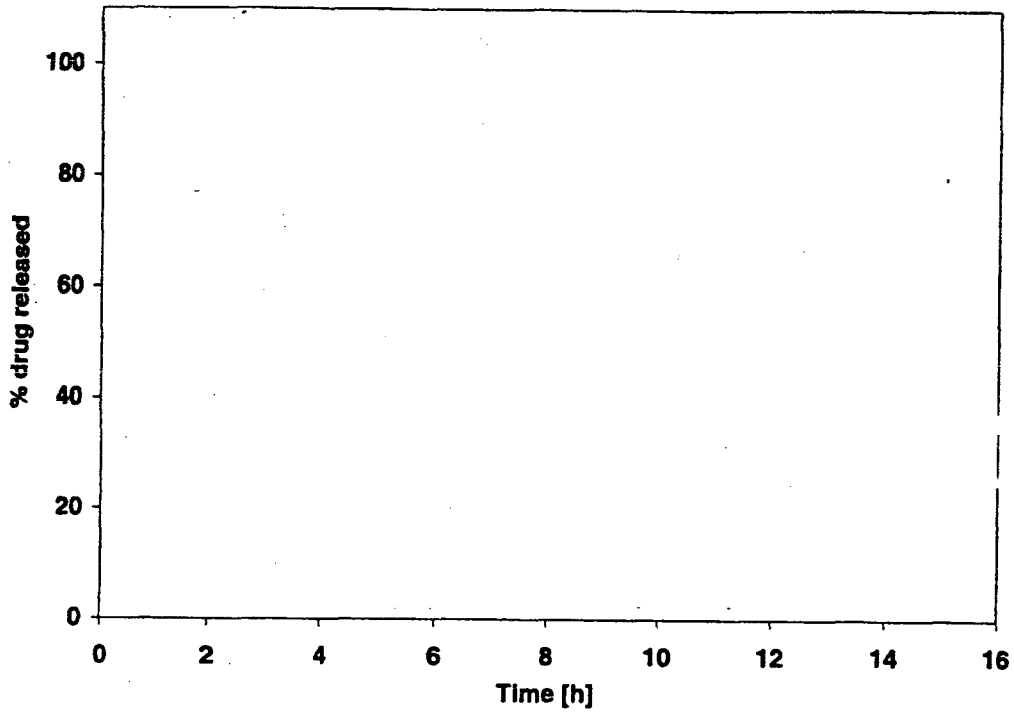


Figure 1. Influence of pH of the medium on Rythmol capsules dissolution rate

However, when the phosphate buffer was assessed as an alternative medium, the capsules dissolved much faster that it would be acceptable for the extended release product (— The results of three different batches tested according to the two methods are shown in the following Figure.



The method proposed by the sponsor simulates the conditions of the human gastrointestinal tract. Therefore, OCPB finds the request by the sponsor to keep the dissolution medium as proposed in the original application reasonable.
Dissolution Method:

Apparatus: Type 2 (Paddle); 50 rpm
Medium: 900 mL
phosphate buffer, pH 6.8.

Specification Q % at –hour
Q % at 4 hours
Q at 12 hours.

2 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I finds the information included in the amendment to the NDA 21,416 for Rythmol SR (sustained release propafenone hydrochloride capsules 225, 325, and 425 mg) acceptable. The following dissolution method and specifications are recommended:

Apparatus: Type 2 (Paddle); 50 rpm
Medium: 900 mL
phosphate buffer, pH 6.8.

Specification Q[ ]% at – hour
Q[ ]% at 4 hours
Q[ ]% at 12 hours.

/S/

_____ Date_____
Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

_____
Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA 21,416, MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

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/s/

Elena Mishina
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Patrick Marroum
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: **21,416 SE5 029**

Submission Dates: March 15, May 8 and September 19, 2002

IND: **54,536 NIM 042** **Submission Date:** June 14, 2000

Drug Name: Rythmol SR (propafenone hydrochloride) extended release capsules

Applicant: Abbott Laboratories

Submission: Original NDA

Reviewer: Elena V. Mishina, Ph.D.

1 EXECUTIVE SUMMARY

This NDA review evaluates whether the sponsor has adequately characterized the pharmacokinetics of Rythmol SR (propafenone hydrochloride) extended release capsules in humans.

Propafenone is classified as a 1C antiarrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes. Propafenone immediate-release (IR) tablet was approved in the US in 1989 under NDA 19-151, Rythmol@ for life threatening ventricular arrhythmias and in 1997 for the prolongation of the time to recurrence of paroxysmal atrial fibrillation and supraventricular tachycardia associated with disabling symptoms. Immediate-release (IR) propafenone tablets (Rythmol@) are available in three dosages, 150, 225 and 300 mg, intended for administration every 8 hours.

The submitted 6 study reports under NDA 21,416 include the key elements necessary to characterize the human pharmacokinetics and bioavailability of a prolonged-release formulation. The sponsor refers to the approved immediate release product (Rythmol) for all other information regarding basic pharmacokinetics, special populations, and drug-drug interaction studies.

OCPB finds the submitted data in NDA 21,416 to be acceptable in meeting the OCPB requirements.

Rythmol prolonged-release capsules (SR, BID) are comparable with the immediate-release Rythmol (IR) tablets. Rythmol SR will allow reducing the dosing frequency and the large fluctuation in propafenone plasma levels resulting from a TID dosage regimen, thus convenience and compliance with the treatment may be improved.

2 RECOMMENDATIONS:

The Office of Clinical Pharmacology and Biopharmaceutics, Division of Pharmaceutical Evaluation I finds the information included in the NDA 21,416 for Rythmol SR (sustained release propafenone hydrochloride capsules 225, 325, and 425 mg) acceptable. The Office of Clinical Pharmacology and Biopharmaceutics recommends adopting the

proposed language for the labeling with some revisions. The following dissolution method and specifications are recommended:

Apparatus Type
Media
Temperature, Volume
Specification

Please forward the Comments 5-7 to the sponsor.

/S/

Date_____

Elena Mishina, Ph. D.
Clinical Pharmacology Reviewer

/S/

Patrick Marroum, Ph. D.
Cardio-Renal Team Leader

cc list: NDA. MehulM, MarroumP, MishinaE, HFD 110 BIOPHARM

Clinical Pharmacology Briefing held on December 11, 2002
Attendees: A. Karkowski, P. Marroum, M. Mehta, C. Sahagwalla, and E. Mishina.

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4 SUMMARY OF CPB FINDINGS

4.1 Background:

RYTHMOL SR (propafenone hydrochloride) is a 1C antiarrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes supplied in prolonged-release capsules of 225, 325 and 425 mg for oral administration twice daily. Propafenone immediate-release (IR) tablet was approved in the US in 1989 under NDA 19-151, Rythmol@ for life threatening ventricular arrhythmias and in 1997 for the prolongation of the time to recurrence of paroxysmal atrial fibrillation and supraventricular tachycardia associated with disabling symptoms. Immediate-release (IR) propafenone tablets (Rythmol@) are available in three dosages, 150, 225 and 300 mg, intended for administration every 8 hours.

The following pharmacokinetic (PK) characteristics have been determined after the oral doses of immediate release Rythmol tablets:

Absorption of propafenone is almost complete after the oral dose with peak plasma levels occurring at 3.5 hours. Propafenone undergoes extensive saturable presystemic biotransformation (CYP2D6 hepatic first-pass effect). Its bioavailability (BA) depends on the dose. A 150 mg dose has an absolute bioavailability (BA) of 3.4% while for a 300 mg dose it was 10.6%. At still larger doses, above those recommended, bioavailability increases still further. Decreased liver function also increases bioavailability.

RYTHMOL follows a nonlinear pharmacokinetic disposition and shows a very high degree of interindividual variability. Although food increased peak blood level and bioavailability in a single dose study, during multiple dose administration of propafenone to healthy volunteers food did not change bioavailability significantly.

There are two genetically determined patterns of propafenone metabolism. In over 90% of patients, the drug is rapidly and extensively metabolized with an elimination half-life of 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone (formed by CYP2D6) and N-depropylpropafenone (norpropafenone, formed by CYP3A4 and CYP1A2). These two metabolites have antiarrhythmic activity comparable to propafenone but their plasma concentrations are less than 20% of propafenone. Nine additional metabolites have been identified, most in only trace amounts. About 10% of patients are slow metabolizers of propafenone (5-hydroxy metabolite is minimally formed) with half-life ranging 10-32 hours. In slow metabolizers propafenone pharmacokinetics are linear.

There are significant differences in plasma concentrations of propafenone in slow and extensive metabolizers, at low doses the differences are greater, with slow metabolizers attaining concentrations more than five times that of extensive metabolizers. The greater variability in blood levels require that the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity.

RYTHMOL is a racemic mixture. The [R]- and [S]-enantiomers of propafenone display stereoselective disposition characteristics. In vitro and in vivo studies have shown that the

R-isomer of propafenone is cleared faster than the S-isomer via the 5-hydroxylation pathway (CYP2D6). This results in a higher ratio of S-propafenone to R-propafenone at steady state. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent beta-antagonist than the R-enantiomer. Following administration of RYTHMOL immediate release tablets the ratio of the area under the plasma concentration-time curve was about 1.7 for the S-enantiomer compared to the R-enantiomer.

The decrease in rate of single and multiple premature ventricular contractions (VPCs) is dose-related and concentration-related. Recurrence of ventricular tachycardia can be suppressed. Trough plasma levels of propafenone ranging from —— µg/mL can provide good (80-90%) suppression of ventricular ectopic activity, with higher concentrations giving a greater rate of good response.

4.2 Current Submission:

In this Application the sponsor compared the pharmacokinetics of Rythmol SR (propafenone hydrochloride) extended release capsules in humans to immediate release propafenone with respect to PK and PD.
Rythmol prolonged release formulation (SR, BID) was developed to reduce the dosing frequency and the large fluctuation in propafenone plasma levels resulting from a TID dosage regimen and to facilitate compliance with the treatment regimen.
The 6 study reports in the Rythmol@ SR NDA 21-416 evaluated the following:

The pharmacokinetics after single and multiple dosing in healthy subjects.

The effect of food on absorption of the drug from the dosage form (single and multiple dosing).

Dose proportionality assessments of propafenone (and metabolites) using the dosage strengths "intended to be marketed" (multiple dosing).

The bioavailability of propafenone and its metabolites from the SR formulation relative to that from the IR formulation (single and multiple dosing).

Bioavailability assessment of SR capsules relative to IR tablets.

The relationship between premature ventricular contractions and plasma concentrations of propafenone and metabolites.

The pharmacokinetics and bioavailability of a prolonged release formulation of Rythmol was compared with the immediate release formulation. The bioavailability of Rythmol SR was smaller compared to Rythmol IR. In general, higher doses of extended release Rythmol SR are required to obtain similar exposure with the immediate release tablets. Doses of 150 mg IR tablet TID may be substituted by doses of 325 mg ER capsule BID, and doses of 300 mg IR tablet BID may be substituted by doses of 425 mg ER capsule BID. The administration of Rythmol SR led to less fluctuation of propafenone and 5-OH-propafenone plasma concentrations. When Rythmol SR was evaluated at steady state, the pharmacokinetics of propafenone and 5-OH-propafenone were nonlinear in extensive metabolizers (CYP2D6) with more than proportional increases of AUC and Cmax. The pharmacokinetics of propafenone and its metabolites were linear in poor metabolizers. The rate and extent of absorption of propafenone and 5-OH-propafenone increased by 3-4

folds when single doses of Rythmol SR were administered with food, the effect of food at steady state was statistically significant for propafenone (16% increase in Cmax and 13% increase in AUC) but not for 5-OH-propafenone. Food effect for norpropafenone was not significant after single and multiple doses. The multiple dose food effect study for Rythmol SR was conducted in 1991 in the Netherlands, where the FDA standardized meal was not used but the fat content of the meal was acceptable. Results of the food effect single and multiple dose studies for Rythmol IR and Rythmol SR are compared below. In the multiple dose studies, AUC values were calculated up to the next dose, and in the single dose studies AUC values were extrapolated to infinity.

Formulation/dose	Fasted		Fed	
Parameter	AUC ng/h/mL	Cmax ng/mL	AUC ng/h/mL	Cmax ng/mL
Rythmol IR (300 mg, single)	2899	314	2991	454
Rythmol IR (225 mg, multiple)	$5064_{(0-8)}$	902	$5341_{(0-8)}$	971
Rythmol SR (425 mg, single)	393	30	1258	134
Rythmol SR (425 mg, multiple)	$5290_{(0-12)}$	542	$6000_{(0-12)}$	628

Although the difference between single dose and multiple dose studies were much larger for the sustained release than for the immediate release formulation, the parameters obtained after the multiple doses of Rythmol IR (300 mg TID) are comparable to the levels obtained with the multiple dose (425 mg BID) study for the Rythmol SR formulation. The immediate release Rythmol tablet was recommended to be administered independently of food intake. In the pivotal clinical trials, Rythmol SR also was administered independently of food intake.

The pharmacodynamic effect of Rythmol SR is comparable with the IR formulation when measured as the reduction of ventricular premature contractions (VPCs, %). Rythmol SR doses of 425 mg BID cause a mean reduction of VPCs of 82.5±22.0% in 10 patients (with 900 mg/day Rythmol IR VPCs reduction was >80%).

In addition, this submission describes the formulation development, analytical and dissolution methods.

The proposed in vitro dissolution method is as follows:

Apparatus Type	Type 2 (Paddle), 50 RPM
Media	Phosphate buffer (pH 6.8)
Temperature, Volume	37°C, 900 mL
Specification	Q( )% at 2 hour, Q( )% at 4 hours and Q( )% at – hours.

The analytical methods are acceptable. The proposed dissolution specification should be changed to Q( )% in 12 hours. Since the dissolution of propafenone was independent of

the pH of the media, in the absence of a justifiable reason, the FDA recommends that the sponsor use one medium throughout the test, i.e. phosphate buffer (pH 6.8).

5 REVIEWER COMMENTS

GENERAL

1. The information provided in the submission for Rythmol extended release formulation meets the OCPB requirements.

COMMENTS TO THE MEDICAL OFFICER

2. The sponsor made a conclusion that the pharmacokinetics of propafenone in extensive metabolizers has changed when administered as an extended release formulation with an increase of the exposure to 5-hydroxypropafenone of 20%. However, the difference was not statistically significant (mean AUC values of 2162 (range of ——— ; ng/mL/h vs 2555 (range of ——— ng/mL/h). Considering a high interpatient variability in pharmacokinetics of both propafenone (CVauc>70%) and 5-hydroxypropafenone (CVauc>30%), this difference is deemed to be irrelevant.
3. Except for the PK/PD study, all clinical pharmacology studies were performed in young healthy adults. Twenty nine (29) patients participated in the studies VPC CR-D1 and VPC CR-D2, including only three patients older than 70 years of age. The effect of age could not be studied in this setting and recommendations on differences in PK and PD for geriatric patients cannot be made.
4. The rate and extent of absorption of propafenone and 5-OH-propafenone increased by 3-4 folds when single doses of Rythmol SR were administered with food. The effect of food at steady state was statistically significant for propafenone (16% increase in Cmax and 13% increase in AUC) but not for 5-OH-propafenone. The multiple dose food effect study for Rythmol SR was conducted in 1991 in the Netherlands, where the FDA standardized meal was not used at that time but the fat content of the meal was acceptable. Although in the pivotal clinical trials Rythmol SR was administered independently of food intake, there is a possibility of an increased exposure with Rythmol SR.
5. Assuming the worst case scenario of a 4.4 fold increase in the steady state plasma concentration due to food effect in the absence of safety data for such an exposure, the Medical Officer is requested to assess the clinical implications of the possible increase in exposure that may be seen at steady state if Rythmol SR is given with food and decide whether Rythmol SR should be given with or without food.

COMMENTS TO THE SPONSOR:

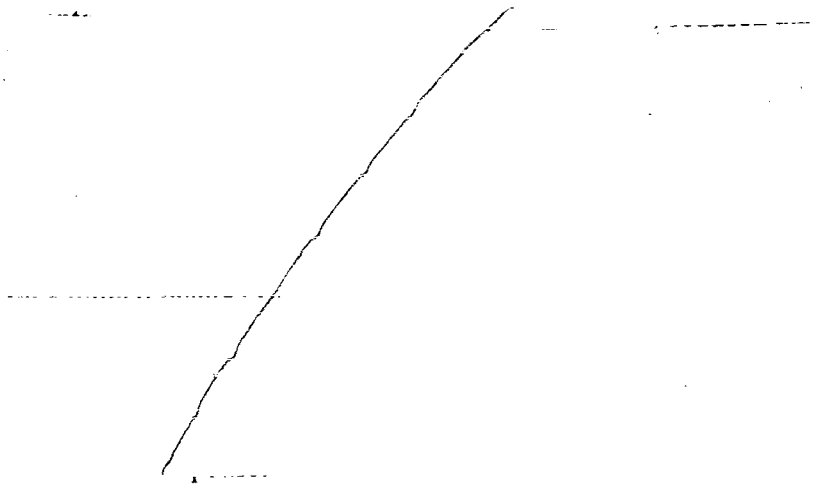
6. The sponsor is requested to update the drug-drug interaction section of the Package Insert.
7. The sponsor is requested to assess the effect of concomitant administeration of CYP3A4 inhibitors to poor metabolizers of CYP2D6.
8. Since the dissolution of Rythmol SR has been shown to be independent of pH, the sponsor is recommended to change the medium to a phosphate buffer (pH 6.8) or to provide a justification for the switching of the medium after 2 hours.

LABELING COMMENTS: (an annotated labeling is provided)

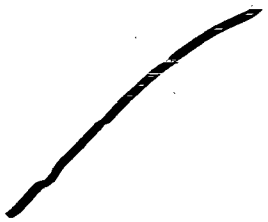
1. CLINICAL PHARMACOLOGY

Electrophysiology:

The paragraph:



Should be replaced with:



2. Pharmacokinetics and Metabolism:

Absorption/Bioavailability

The paragraph:

1 pages redacted from this section of the approval package consisted of draft labeling

Geriatric Use

The paragraph:

"The effect of age on the pharmacokinetics and pharmacodynamics of propafenone has not been . ———

Should be added.

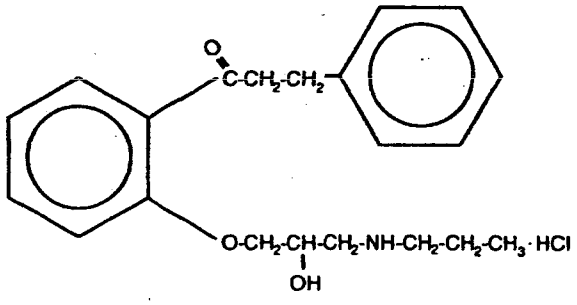
APPEARS THIS WAY
ON ORIGINAL

6 QUESTION-BASED REVIEW

6.1 General Attributes

What is the structural formula and what are the physicochemical characteristics of propafenone hydrochloride?

The structural formula of propafenone is shown below:



$C_{21}H_{27}NO_3 \cdot HCl$ M.W. = 377.92

Propafenone occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20°C), chloroform and ethanol.

What is propafenone's mechanism of action?

Propafenone is classified as a 1C antiarrhythmic agent with local anesthetic effects and a direct stabilizing action on myocardial membranes. The electrophysiological effect of RYTHMOL manifests itself in a reduction of upstroke velocity (Phase 0) of the monophasic action potential. In Purkinje fibers, and to a lesser extent myocardial fibers, RYTHMOL reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and the effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

What are the indication and recommended doses of Rhythmol?

RYTHMOL SR is indicated to

The dose of RYTHMOL SR must be individually titrated on the basis of response and tolerance. It is recommended that therapy be initiated with RYTHMOL SR 225 mg given every twelve hours. Dosage may be increased at a minimum of 5 day interval to 325 mg

given every twelve hours. If additional therapeutic effect is needed, the dose of RYTHMOL SR may be increased to 425 mg given every twelve hours.

In those patients in whom significant widening of the QRS complex or second or third degree AV block occurs, dose reduction should be considered.

6.2 Formulation

How is the capsule of Rhythmol SR formulated?

Rythmol SR formulation represents 3 capsule strengths containing 225, 325 or 425 mg of propafenone. Capsules are filled with microtablets, which are "small cylinders" 2 mm in diameter and 2 mm in height. They are identical, and therefore, have the same release patterns. An advantage of microtablets use is that they can be filled into capsules at all dosages and the slow release properties of the drug are not affected. The following inactive ingredients are contained in the prolong release capsule: antifoam, gelatin, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, shellac, sodium lauryl sulfate, soy lecithin and titanium dioxide. Each capsule contains

Propafenone	— %
Hydroxypropyl methylcellulose	— %
Magnesium stearate	— %

All clinical studies used Rythmol SR capsules of the same composition, and for each strength the to-be-marketed formulations were identical with the capsules used in clinical studies (see Appendix 7.1).

6.3 In Vivo Relative Bioavailability Studies

Were the pharmacokinetics of immediate release and sustained release Rythmol compared in vivo?

The sponsor has conducted a study to compare and investigate the pharmacokinetics of propafenone and its metabolites after multiple dose administration of two immediate-release and two controlled-release preparations.

The four treatments were:

A = one Rythmonorm 150 mg IR tablet tid
B = one Rythmonorm 300 mg IR tablet bid
C = one propafenone 325 mg CR capsule bid
D = one propafenone 425 mg CR capsule bid

The exposure ($AUC_{120-144}$) and maximum plasma concentrations (Cmax) were compared between treatments A and C as well as between treatments B and D. The absolute values were similar in the groups of comparison for propafenone. For 5-OH-propafenone, both exposure and Cmax were about 20% higher in the extended release groups. The sponsor speculated that "the gradual release of propafenone from the prolonged-release

preparations resulted in less saturation of the CYP2D6 isozyme, which resulted in an increase in the overall first pass metabolism to 5-hydroxypropafenone". This conclusion cannot be justified based on the available data. First, propafenone and its metabolites exhibit a high interpatient variability, and this study included a relatively small number of subjects (24). Additionally, plasma concentrations of 5-OH-propafenone are about 20% that of the parent drug.

Table 1. Comparison of mean values of AUC and Cmax in Study MP/HP 9415E

Propafenone	Daily Dose	AUC	Cmax
A	450	4616	441
B	600	8933	822
C	650	4817	350
D	850	9324	589
5-HO-Propafenone			
a	450	1649	106
b	600	2162	126
c	650	2052	112
d	850	2555	135

Is the exposure of extended release capsules similar to the exposure of immediate release?

No, higher doses of extended release Rythmol SR are required to obtain similar exposure with the immediate release tablets. Doses of 150 mg IR tablet tid may be substituted by the 325 mg ER capsule bid, and doses of 300 mg IR tablet bid may be substituted by the 425 mg ER capsule bid.

What was the advantage of the use of extended release capsules?

The plasma concentrations of propafenone and 5-OH-propafenone have less fluctuations with the sustained release Rythmol. The secondary pharmacokinetic parameters (PTF, AUCF) calculated for each propafenone, 5-OH-propafenone and norpropafenone confirm that finding (Table 2).

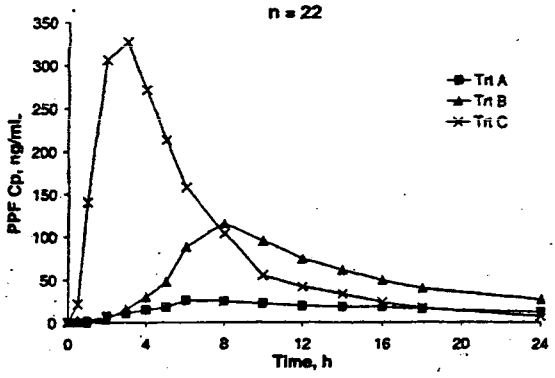
Table 2. Comparison of the secondary PK parameters.

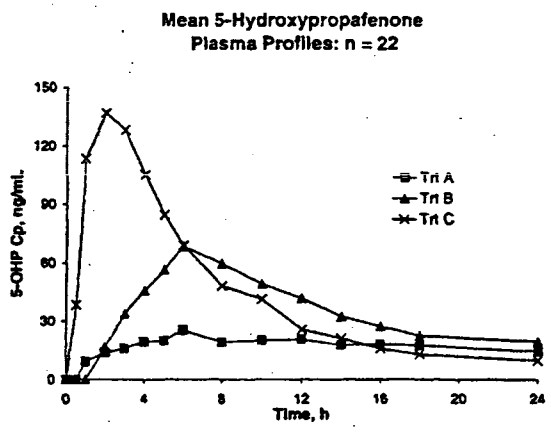
parameter	treatment	propafenone mean*	propafenone min-max	5-hydroxypropafenone mean*	5-hydroxypropafenone min-max	norpropafenone mean*	norpropafenone min-max
t_{max} (h)	A	2.0		2.0		2.0	
	B	2.0		2.0		2.0	
	C	6.0		4.0		6.0	
	D	6.0		6.0		6.0	
t_{75} (h)	A	3.16		9.29		6.23	
	B	4.39		12.30		6.10	
	C	8.12		14.35		11.74	
	D	9.96		15.96		15.55	
PTF (%)	A	201		98		109	
	B	196		76		118	
	C	134		58		84	
	D	98		50		59	
AUCF (%)	A	38.8		19.5		22.3	
	B	45.4		18.4		26.8	
	C	29.6		12.2		17.6	
	D	22.2		10.2		13.7	

6.4 Food-effect studies

How does food affect the pharmacokinetics of Rythmol SR after single dose?

After single dose of Rythmol SR, the PK of propafenone and its metabolites was compared in a 3 treatment study (A: 425 mg Rythmol SR capsule, fasting; B: 425 mg Rythmol SR capsule, fed; and C: 300 mg Rythmol tablet, fasting). In the fed treatment, the drug was administered immediately after the standardized high fat breakfast.





Food increased the bioavailability of propafenone capsule (Cmax and AUC) by 4.4 and 3.1 fold, respectively. Peak plasma concentrations of propafenone were decreased and occurred at a later time with the slow release capsule compared to the immediate release tablet. Plasma profiles of 5-hydroxypropafenone followed the same patterns as parent

drug. The differences in Cmax and AUC were calculated as 3.1 and 2.4 fold, respectively. Plasma concentrations of norpropafenone were measurable (limit of detection of 25 ng/mL) only for the treatment with Rythmol IR.

Therefore, the effect of food on the pharmacokinetics of Rythmol SR after administration of a single dose was significant.

How does food affect the pharmacokinetics of Rythmol SR at steady state?

The sponsor investigated the effect of food on steady state PK of propafenone and its metabolites after multiple doses of 425 mg of Rythmol SR. The SR formulation was administered BID, plasma samples were taken after the high fat breakfast and parameters were calculated for the 12 hours period on Day 6. Cmax, and $AUC_{120-132}$ for propafenone were higher after administration of Rythmol SR with food than after administration in the fasting state (16% increase of Cmax and 13% increase of AUC, Table 3).

Table 3. Pharmacokinetic parameters of propafenone, norpropafenone, and 5-hydroxy propafenone after multiple doses of 425 mg of Rythmol SR under fed (A) and fasted (B) conditions.

Parameter	Treatment	Propafenone			Norpropafenone			5-hydroxypropafenone		
		Geometric mean	90% confidence interval and point estimate		Geometric mean	90% confidence interval and point estimate		Geometric mean	90% confidence interval and point estimate	
C_{max}	A	628	103 - 130	116	47.4	97 - 116	106	176.3	96 - 108	102
($\mu g \cdot L^{-1}$)	B	542			44.5			172.6		
C_{min}	A	343	97 - 135	114	33.7	98 - 119	108	128.8	92 - 109	100
($\mu g \cdot L^{-1}$)	B	300			31.1			128.8		
$AUC_{120-132}$	A	6000	101 - 128	113	492	98 - 116	107	1805	94 - 105	99
($\mu g \cdot L^{-1} \cdot h$)	B	5290			460			1814		

Therefore, after multiple doses of 425 mg of Rythmol, the food effect was apparent for the parent drug. The 90% confidence intervals for Cmax, and $AUC_{120-132}$ for norpropafenone and 5-hydroxy-propafenone were all within 80 - 125%. The effect of food on the pharmacokinetic parameters of both metabolites was not significant. At steady state, propafenone plasma concentrations are about 4-fold larger than after single dose administration. The sponsor concluded that most likely, the effect of drug accumulation is masking the food effect.

The effect of food on the PK of the immediate release Rythmol tablets was significant in a single dose study (for the extensive metabolizers in a fed state the increase in Cmax was 2-folds and in AUC 60%). In the multiple dose study, the differences in Cmax and AUC_{0-8hr} were not significant. However, the FDA reviewer pointed out that the breakfast meal was only 522 calories instead of the required 1000 calories. Although the immediate release Rythmol formulation has been administered regardless of food intake, there is a possibility of increased exposure with Rythmol SR.
The Medical Officer is requested to assess the clinical implications of the possible increase in exposure that may be seen if Rythmol SR will be given with food.

6.5 Dose-Proportionality

For the proposed dose regimen of Rythmol SR, were the pharmacokinetics proportional to the dose?

Dose proportionality at steady state was studied for all proposed doses of Rythmol SR (225, 325, and 425 mg) in extensive (N=18) and poor (N=8) metabolizers of CYP2D6. In extensive metabolizers, the compared parameters (AUC0-t, Cmax, Cmin, and Caverage) for propafenone and norpropafenone increase more than dose proportional across all doses (Table 4).

Table 4. Comparison of the pharmacokinetic parameters for Rythmol SR doses of 225, 325, and 425 mg.

Parameter	Dose, mg			Ratio	
AUC, ng/mL/h	225	325	425	325 vs 225	425 vs 225
Propafenone	3238	6424	11134	1.37	1.82
5-Hydroxypropafenone	1348	1914	2237	0.98	0.88
Norpropafenone	236	502	812	1.47	1.82
Cmax, ng/mL					
Propafenone	371	698	1151	1.30	1.64
5-Hydroxypropafenone	148	202	223	0.96	-0.80
Norpropafenone	26	49	77	1.31	1.57

For propafenone and norpropafenone, AUC was about 40% larger for the 325 mg dose vs the 225 mg dose, and 82% larger for the 425 mg dose vs the 225 mg dose, and Cmax was 30% higher for the 325 mg dose vs the 225 mg dose, and about 60% higher for the 425 mg dose vs the 225 mg dose. For 5-hydroxypropafenone, AUC and Cmax changed less than dose-proportional with the dose from the comparison of the 425 dose vs the 325 dose. These results were similar to the immediate release formulation and were probably due to saturable first pass mechanism.
For the poor metabolizers, all parameters increase dose proportionally (Table 7.2.7, Appendix).

Were there differences in the pharmacokinetics of the extended release Rythmol between patients and healthy volunteers?

No. The comparison of plasma concentration levels at steady state and the PK parameters for propafenone was made using the data from all submitted studies. Table 5 contains a comparison of AUCss (ng/mL/h) and Cmax (ng/mL) for patients and healthy subjects administered 425 mg propafenone SR.

Table 5. Geometric means of selected propafenone PK parameters at steady state in patients and healthy volunteers following 425 mg propafenone SR administration.

	Patients	Healthy Subjects	Healthy Subjects
Reports	MPF/CP 0006E	MPF/HP9415	MPF/HP9217
	N=11	N=24	N=24
AUC, ng/mL/h	5200	4662 [a]	5290
Cmax, ng/mL	615	590	542

[a] this is 1/2 of 9324 value for a 24 hour AUC

The PK parameters calculated in patients and in healthy subjects receiving the same dose of propafenone SR were comparable.

6.6 Pharmacokinetic/Pharmacodynamic Relationship

Were the pharmacodynamics of extended release Rythmol comparable with the immediate release formulation?

Yes. The pharmacodynamics of Rythmol ER was investigated in Studies VPC-CRD1 and VPC- CRD2. The response was measured in patients with symptomatic ventricular arrhythmia as a decrease (%) of ventricular contractions (VPC) after doses of 225, 325, and 425 mg of Rythmol SR at steady state. The reduction was calculated over the time period of the complete Holter interval as well as for each hourly subinterval. The measurement compared at baseline and after treatment at steady state. In the placebo group, no changes were found, and the group receiving 325 mg of propafenone had uninterpretable results (most likely to the small size, N=5). Patients in the groups receiving propafenone doses of 225 mg (N=10) and 425 mg (N=10) had significant changes in comparison with the baseline (Table 6).

Table 6. Summary statistics for reductions of VPCs

Variable	Dose (mg)	n	Mean	STD	CV(%)
Relative	Placebo	3	17.8	47.9	268.7
Reduction (%)	225	10	53.5	37.4	69.9
VPCs/hr	325	5	8.57	86.7	1012.4
	425	10	82.5	22.0	26.7

The findings for the 425 mg BID dose of Rythmol SR are comparable with the previously published data on the reduction of VPCs in patients receiving Rythmol IR at doses from 300 to 900 mg/day (77-88% reduction).

Was the pharmacokinetics/pharmacodynamics relationship established for the extended release Rythmol?

No. In Studies VPC-CRD1 and VPC- CRD2 plasma concentrations of propafenone and its metabolites were measured. The sponsor attempted to fit an Emax model to the pooled data of the response vs average plasma concentrations. The models were fitted separately for propafenone and 5-OH-propafenone data. Both fits described the data sets poorly.

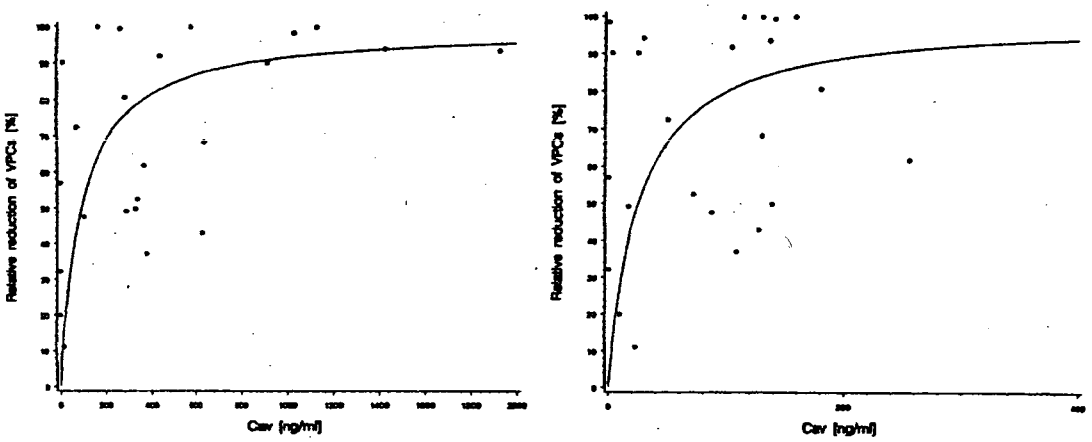


Figure 2. Relative reduction of VPCs vs Caverage of propafenone (left panel) and of 5-OH-propafenone (right panel). The lines are the model predictions.

Although the sponsor has mentioned that the data from the group receiving 325 mg of Rythmol were not interpretable, the data points from all 25 patients were included in the plots. Only data from 20 patients (groups receiving the 225 and 425 mg doses) could be used. Plasma concentrations for both propafenone and 5-OH-propafenone have a quite high interpatient variability. Additionally, the spartein test was performed only in Study VPC-CRD1 and more complexity into the modeling was added with the genetic differences. Overall, there were not enough data to perform this modeling. This may explain why the results were unsatisfactory.
The conclusion that the threshold of ~ ng/mL propafenone plasma concentrations exists for achievement of the higher than ~% response seems to be inconclusive and should not be included in the Package Insert.

6.7 In Vitro Dissolution Method and Specification.

Which in vitro dissolution method and specifications are proposed by the sponsor?

The sponsor has proposed the following in vitro dissolution method and specifications for the Rythmol extended release capsules.

Dosage Form, Strength	Capsules, 225, 325, 425 mg
Apparatus Type	Type 2 (Paddle), 50 RPM
Media	Phosphate buffer (pH 6.8)
Temperature, Volume	37°C, 900 mL
Specification	Q1 [ ]% at — hour, Q2 [ ]% at 4 hours and Q3 [ ]% at — hours

A validated HPLC method with UV detection was used for the assays of propafenone and metabolites, 5-hydroxypropafenone and norpropafenone. In the absence of a justifiable reason, and since the dissolution of propafenone was not pH dependent; the proposed method should use only one media, phosphate buffer (pH 6.8). Specification should include the following time points: 2, 4, and 12 hours. The last time point should be at 12 hours — hours because the drug is administered BID and — dissolution is achieved around 12 hours. For details, see Appendix, Section 7.3 for the tabulated data and Figures.

6.8 Bioanalytical Method

Which analytical method was used in the plasma analyses? Is the method acceptable?

The sponsor used a validated high performance liquid chromatography (HPLC) method with UV detection for the assays of propafenone and metabolites, 5-hydroxypropafenone and norpropafenone. This method was separately validated for each report and is summarized in Tables 6, 7 and 8.

Table 6. Main features of the assay in the Reports 91 12E, 9217E, 9415E.

Analyte	propafenone	5-OH-propafenone	norpropafenone
LOQ, ng/mL		—	
Linearity, ng/mL		—	
Mean Recovery, %	94	94.5	93
Inter-day precision, %		—	

The intraday precision and accuracy was determined by assaying 7 calibration pools on the same day. It was — % while the intraday accuracy did not exceed —% deviation from the nominal value. Inter-day precision and accuracy was determined using 7 runs for the analytes. The accuracy for norpropafenone did approach — % deviation from the nominal value at the 12.5 ng/mL concentration. The accuracy, however, for the 6.25 ng/mL sample did not exceed — % deviation from the nominal value.

Table 7. Main features of the assay in the Report CD00006.

Analyte	propafenone	5-OH-propafenone	norpropafenone
LOQ, ng/mL		[redacted]	
Linearity, ng/mL		[redacted]	
Accuracy, %		[redacted]	
Inter-day precision, %CV		[redacted]	

Table 8. Main features of the assay in the Report CD00006.

Analyte	propafenone	5-OH-propafenone	norpropafenone
LOQ, ng/mL		[redacted]	
Linearity, ng/mL		[redacted]	
Recovery, %		[redacted]	
Inter-day precision, %CV		[redacted]	

Precision and accuracy were determined by the analysis of quality control (QC) samples at 3 concentrations performed over 5 runs. There were 6 replicates in Runs 1,2, 3, and 5 and 3 replicates in Run 4. Potassium EDTA and heparin anticoagulated plasma samples were evaluated and showed similar results. Quality control samples were 60, 400 and 800 ng/mL for 5-hydroxypropafenone and norpropafenone and 60, 800 and 1600 ng/mL for propafenone. The mean accuracy did not exceed [redacted] for any analyte at any QC concentration.

The analytical methods described in this submission are acceptable.

7 APPENDIX

APPEARS THIS WAY
ON ORIGINAL

7.1 Drug Substance and Formulation

7.1.1 Drug substance.

The chemical name of propafenone hydrochloride is 2'-[2-hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride. The drug substance occurs as colorless or white crystals or a crystalline powder. The drug is slightly soluble in water (20°C), and sparingly soluble in methanol, hot water and hot chloroform. It is practically insoluble in ethanol —— The pH of a 0.5% mass to volume solution in water is 5.2 to 6.2. Propafenone HCL is a strong acid salt of a weak base with a pKa of 8.8 ~ 0.3. The propafenone molecule contains one chirality center. The drug product exists as a racemate.

7.1.2 Formulation development.

The formulations used throughout the development program for Rythmol@ SR were developed by Knoll AG, located in Ludwigshafen, Germany.
There were 4 early Phase I studies performed in Europe using a propafenone —— formulation; however the microtablet formulation was chosen for clinical development and the present submission includes only data for this formulation using 4 capsule strengths containing 225, 325, 400 or 425 mg of propafenone.
Microtablets are "small cylinders" 2 mm in diameter and 2 mm in height. They are identical, and therefore, have the same release patterns. An advantage of microtablets use is that they can be filled into capsules at all dosages and the slow release properties of the drug are not affected.

7.1.3 Summary of clinical batches.

The formulations used in the clinical development program of propafenone SR prolonged release capsules are listed in Tables 7.1 through 7.3, organized according to study within each phase of the development program. The tables identify the clinical study protocol, the clinical study report, the dosage form, batch (lot) number, product code and batch size of formulations used in the clinical and pharmacokinetic development program.
The size of the first 225 mg, 325 mg, and 425 mg capsules batches was — kg. Later batches were prepared with size increased up to — kg. The scale of production was the same from an early stage on throughout the development phase. All capsule batches originating from —— batch sizes of at least — kg are considered representative of product and process intended for marketing.

Table 7.1. Phase 1 drug products.

Clinical study protocol no.	Clinical study report no.	Dosage form and strength	Knoll lot or batch no.[a]	Product code[b]	Microtablet batch size (k
Phase I studies					
SR-HP D27/90E	MPF/HP 9112 E	400 mg SR Capsule	0005-01-A-1-VS	A	
		400 mg SR Capsule	0005-02-A-1-VS	B	
		400 mg SR Capsule	0005-03-A-1-VS	C	
SR HPD-29/90E	MPF/EH 9422	225 mg SR Capsule	100800A1	D	
		325 mg SR Capsule	100900A1	I	
		425 mg SR Capsule	101000A1	N	
		Placebo SR Capsule	100700P1	R	
SR HP D28/91E	MPF/HP 9217 E	425 mg SR Capsule	101000A1	N	
OR-HP-N 31/93E	MPF/EH 9415 E	150 mg IR Tablet	30350001	V[c]	
		300 mg IR Tablet	30260001	W[c]	
		325 mg SR Capsule	282000A1	J	
		425 mg SR Capsule	282100A1	O	
P-86-CP	P-86-CP	425 mg SR Capsule	780101A0 (RYT-0367)	O	
		300 mg IR Tablet	2145-0067	X[c]	
PN102	PN102	225 mg SR Capsule	980310A0 (RYT-0229)	E	
		325 mg SR Capsule	980311A0 (RYT-0239)	J	
		425 mg SR Capsule	980211A0 (RYT-0249)	O	

Table 7.2. Phase 2 drug products.

Clinical study protocol no.	Clinical study report no.	Dosage form and strength	Knoll lot or batch no.[a]	Product code[b]	Microtablet batch size (kg)
Phase II studies					
VPC CR-D1	MPF/H 9408	225 mg SR Capsule	100800A1	D	
		325 mg SR Capsule	100900A1	I	
		425 mg SR Capsule	101000A1	N	
		Placebo SR Capsule	100700P1	R	
SR VPC CR-D2	CD00001	225 mg SR Capsule	281900A1	E	
		425 mg SR Capsule	282100A1	O	
		Placebo SR Capsule	281800P1	S	
SVA CR-D1	CD99018	225 mg SR Capsule	281900A1	E	
		325 mg SR Capsule	282000A1	J	
		425 mg SR Capsule	282100A0	O	
		Placebo SR Capsule	281800P1	S	
SVA CR-I1	CD99021	225 mg SR Capsule	281900A1	E	
		325 mg SR Capsule	282000A1	J	
		425 mg SR Capsule	282100A0	O	
		Placebo SR Capsule	281800P1	S	
VPC CR-I1	CD99022	225 mg SR Capsule	281900A1	E	
		325 mg SR Capsule	282000A1	J	
		Placebo SR Capsule	281800P1	S	
		150 mg IR Tablet	2023001	V[c]	
		Placebo IR Tablet	001100P0	Y	

Table 7.3. Phase 3 drug product.

Clinical study protocol no.	Clinical study report no.	Dosage form and strength	Knoll lot or batch no.[a]	Product code[b]	Microtat batch size
Phase III studies					
P-85-AF (RAFT)	P-85-AF	225 mg SR Capsule	780100A0 (RYT-0507)	E	
		225 mg SR Capsule	780200A0 (RYT-0039)	E	
		225 mg SR Capsule	980310A0 (RYT-0229)	E	
		325 mg SR Capsule	780100A0 (RYT-0377)	J	
		325 mg SR Capsule	980311A0 (RYT-0239)	J	
		425 mg SR Capsule	780101A0 (RYT-0367)	O	
		425 mg SR Capsule	980211A0 (RYT-0249)	O	
		Placebo SR Capsule	780101P0 (RYT-0357)	T	
		Placebo SR Capsule	980201P0 (RYT-0219)	T	
PROPASR 008 (ERAFT)	PN008	325 mg SR Capsule	780200A0	J	
		325 mg SR Capsule	980312A0	J	
		425 mg SR Capsule	780102A0	O	
		425 mg SR Capsule	980212A0	O	
		Placebo SR Capsule	780102P0	T	
		Placebo SR Capsule	980202P0	U	

[redacted]

[a] Knoll AG manufacturing batch number is listed. Knoll Pharmaceutical Development control number (first number in [redacted]

7.1.4 Formulation information.

All clinical studies involving propafenone SR prolonged release capsules used microtablets of the same composition. The compositions of all capsule formulations, including the qualitative composition of the capsule shell where available, are presented in Tables 7.4-7.7 for the 400 mg, 425 mg, 325 mg, and 225 mg active products, respectively.

Table 7.4. 400 mg capsules.

	Product code		
Single letter code	A	B	C
Knoll AG Artikelnummer	17 100 896 A	17 100 896 B	17 100 896 C
Knoll FIC	-	-	-
Ingredient			
Propafenone HCl	400.0 mg	402.6 mg	403.9 mg
Hydroxypropyl Methylcellulose,	[redacted]		
Magnesium Stearate	[redacted]		
Gelatin Capsule Size 0+, White Opaque/ White Opaque[f]			
Use	Clinical studies	Clinical studies	Clinical studies

Table 7.5. 425 mg capsules.

	Product code			
Single Letter Code	N	O	P	Q
Knoll AG Artikelnummer	17 100 981	17 101 084 17 101 872	17 102 216	14 466 666
Knoll FIC	-	3060-E-53	3060-I-53	3060-L-53
Ingredient				
Propafenone HCl		425.0 mg		
Hydroxypropyl Methylcellulose,				
Magnesium Stearate				
Gelatin Capsule Size 0+, Green/Green[1]		-	-	-
Gelatin Capsule Size 0+, Red Brown Opaque/ White Opaque[2]	-		-	-
Gelatin Capsule Size 0+, Dark Blue Opaque/ White Opaque; red logo[3]	-	-		-
Gelatin Capsule Size 0+, White Opaque/ White Opaque; imprinted, 3 rings[4]	-	-	-	
Use	Clinical studies	Clinical studies	Registration stability	Proposed market form

Table 7.6. 325 mg capsules

	Product code				
Single Letter Code	I	J	K	L	M
Knoll AG Artikelnummer	17 100 980	17 101 086 17 101 873	17 101 179	17 102 217	14 466 566
Knoll FIC	-	3060-F-53	-	3060-J-53	3060-M-53
Ingredient					
Propafenone HCl		325.0 mg			
Hydroxypropyl Methylcellulose,					
Magnesium Stearate					
Gelatin Capsule Size 0+, Green/Green[1]		-	-		-
Gelatin Capsule Size 0+, Red Brown Opaque/ White Opaque[2]	-		-	-	-
Gelatin Capsule Size 0, Red Brown Opaque/Yellow Opaque[3]	-	-		-	-
Gelatin Capsule Size 0, Medium Blue Opaque/ White Opaque; red logo[4]	-	-	-		-
Gelatin Capsule Size 0, White Opaque/White Opaque; imprinted, 1 ring[5]	-	-	-	-	
Use	Clinical studies	Clinical studies	Stability studies	Registration stability	Proposed market form

Table 7.7 lists the composition of placebo capsules used for blinding purposes in the clinical studies.

Table 7.7.

	Product code			
Single Letter Code	R	S	T	U
Knoll AG Artikelnummer	17 100 982	17 101 087	17 101 875	17 101 874
Knoll FIC	-	-	3060-FO-53	3060-EO-53
Ingredient				
Microcrystalline Cellulose	-	-	-	-
Magnesium Stearate	-	-	-	-
Gelatin Capsule Size 0+, Green/Green[2]	-	-	-	-
Gelatin Capsule Size 0+, Red Brown Opaque/ White Opaque[3]	-	-	-	-
Use	Clinical studies	Clinical Studies	Clinical studies	Clinical studies

7.2 Individual Study Summaries

7.2.1 Relative Bioavailability/Bioequivalence Studies (multiple doses)

Volume 27
Study Title:
Comparative pharmacokinetics of propafenone after multiple dose oral administration of two immediate-release and two controlled-release preparations. (Report MP/EH 9415 E)

Study Period:
July 1993-August 1993.

Investigator and Center:

Objectives:
To compare and investigate the pharmacokinetics of propafenone and its metabolites after multiple dose administration of two immediate-release and two controlled-release preparations.

Design:
This pharmacokinetic study had an open label, randomized, multiple dose, four-period crossover design, without any washout between the periods. All 24 participants completed the four treatments. The participants were healthy male volunteers aged between 18-43 years, weight within 15% of normal range and all were normal metabolizers of dextromethorphan (dextromethorphan/dextrorphan urinary ratio <0.3). The four treatments were:

A = one Rythmonorm 150 mg IR tablet tid, batch 30350001
B = one Rythmonorm 300 mg IR tablet bid, batch 30260001
C = one propafenone 325 mg CR capsule bid, batch 282000A1
D = one propafenone 425 mg CR capsule bid, batch 282100A1

Each treatment was given orally for six days. Total study duration was 24 days. During Treatment A, medication was given at 08:00 h, 16:00 h, and 24:00 h, after breakfast, and an afternoon and evening snack, respectively. During Treatments B, C and D, medication was given at 08:00 h and 20:00 h after breakfast and dinner, respectively.

ECG monitoring was performed prior to the morning dose on Days 1, 3 and 6 and at 2, 4, 6, and 8 (Treatment A) or 12 hours (Treatments B, C, and D) after the morning dose on Day 6 of each period.

During each treatment period, blood samples were taken pre-dose on the morning of Days 1 (only the first period), 4, 5 and 6 and at regular intervals after drug administration on Day 6. For Treatment A, blood samples were taken at 1, 2, 3, 4, 6, 8 (predose), 9, 10, 11, 12, 14, 16 (predose), 17, 18, 19, 20, 22 and 24 hours after the morning dose on Day 6. For Treatments B, C, and D blood samples were taken 1, 2, 3, 4, 6, 8, 12 (predose), 13,

14, 15, 16, 18, 20 and 24 hours after the morning dose on Day 6. The pharmacokinetic parameters of propafenone, 5-hydroxypropafenone and norpropafenone were determined. The following primary PK parameters were calculated using non-compartmental methods: Cmax, Cmin, and $AUC_{120\text{-}144hr}$ of propafenone and 5-hydroxypropafenone.

Statistical methods: ANOVA and Dunnet's t-test on logarithmically transformed trough plasma concentrations of propafenone and 5-hydroxypropafenone (Days 4, 5, and 6) to verify the attainment of steady state.

The sponsor performed a statistical comparison of the primary PK parameters pairwise with ANOVA by constructing the 95% confidence intervals.

Results:
For each treatment, plasma concentrations were generally attained on Days 4-6. Figures 1 and 2 illustrate the geometric mean propafenone and 5-hydroxypropafenone plasma concentration time curve observed on Day 6 for Treatments A and C and Treatments B and D, respectively. Both prolonged release formulations showed less fluctuation in steady state plasma concentrations in comparison with the immediate release formulations.

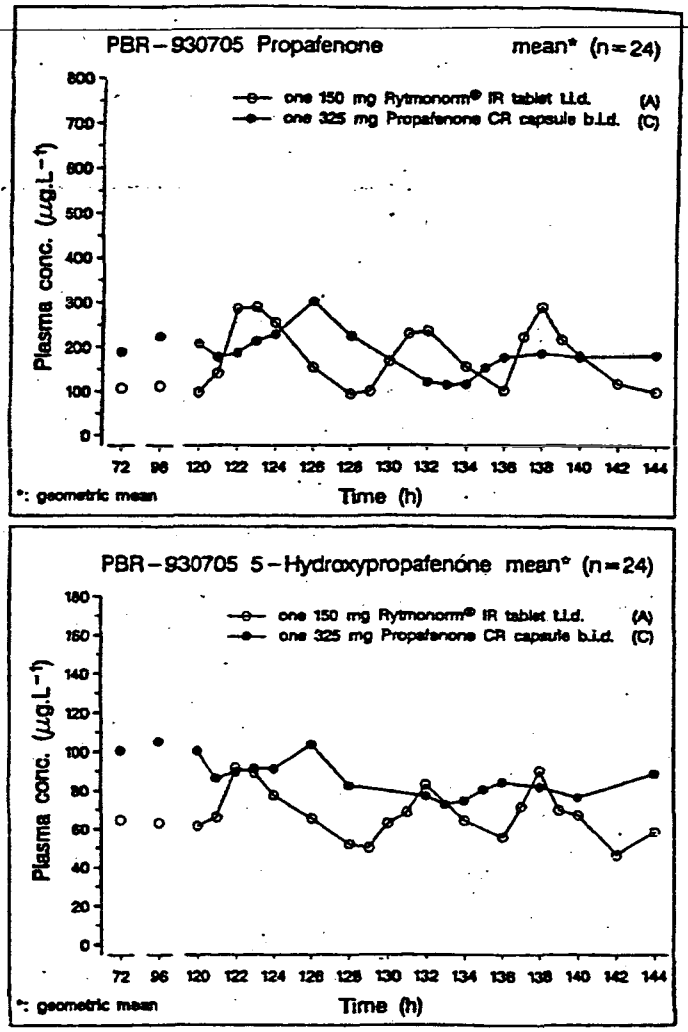


Figure 7.2.1. Geometric mean propafenone and 8-hydroxypropafenone plasma concentration-time curves as observed during multiple dose oral administration of propafenone HCL for six days to 24 subjects
A = one Rythmonorm 150 mg IR tablet tid
C = one propafenone 325 mg CR capsule bid

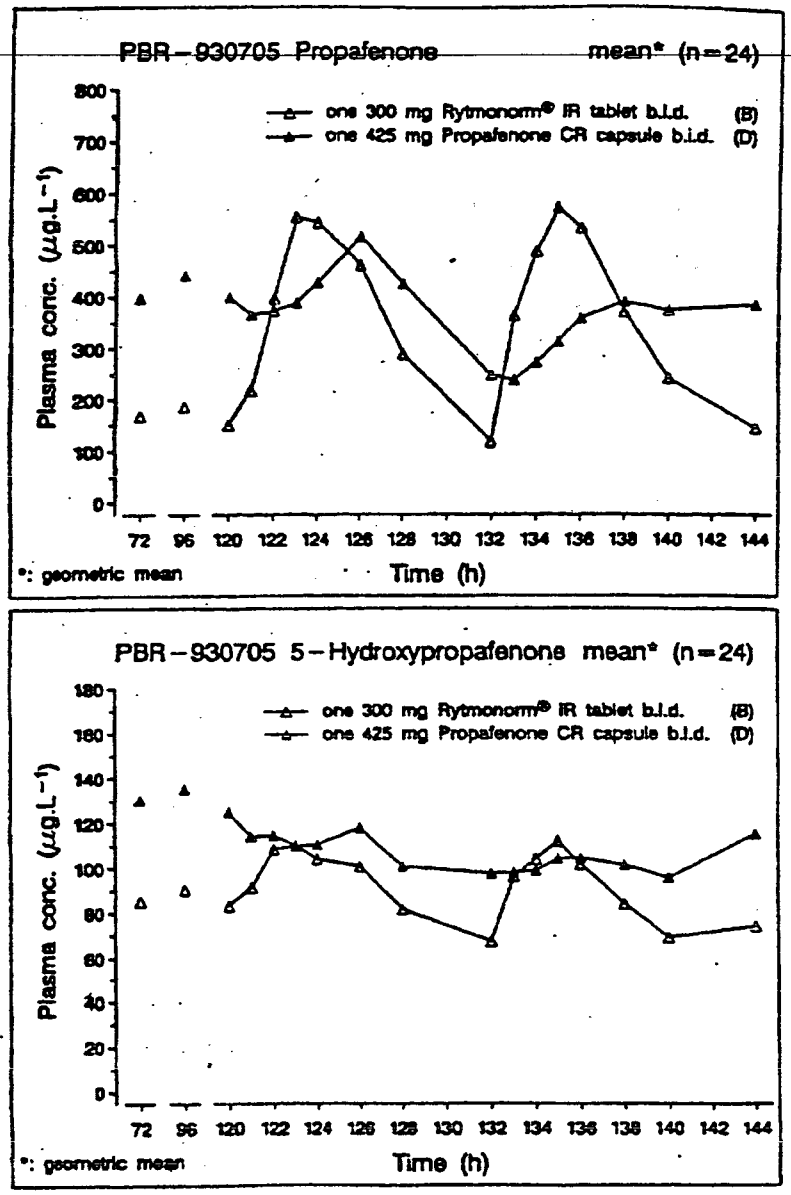


Figure 7.2.2. Geometric mean propafenone and 5-hydroxypropafenone plasma concentration-
time curves as observed during multiple dose oral administration of propafenone HCL for six days to 24 subjects
B = one Rybnonorm 300 mg IR tablet bid
D = one propafenone 425 mg CR capsule bid

The pharmacokinetic parameters of propafenone and 5-hydroxypropafenone on Day 6 are shown in Table 1.

Table 7.2.1. Pharmacokinetic parameters of propafenone and 5-hydroxypropafenone derived under steady state conditions after multiple dose oral administration of two immediate release and two controlled-release preparations.

Parameter		Treatment	Geometric mean	Min - Max
Propafenone				
C_{max}	$\mu g \cdot L^{-1}$	A	440.5	
		B	822.5	
		C	350.1	
		D	589.9	
C_{min}	$\mu g \cdot L^{-1}$	A	71.4	
		B	108.5	
		C	89.3	
		D	212.3	
$AUC_{120-144}$[b]	$\mu g \cdot L^{-1} \cdot h$	A	4616	
		B	8933	
		C	4817	
		D	8324	
5-Hydroxypropafenone				
C_{max}	$\mu g \cdot L^{-1}$	A	105.6	
		B	126.3	
		C	112.3	
		D	134.8	
C_{min}	$\mu g \cdot L^{-1}$	A	39.9	
		B	59.0	
		C	63.1	
		D	81.3	
$AUC_{120-144}$	$\mu g \cdot L^{-1} \cdot h$	A	1649	
		B	2162	
		C	2052	
		D	2555	

Daily dose

A: 450 mg
B: 600 mg
C: 650 mg
D: 850 mg

The sponsor compared treatment A (450 mg daily dose of IR) to treatment C (650 mg daily of SR) as well as treatment B (600 mg daily dose of IR) to treatment D (850 mg daily dose of SR). The mean values of $AUC_{120\text{-}144hr}$ for propafenone were similar for each of the comparisons. Cmax in each comparisons differ by 24 and 18%. The sponsor concluded that more gradual release of propafenone from the prolonged-release preparations resulted in less saturation of the CYP2D6 isozyme, which resulted in an increase in overall first pass metabolism to 5-hydroxypropafenone. Higher daily doses of propafenone were therefore needed from the SR formulation relative to the IR formulation to obtain similar exposure to propafenone.
Secondary pharmacokinetic parameters calculated by the sponsor indicate less plasma fluctuations obtained with the sustained release Rythmol (Table 2).

Table 7.2.2. Comparison of the secondary PK parameters.

parameter	treatment	propafenone mean*	propafenone min-max	5-hydroxypropafenone mean*	5-hydroxypropafenone min-max	norpropafenone mean*	norpropafenone min-max
t_{max} (h)	A	2.0		2.0		2.0	
	B	2.0		2.0		2.0	
	C	6.0		4.0		6.0	
	D	6.0		6.0		6.0	
t_{75} (h)	A	3.16		9.29		6.23	
	B	4.39		12.30		6.10	
	C	8.12		14.35		11.74	
	D	9.96		15.90		15.55	
PTF (%)	A	201		98		109	
	B	196		76		118	
	C	134		58		84	
	D	98		50		59	
AUCF (%)	A	38.8		19.5		22.3	
	B	45.4		18.4		26.8	
	C	29.6		12.2		17.6	
	D	22.2		10.2		13.7	

Comments:
This was one of the early studies in healthy volunteers to compare the pharmacokinetics of immediate release and controlled release propafenone at steady state. The comparison of the exposure at day 6 (AUC) performed by the sponsor was based on the absolute values. The reviewer normalized the mean AUC (Table 7.2.3 and Figure 7.2.3) values for the parent drug and metabolite to the daily dose. With the 25% increase in dose, there was a 45% increase in exposure for the IR formulation and 48% increase in exposure for the SR formulation. The difference of the mean dose normalized exposure to 5-hydroxypropafenone was in the range of 20% and Cmax in all treatments.

Table 7.2.3. Dose normalized AUC(122-144hr)

Propafenone	AUC	Daily Dose	AUCnorm
A	4616	450	1026
B	8933	600	1489
C	4817	650	741
D	9324	850	1097
5-HO-Propafenone			
a	1649	450	366
b	2162	600	360
c	2052	650	316
d	2555	850	301

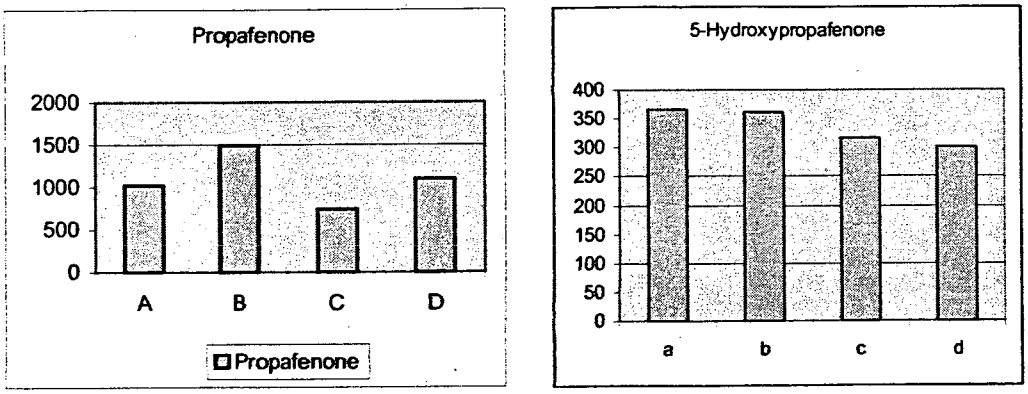


Figure 7.2.3. Dose normalized AUC on Day 6 for propafenone (left panel) and 5-hydroxypropafenone (right panel).

The same calculation was performed for Cmax (Table 7.2.4, Figure 7.2.4).
The sponsor indicated that the controlled release formulation also saturated the metabolite enzyme and its first-pass metabolism is increased, which is reflected by an increase in 5-OH-propafenone plasma concentrations. Only absolute values of 5-OH-propafenone plasma concentrations show an increase. Normalized by the daily dose 5-OH-propafenone peak plasma concentrations are relatively smaller with the higher dose.

Table 7.2.4. Dose normalized Cmax values.

Propafenone	Cmax	Daily Dose	Cm_norm
A	441	450	98
B	822	600	137
C	350	650	54
D	589	850	69
5-HOpropafenone			Cn_norm
a	106	450	24
b	126	600	21
c	112	650	17
d	135	850	16

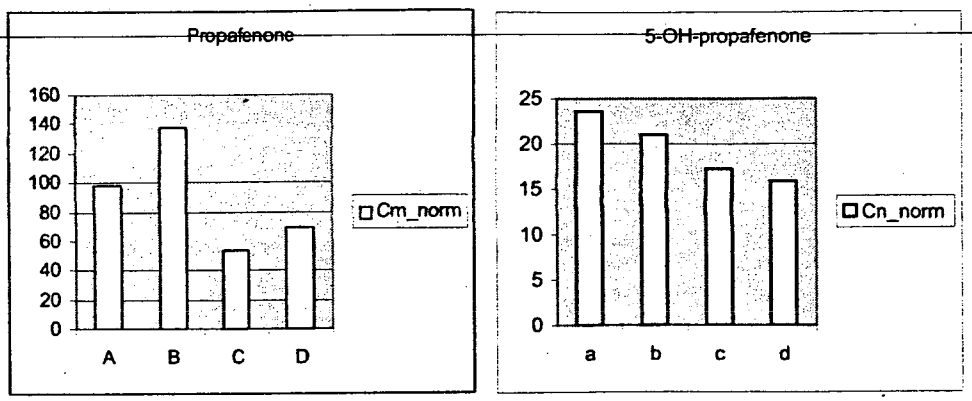


Figure 7.2.4. Dose normalized Cmax on Day 6 for propafenone (left panel) and 5-hydroxypropafenone (right panel).

7.2.2 Food Effect/Bioavailability Studies Reports P-86-CP (Single Dose) and MPF/HP 9117E (Multiple Dose)

Volumes 16-18
Study Title:
An open-label, single-dose, pharmacokinetic evaluation of slow release (Rythmol* SR) capsules with and without concomitant administration of food. (Report P-86-CP)

Objectives:
To evaluate the effects of food on the pharmacokinetic profile of Rythmol@ SR. This study also examined the pharmacokinetics of propafenone under fasting conditions from immediate-release Rythmol@ as a reference.

Study Period:
February 1998.

Design:
An open label, single-center, single-dose, randomized, three-way crossover design. Twenty-four subjects enrolled (10 men, 14 women) with 22 completing all three treatments (9 men, 13 women). Subjects were non-smoking, healthy subjects, between the ages of 21 and 39.
The three treatments were:

Treatment A (one 425 mg Rythmol SR capsule, fasting), Lot No RYT-0367
Treatment B (one 425 mg Rythmol SR capsule, fed), Lot No RYT-0367
Treatment C (one 300 mg Rythmol tablet, fasting), Lot No 2145-0067.

The drug was administered immediately after the breakfast with 240 mL of water. The standardized high fat breakfast consisted of the following items:

One buttered English muffin
One fried egg
One slice of American cheese
One slice of Canadian bacon
One serving of hash brown potatoes
Eight fluid ounces (240 mL) of whole milk
Six ounces (180 mL) of orange juice.

In the fasted group, breakfast was given 5.5 hours after the dose.
Blood samples were collected immediately before drug administration and at 0.5, 1, 2, 3,4, 5, 6, 8, 10, 12, 14, 16, 18 and 24 hours post dose for each treatment period. The pharmacokinetics of propafenone and 5-hydroxypropafenone were determined. Measurable plasma concentrations of norpropafenone were insufficient in number to calculate the pharmacokinetic parameters for this metabolite.

Results

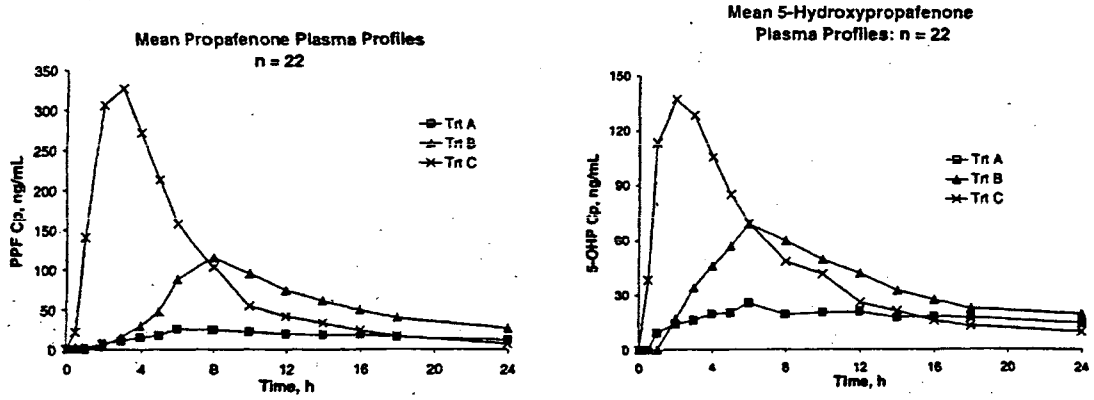
Mean (SD) PK parameters in 22 fed and fasted subjects for propafenone and 5-hydroxypropafenone after Rythmol SR 425 mg (treatment A, fasted or B, fed) and Rythmol IR 300 mg, treatment C, fasted are shown in Table 7.2.5.

Table 7.2.5. Mean PK parameters for propafenone (upper panel) and 5-hydroxypropafenone (lower panel) after Rythmol SR 425 mg (treatment A, fasted or B, fed) and Rythmol IR 300 mg, treatment C, fasted.

Parameter	Treatment A Mean (SD)	Treatment B mean (SD)	Treatment C mean (SD)
C_{max} (ng/mL)	30.4 (44.1)	134.1 (159.5)	368.3 (202.0)
t_{max} (h)	8.7 (3.9)	8.3 (3.9)	2.4 (0.9)
AUC_{0-24} (ng•h/mL)	393 (739)	1258 (2011)	2087 (1822)
$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	2171 (1975)
k_e (h^{-1})	NC	NC	0.243 (0.065)
$t_{1/2}$ (h)	NC	NC	[illegible]

Parameter	Treatment A Mean (SD)	Treatment B mean (SD)	Treatment C mean (SD)
C_{max} (ng/mL)	25.4 (16.9)	79.1 (55.4)	157.8 (84.3)
T_{max} (h)	8.2 (5.2)	7.6 (4.0)	2.8 (1.7)
AUC_{0-24} (ng•h/mL)	314.4 (257.6)	749 (474)	986 (423)
$AUC_{0-\infty}$ (ng•h/mL)	NC	NC	1198 (544)
k_e (h^{-1})	NC	NC	0.101 (0.048)
$t_{1/2}$ (h)	NC	NC	12.9 (22.6)

For propafenone, the mean Fed/Fasting ratios were 6.2 for Cmax (range [redacted]), 7.4 for AUC (range of [redacted]). For 5-OH-propafenone, the mean Fed/Fasting ratios were 3.6 for Cmax (range of [redacted]), 5.5 for AUC (range ot [redacted]. These treatments are compared graphically in Figure 7.2.5.



The intersubject variability was very high for both propafenone and 5-OH- propafenone. Pairwise comparison assessed the food effect on SR formulation as well as the effect of sustained release formulation at fasted conditions. The ratios of the mean parameter values of the fed/fasted treatments of Cmax and AUC for propafenone were 4.4 and 3.2, respectively. The ratios of the mean parameter values of the fed/fasted treatments of Cmax and AUC for 5-hydroxypropafenone were 3.1 and 2.4, respectively. These values indicate that the effect of food on both parent drug and metabolite was significant.

Volume 19

Study Title:
The influence of food intake on the pharmacokinetics of propafenone HCL (425 mg) during multiple dose administration of a prolonged-release formulation. (Protocol HP D28/91E, Report No. MPF/HP 9217 E)

Objectives:
To study the influence of food intake on the pharmacokinetics of propafenone during bid multiple dose administration of a sustained release formulation for six days in healthy young male volunteers (24 normal metabolizers of dextromethorphan).

Study Period:
August-September 1991. The clinical part of the study was conducted

Design:
This was a multiple dose, open label, randomized, two-period crossover study consisting of two successive periods (six days each, no washout period) with drug administered under fed or fasted conditions. Twenty-four healthy male volunteers (19-38 years of age) participated in this study and all have completed it. All subjects were normal metabolizers of dextromethorphan (dextromethorphaddextrorphan urinary ratio <0.3). Each treatment (Treatment A-fed conditions, Treatment B-fasted conditions) consisted of oral administration of a 425 mg propafenone prolonged-release formulation (Dosage form: hard gelatine capsule containing microtablets, Batch # 1010-00A1) given bid at 08:00 h and 20:00 h for six days each.

Treatment A: the drug was administered after high fat breakfast and lean dinner.
Treatment B: fasting conditions (8 hours prior to dosing and 4 hours post-dosing for the morning dose; 3 hours prior to and 3 hours post-dosing for the evening dose.

Meal content, breakfast (07:30 h)
-3 slices of whole wheat bread 105 g
-1 Dutch rusk 10 g
-margarine 15 g
-marmalade 15 g
-honey 15g
-cheese 20 g
-ham or chicken fillet or roast beef 20 g
-orange juice 150 mL
-milk 200 ml (diminished fat content)

The prestudy physical examination (within a 3-week period) included a 12-lead ECG, vital signs, clinical chemistry (urine and blood), hematology, demographics and medical history. During the study, systolic and diastolic blood pressure, heart rate and oral body temperature were recorded daily between 06:00 and 08:00 h. A 12-lead ECG was

recorded daily between 06:00 and 08:00 h and also at 1, 2, 3, 4, 6, 8, 10 and 12 hours after study drug administration on Day 6.
Blood samples were collected just before the morning drug administration on Day 1 of the first period and on Days 4, 5 and 6 and at 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after morning dosing on Day 6 of each study period. The pharmacokinetics were determined for propafenone, 5-hydroxypropafenone and norpropafenone. The primary PK parameters were Cmin, Cmax, and $AUC_{120-132}$. Secondary PK parameters included t75 (time during which the plasma concentrations exceed 75% of the Cmax), PTF (peak-trough fluctuation) and AUCF (fluctuation in AUC).

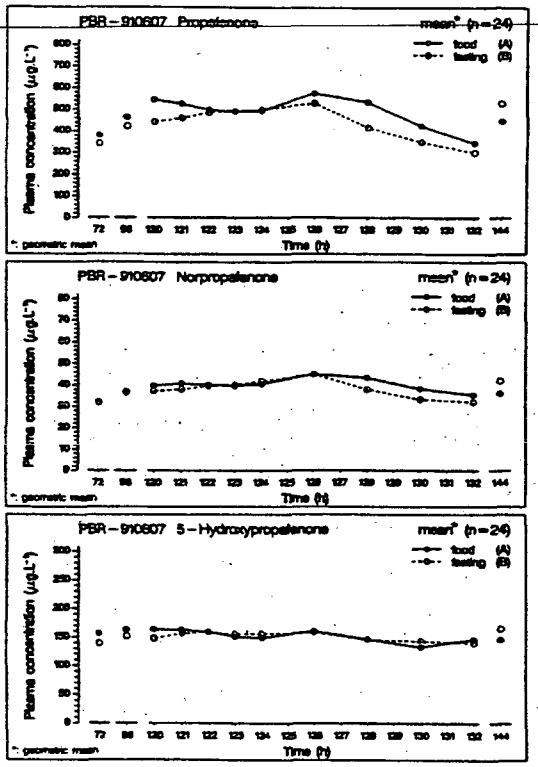
Results:
The steady state conditions were reached by Day 5 of both treatment periods. Pharmacokinetic parameters were derived from plasma concentrations obtained after the morning treatment on Day 6. The pharmacokinetic results are listed in Table 7.2.6.

Table 7.2.6. Pharmacokinetic parameters of propafenone, norpropafenone, and 5-hydroxypropafenone after multiple doses of 425 mg of Rythmol SR under fed (A) and fasted (B) conditions.

Parameter	Treatment	Propafenone			Norpropafenone			5-hydroxypropafenone		
		Geometric mean	90% confidence interval and point estimate		Geometric mean	90% confidence interval and point estimate		Geometric mean	90% confidence interval and point estimate	
C_{max}	A	628	103 - 130	116	47.4	97 - 116	106	176.3	96 - 108	102
($\mu g \cdot L^{-1}$)	B	542			44.5			172.6		
C_{min}	A	343	97 - 135	114	33.7	98 - 119	108	128.8	92 - 109	100
($\mu g \cdot L^{-1}$)	B	300			31.1			128.8		
$AUC_{120-132}$	A	6000	101 - 128	113	492	98 - 116	107	1805	94 - 105	99
($\mu g \cdot L^{-1} \cdot h$)	B	5290			460			1814		

Cmin, Cmax, and $AUC_{120-132}$ for propafenone were higher after administration with food than after administration in the fasting state, and the Cmax differences were statistically significant (p=0.041). The upper limit of the calculated 90% confidence interval for $AUC_{120-132}$ for propafenone exceeded 125%. The 90% confidence interval for Cmax for propafenone was confined within an 80-143% confidence interval. The 90% confidence intervals for Cmin, Cmax, and $AUC_{120-132}$ for norpropafenone and 5-hydroxy-propafenone were all within 80 - 125%. Arithmetic mean values for propafenone, for Treatments A (fed) and B (fasted), were 8.1 hours and 8.6 hours for t75, 56.3% and 53.6% for PTF and 12.4% and 13.9% for AUCF, respectively.

Plots of geometric mean plasma concentration-time profiles for all 24 subjects for each molecular entity for both treatments are shown in Figure 7.2.5.



Geometric mean propafenone, norpropafenone and 5-hydroxypropafenone plasma concentration-time curves as observed during multiple dose oral administration of 425 mg of propafenone.HCl (Rytmonorm® Retard) b.i.d. for six days to 24 subjects
A = Rytmonorm® Retard given with food
B = Rytmonorm® Retard given under fasting conditions

Figure 7.2.5. Mean plasma concentration-time profiles for propafenone, 5-hydroxypropafenone and norpropafenone.

Therefore, after multiple doses of 425 mg of Rythmol, the food effect was apparent for the parent drug. The effect of food on the pharmacokinetics of both metabolites was not significant.

Comments:

1. After single 425 mg dose of Rythmol, the mean ratios of the fed/fasted treatments of Cmax and AUC for propafenone were 4.4 and 3.2, respectively. The mean ratios of the fed/fasted treatments of Cmax and AUC for 5-hydroxypropafenone were 3.1 and 2.4, respectively. These values indicate that the effect of food on both parent drug and metabolite was significant.
2. After multiple 425 mg doses of Rythmol (at steady state), the effect of food was significant for the parent drug but not for the both measured metabolites.
3. In the fed condition, mean Cmax and AUC values of propafenone at steady state were at least 4 fold higher than after the single dose. The sponsor concluded that

most likely, the effect of drug accumulation is masking the food effect, and therefore, food effect is not clinically significant.

4. It is not known whether the food effect would be pronounced if the drug would be given immediately after a high fat meal. The multiple dose study conducted in 1991 did not use a standardized high fat breakfast and the drug was given 30 minutes after the ingestion of the meal.
5. In the food effect single dose study for Rythmol IR (dose of 300 mg) Cmax under the fed condition was 454 ng/mL with an $AUC_{0-\infty}$ of 2991 ng/h/mL. In the multiple dose study for Rythmol IR Cmax under the fed condition was 971 ng/mL with an AUC_{0-8hr} of 5341 ng/h/mL. These plasma levels are comparable to the levels obtained with the multiple dose (425 mg BID) study for the Rythmol SR formulation (Cmax of 628 ng/mL and AUC0-12h of 6000 ng/h/mL) under fed condition.
6. The Medical Officer is requested to assess the clinical implications of the possible increase in exposure that may be seen if Rythmol SR will be given with food.

7.3 Pharmacokinetic Studies of Dose-proportionality (Report # PN102)

Volumes 20-23
Study Title:
A randomized, multiple-dose, open-label, three-way crossover study to assess dose-proportionality and pharmacokinetics of propafenone and two active metabolites at steady-state following 225, 325, and 435 mg prolonged-release propafenone (Rythmol@ SR) capsules administered twice daily to healthy, adult subjects.

Investigator/Study Center:

Objectives:
Primary:
To assess dose-proportionality and pharmacokinetics of propafenone and it's two active metabolites at steady state following 225, 325, and 425 mg prolonged-release propafenone (Rythmol@ SR) administered twice daily to healthy, adult subjects.
Secondary:
To assess pharmacokinetics of Rythmol@ SR in extensive and poor metabolizers separately and to determine R/S ratios of the stereospecific isomers of propafenone and its active metabolites.

Study Period:
February-March 2000.

Design:
This was an open-label, steady-state, multiple-dose, randomized, three-way crossover study in 26 healthy, adult, male and female subjects genotyped for CYP2D6. During screening, genomic DNA isolation and molecular genotyping analysis of CYP2D6 A, B, D, E. G and T alleles was performed using a multiplex polymerase chain reaction. There were 18 extensive metabolizers (EM) and 8 poor metabolizers (PM) with respect to CYP2D6 substrates. The data from twenty-three subjects (18 EM and 5 PM) were analyzed for pharmacokinetics. The design consisted of a screening phase and three 7-day treatment periods consisting of twice daily oral doses of 225, 325, or 425 mg Rythmol@ SR. Doses were administered 12 hours apart. Treatment was continuous without washout intervals. Blood samples for the pharmacokinetic evaluation of propafenone and its active metabolites were taken at the following times on the 7th day of each treatment period: 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, and 12.0 hours after morning study drug administration. Additional blood samples for propafenone and its metabolites were taken at trough and peak on all study days of each period. Steady-state evaluations were performed on trough levels.

Chiral analyses for determination of R- and S-stereo isomers of propafenone were performed at trough (Time 0) and estimated peak time (6h) on the 7th day of each period during the study.

Study Drug:

Rythmol SR 225, 325, and 425 mg capsules BID oral doses and batch #:
Rythmol SR 225mg capsules RYT-0229 (980310A0)
Rythmol SR 325mg capsules RYT-0239 (980311A0)
Rythmol SR 425 mg capsules RYT-0249 (980211A0)
Duration of treatment: 21 days.

Pharmacokinetics:

Pharmacokinetic parameters estimated: Cmax, Cmin, Caverage, Tmax, Tmin, Raccumulation and Fi, kel, t1/2 and R/S ratios. For the assessment of dose proportionality, the parameters were dose normalized to 225 mg dose and regression models were fitted to the non-normalized AUC0-t, Cmax, Cmin and Caverage across the three dose groups. The data were analyzed and described for propafenone, 5-hydroxypropafenone and norpropafenone separately. Most of analyses were performed separately for EM and PM.

Results:

Steady state was achieved by day 5 at all doses. Plasma concentration profiles for propafenone, 5-hydroxypropafenone and norpropafenone were considerably flat; however, the mean plots of the data indicate high inter-subject variability.
Following figures 7.2.6-7.2.8 show the propafenone, 5-hydroxypropafenone and norpropafenone plasma profiles respectively in extensive (panels A) and poor (panels B) metabolizers.

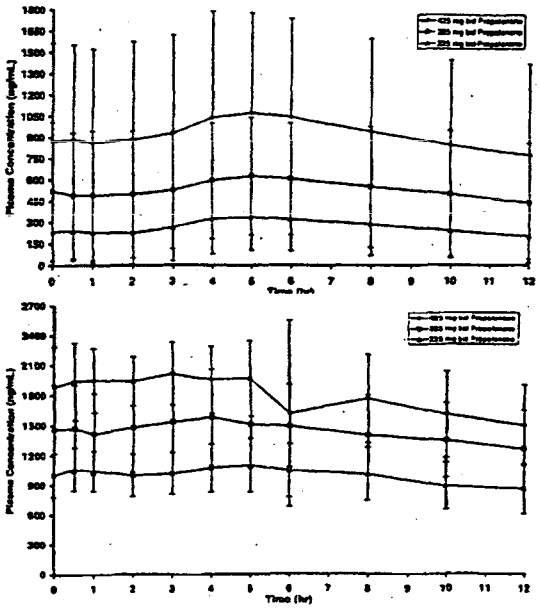


Figure 7.2.6. A, upper panel, B, lower panel, propafenone.

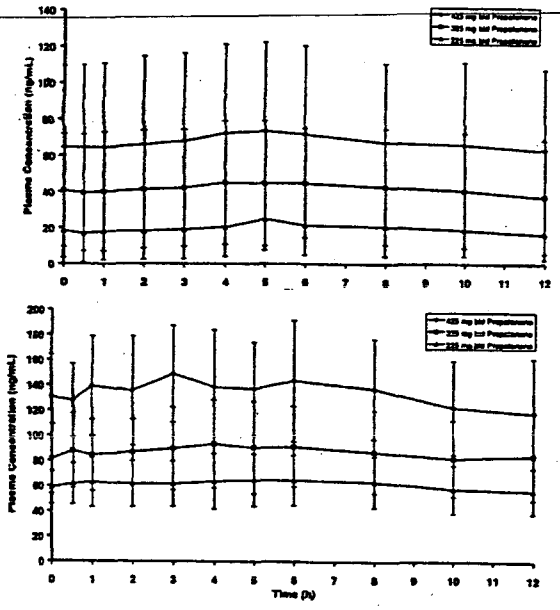


Figure 7.2.7. Norpropafenone A, upper panel, B lower panel

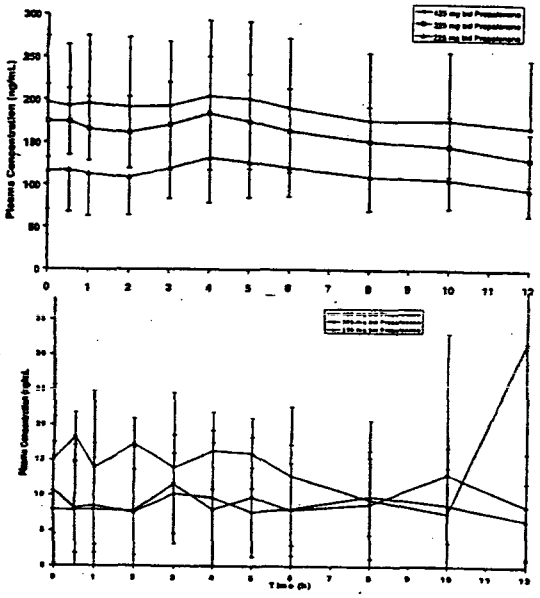


Figure 7.2.8. 5-hydroxypropafenone A, upper panel, B lower panel.
Poor metabolizers have two- to threefold higher plasma concentrations of propafenone and norpropafenone relative to extensive metabolizers. 5-hydroxypropafenone forms through the CYP450 2D6 isoenzyme, and poor metabolizers have much lower (10-20 times) plasma concentrations than extensive metabolizers.

Table 7.2.7 compares PK parameters stratified by the genotype.

Table 7.2.7. Dose-proportionality: Comparison of dose-normalized pharmacokinetic parameters.

Species		Mean±SD of PK Parameters At Each Dose Level (not normalized)			Dose Level Comparisons (p-values**)		
	Geno	225 mg	325 mg	425 mg	225 vs 325	225 vs 425	325 vs 425
AUC_{0-t} - Area Under the Curve							
Propafenone	EM	3238+/-2445	6424+/-4969	11134+/-7916	**0.001**	**0.000**	**0.010**
Propafenone	PM	11971+/-2767	17246+/-4901	21451+/-4921	0.545	0.531	0.858
5-Hydroxypropafenone	EM	1348+/-433	1914+/-461	2237+/-942	0.831	0.105	0.068
5-Hydroxypropafenone	PM	104+/-65	113+/-115	171+/-101	0.308	0.582	0.678
Norpropafenone	EM	236+/-183	502+/-381	812+/-554	**0.005**	**0.000**	0.181
Norpropafenone	PM	740+/-226	1048+/-379	1615+/-479	0.792	0.374	0.279
C_{av} - Average Plasma Concentration							
Propafenone	EM	270+/-204	535+/-414	928+/-660	**0.001**	**0.000**	**0.010**
Propafenone	PM	998+/-231	1437+/-408	1788+/-410	0.545	0.531	0.858
5-Hydroxypropafenone	EM	112+/-36	159+/-38	186+/-79	0.850	0.104	0.072
5-Hydroxypropafenone	PM	9+/-5	9+/-10	14+/-8	0.308	0.583	0.677
Norpropafenone	EM	21+/-15	42+/-32	68+/-46	**0.005**	**0.000**	0.184
Norpropafenone	PM	62+/-19	87+/-32	135+/-40	0.793	0.371	0.277
C_{max} - Maximum Plasma Concentration							
Propafenone	EM	371+/-244	698+/-460	1151+/-711	**0.002**	**0.000**	**0.010**
Propafenone	PM	1176+/-230	1637+/-501	2106+/-321	0.735	0.559	0.402
5-Hydroxypropafenone	EM	148+/-49	202+/-64	223+/-85	0.571	**0.002**	**0.009**
5-Hydroxypropafenone	PM	16+/-10	19+/-16	37+/-35	0.479	0.251	0.477
Norpropafenone	EM	26+/-17	49+/-35	77+/-49	0.097	**0.002**	0.107
Norpropafenone	PM	69+/-20	97+/-33	154+/-43	0.733	0.258	0.172
C_{min} - Minimum Plasma Concentration							
Propafenone	EM	178+/-143	399+/-357	725+/-607	**0.000**	**0.000**	**0.002**
Propafenone	PM	834+/-225	1249+/-377	1494+/-409	0.121	0.571	0.470
5-Hydroxypropafenone	EM	89+/-34	128+/-31	158+/-73	0.465	0.767	0.307
5-Hydroxypropafenone	PM	7+/-5	7+/-8	5+/-10	NC	NC	NC
Norpropafenone	EM	15+/-14	32+/-30	58+/-43	**0.029**	**0.000**	**0.000**
Norpropafenone	PM	53+/-15	77+/-31	114+/-41	0.986	0.831	0.838

** Displayed concentrations and areas are un-normalized; the comparisons were done on log-transformed dose-normalized data. Values of p<=0.05 (in bold type) indicates significant non-proportionality for the two dose groups being compared. Values of p>0.05 are consistent with dose-proportionality.

EM= extensive metabolizer

PM= poor metabolizer

NC- not calculated (inadvertently), small sample size and similarity of the means suggests no practical difference

Data source: Section 9, Tables 9.2.1 through 9.2.29 and 9.2.185 through 9.2.190

In extensive metabolizers, the following compared parameters: AUC0-t, Cmax, Cmin, and Caverage for propafenone increase more than dose proportional for all comparisons. Same trend was found for norpropafenone. This fact may be explained by the saturation of CYP2D6 pathway with the increased propafenone concentration. For 5-hydroxy-propafenone, only Cmax changed less than dose-proportional with the dose increase for the comparisons of 225 vs 425 and 325 vs 425 doses.

For the poor metabolizers, all parameters increase dose proportionally. The comparisons were performed pairwise on log-transformed data.

Stereoselectivity:

Rythmol is a racemic mixture. The [R]- and [S]-enantiomers of propafenone display stereoselective disposition characteristics. R-enantiomer is cleared more quickly than S-enantiomer. Following the administration of propafenone IR the ratio of the area under the plasma concentration-time curve was about 1.7 for the S-enantiomer compared to the R-enantiomer. Both enantiomers have equivalent potency to block sodium channels; however, the S-enantiomer is a more potent P-antagonist than the R-enantiomer.
The ratios for propafenone enantiomers were calculated at pre-dose and 6 hours after the dose on the 7th day of each treatment sequence and were compared across dose levels for EM and PM subjects. The mean (± standard deviation) values and the results of the statistical comparisons stratified by dose, time and genotype are summarized in Table 7.2.8.
The values of the R: S ratios of propafenone were similar at either 0 or 6 hours, at different dose levels, for either poor or extensive metabolizers.

Table 7.2.8. Comparison of R:S values

	Mean±SD of PK Parameters At Each Dose Level			Dose Level Comparisons (p-values)		
	225 mg	325 mg	425 mg	225 vs 325	225 vs 425	325 vs 425
R/S Ratio at 0 Hours						
Poor Metabolizers	0.55±0.12	0.59±0.09	0.54±0.05	p=0.202	p=0.624	p=0.589
Extensive Metabolizers	0.62±0.08	0.57±0.05	0.57±0.07	p=0.165	p=0.077	p=0.708
R/S Ratio at 6 Hours						
Poor Metabolizers	0.58±0.11	0.63±0.10	0.59±0.05	p=0.077	p=0.375	p=0.538
Extensive Metabolizers	0.63±0.09	0.61±0.07	0.57±0.16	p=0.542	p=0.530	p=0.961

Therefore, the R: S ratios of propafenone appear to be independent of dose and genotype as well as of the time.

COMMENTS:

After multiple doses of Rythmol SR BID, steady state was achieved at day 5 for each of 225, 325, and 425 mg doses. Genetic differences for the extended release formulation were similar to previously observed differences for the immediate release formulation.

In extensive metabolizers, plasma levels increase disproportionally relative to dose for propafenone and norpropafenone. All pharmacokinetic parameters for propafenone and norpropafenone were larger than dose proportional. The comparison of PK parameters is shown in Table 7.2.9.

Table 7.2.9. Comparison of the pharmacokinetic parameters for Rythmol SR doses of 225, 325, and 425 mg.

Parameter	Dose, mg			Ratio	
AUC, ng/mL/h	225	325	425	325 vs 225	425 vs 225
Propafenone	3238	6424	11134	1.37	1.82
5-Hydroxypropafenone	1348	1914	2237	0.98	0.88
Norpropafenone	236	502	812	1.47	1.82
Cmax, ng/mL					
Propafenone	371	698	1151	1.30	1.64
5-Hydroxypropafenone	148	202	223	0.96	-0.80
Norpropafenone	26	49	77	1.31	1.57

For propafenone and norpropafenone, AUC was about 40% larger for the 325 mg dose vs the 225 mg dose, and 82% larger for the 425 mg dose vs the 225 mg dose, and Cmax was 30% higher for the 325 mg dose vs the 225 mg dose, and about 60% higher for the 425 mg dose vs the 225 mg dose. For 5-hydroxypropafenone, AUC and Cmax increased less than dose-proportional with dose for the comparison of the 425 dose vs the 325 dose. The number of poor metabolizers was small (N=5 and in some cases N=4), and the sponsor could not make a statistically valid conclusion. For the poor metabolizers, all parameters tend to increase dose proportionally. These results were similar to the immediate release formulation and were probably due to saturable first pass mechanism. The ratio of the exposure to R- and S-stereoisomers (1.7) was not affected either by the formulation or by the genetic differences.

7.3.1 Pharmacodynamic Studies VPC CR-D1 and VPC CR-D2 (Report MPF/CP 0006E)

Volumes 24, 25

Protocol Titles:

Protocol VPC CR-D1: Double-blind randomized, placebo controlled, dose finding study of sustained release propafenone SR in symptomatic ventricular arrhythmia.
Protocol VPC CR-D2: Randomised, double-blind study on haemodynamics and pharmacokinetics of two different dosages of propafenone SR in patients with symptomatic ventricular arrhythmias.

Investigator/Study Center:

Objectives:
Study VPC CR-D2 was designed to extend the database on hemodynamics and pharmacokinetics of propafenone SR provided in Protocol VPC CR-D1.

VPC CR-D 1: To compare anti-arrhythmic efficacy, tolerability and kinetics of three different dosages (225 mg bid, 325 mg bid, 425 mg bid) of a new propafenone sustained-release formulation in patients with symptomatic ventricular arrhythmia and/or ventricular arrhythmia warranting treatment, against each other and against placebo.
VPC CR-D2: To evaluate pharmacokinetics and hemodynamics of two doses of propafenone SR (225 mg bid and 425 mg bid) in patients with symptomatic ventricular arrhythmias.
The overall objective of final report (MPF/CP 0006 E) was to assess the pharmacokinetics of propafenone SR in patients and the relationship between plasma concentrations and antiarrhythmic effect.

Study Period:
VPC CR-D1: October 1992-October 1993,
VPC CR-D2: February 1993-March 1994.

Study Design:
The essential design features were the same for protocols VPC CR-D1 and VPC CR-D2. Men and women with a history of either treated or untreated arrhythmia, aged between 18 and 70 years, were admitted to the studies. Only patients with organic heart disease and ventricular arrhythmia warranting treatment were enrolled. All patients had confirmed premature ventricular contractions. Women were either post-menopausal or used effective contraception for the duration of their participation in the study.
The protocols were randomized, double-blind, placebo controlled (VPC CR-D1 only), multiple (VPC CR-D1) or single center (VPC CR-D2) parallel-group designs: with a

mandatory 3-5-day placebo run-in period preceded by a placebo wash-out period (if patients were pre-treated with antiarrhythmic agents or beta-blockers). On the first day of the placebo run-in period, a 24-hour Holter ECG was recorded to determine the frequency of arrhythmia. After the placebo run-in period, patients underwent a 5-10-day BID treatment with either 225, 325 or 425 mg propafenone SR or placebo (VPC CR-D1) or with either 225 or 425 mg propafenone SR (VPC CR-D2). A 24-hour Holter ECG was started on the morning of the first day after the patient had taken the first dose of propafenone SR. From Day 5 (at latest on Day 9) another 24 hour Holter ECG was recorded and blood samples for determination of plasma levels of propafenone and metabolites were obtained pre-dose and at 1, 2, 3, 4, 6, 8, 10, and 12 hours after dosing. From Day 6 radionuclide ventriculography was performed 24 hours after the morning dose and a blood sample to determine the plasma levels of propafenone and metabolites was taken.
Pharmacokinetic parameters of propafenone, 5-hydroxypropafenone and norpropafenone were calculated using non-compartmental method. The frequency of ventricular premature contractions in the 24-hour Holter ECG determinations was recorded.

Treatments:
Placebo capsules: 1007-00-P1 (VPC CR-D1) and 281800P1 (VPC CR-D2).
Propafenone SR 225 mg capsules: 1008-00-A1 (VPC CR-D1), 281900A1 (VPC CR-D2).
Propafenone SR 325 mg capsules: 1009-00-A1 (VPC CR-D1).
Propafenone SR 425 mg capsules: 1010-00-A1 (VPC CR-D1), 282100A1 (VPC CR-D2).
The capsules with microtablets of propafenone HCL were identical in appearance.

Results:
There were a total of 37 patients in the "all PK patient population", which included all patients in the pharmacokinetic portion of VPC CR-D1 (25 patients) and all patients in VPC CR-D2 (12 patients). All 29 patients with concentration time profiles of propafenone at steady state were included in the "PK population". Of these patients, 21 (72%) were males and 8 (28%) were females. The mean age of the male and female patients was 59 years (range 34 to 76) and 57 years (range 45 to 66), respectively. There were 28 patients included in the PD population, 21 (75%) were males and 7 (25%) were females.
Spartein test was conducted for the patients in VPC CR-D1. Only patients #176 and #7 (225 mg dose group) were poor metabolizers. Their propafenone levels were much higher, and 5-OH-propafenone levels much lower (#7) that the average for their group and BLQ for #176. Additionally to these 2 patients, three others (##169, 1, and 9) had much higher propafenone plasma concentrations than that in their group, and normal values for 5-OH-propafenone. The reasons for the high propafenone levels for these patients were not explained by the sponsor and their data were included in the statistical analyses. All these 5 patients have Caverage > 800 ng/mL for propafenone.
Individual plasma concentrations vs times for propafenone are shown in Figure 7.2.9.

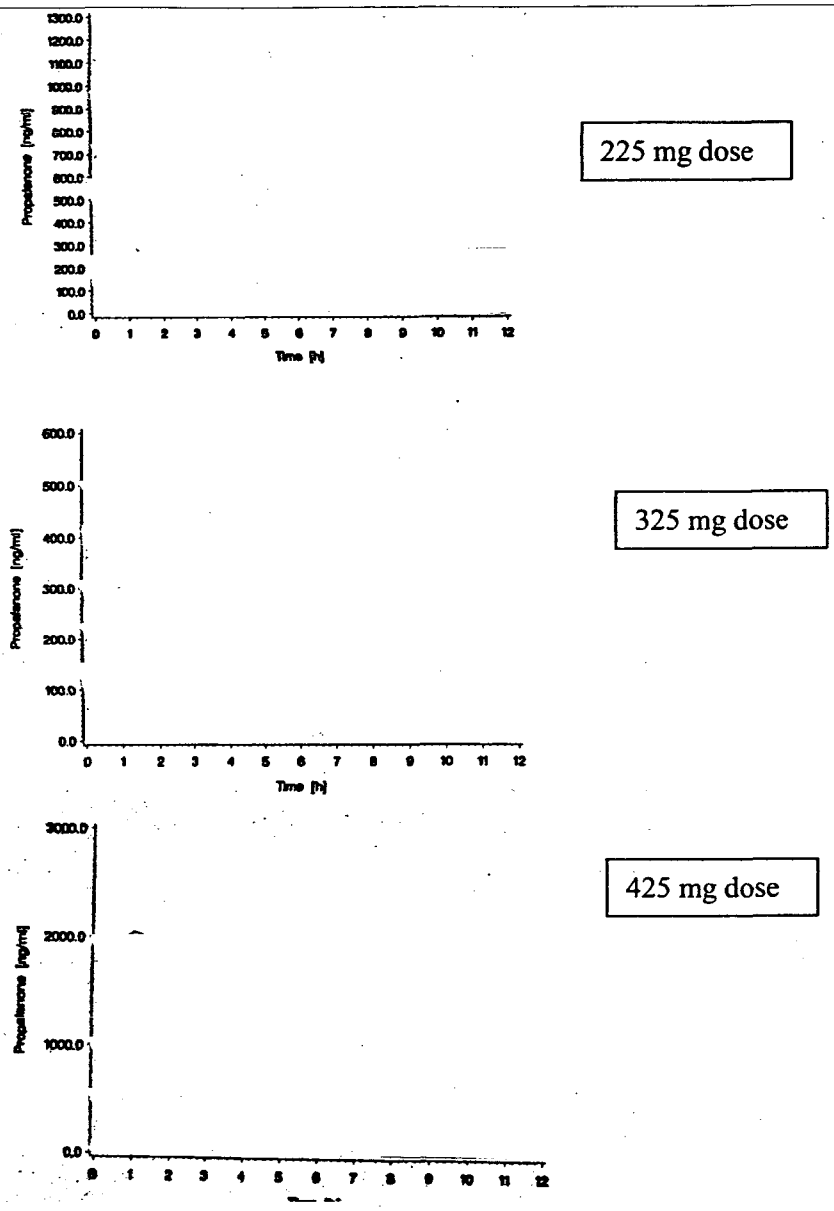


Figure 7.2.9. Individual plasma concentrations vs times for propafenone. Upper panel, dose of 225 mg; middle panel, dose of 325 mg; lower panel, dose of 425 mg. Stars are for the patients 176 and 7.

Individual plasma concentrations vs times for 5-OH-propafenone are shown in Figure 7.2.10.

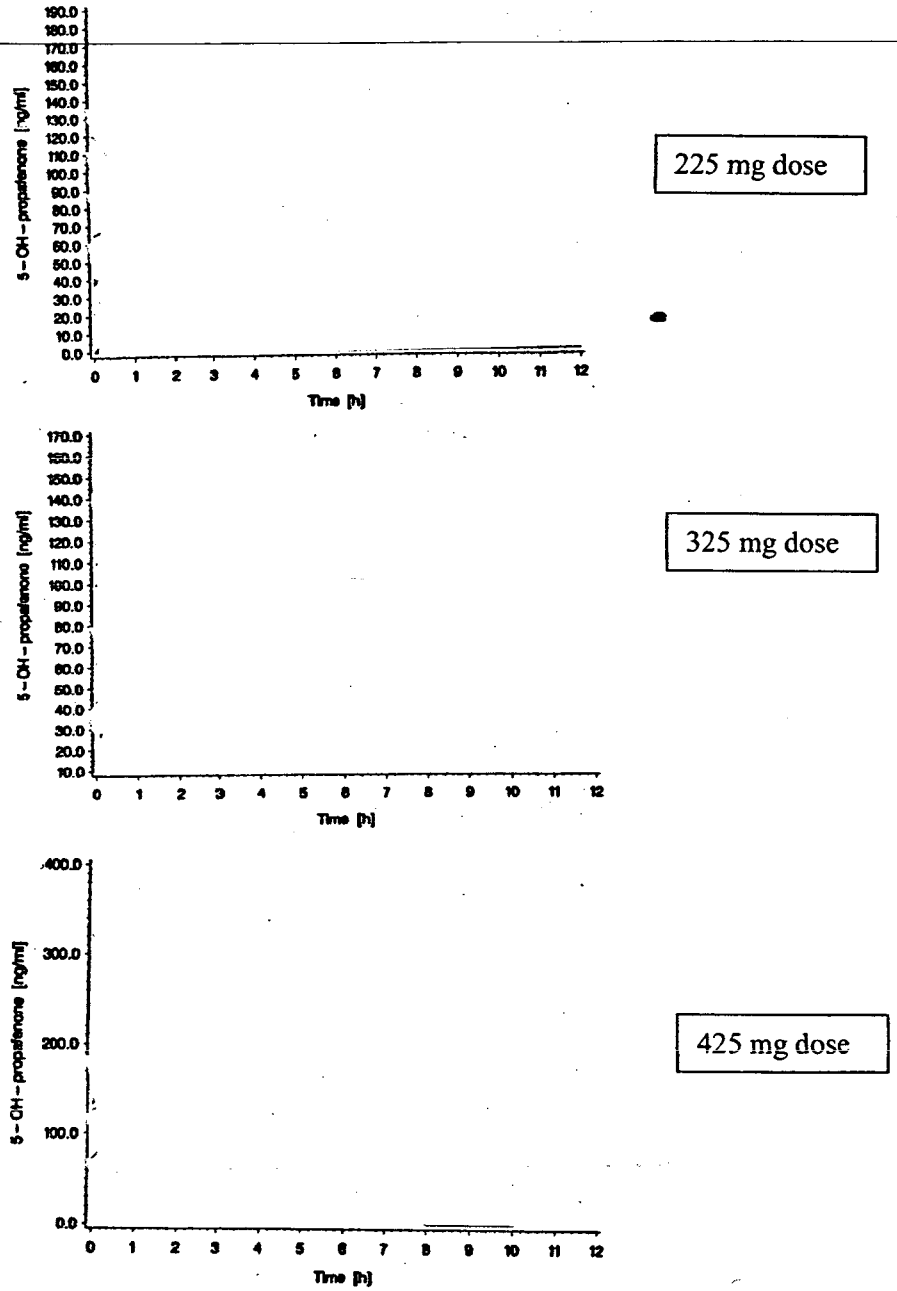


Figure 7.2.10. Individual plasma concentrations vs times for 5-OH-propafenone. Upper panel, dose of 225 mg; middle panel, dose of 325 mg; lower panel, dose of 425 mg.

Very high interindividual variability can be seen in these plots.
The sponsor presented a descriptive statistics for the plasma concentrations as well as for the pharmacokinetic parameters obtained for the individual patients (AUC, Cmin, Cmax, Caverage, CLss, PTF, Tmax). Summary statistics is shown in Table 7.2.9.

Table 7.2.9. Geometric means (90% confidence intervals) of propafenone PK parameters.

Parameter	225 mg (n=11)	325 mg (n=7)	425 mg (n=11)
AUC_{ss} [ng*h/mL]	1053 (329, 3373)	2355 (1350, 4110)	5200 (3005, 8999)
C_{max} [ng/mL]	154 (55, 426)	275 (164, 463)	615 (396, 955)
CL_{ss} [l/h]	214 (67, 684)	138 (79, 241)	82 (47, 141)
PTF [%]	111 (74, 169)	75 (57, 100)	72 (48, 107)
T_{max} [h]	4 (1-10)*	6 (0-10)*	3 (0-8)*

Pharmacokinetics of propafenone was nonlinear (as was shown in the other studies). Due to the high interpatient variability as well as low number of patients, nonlinerarity for both AUC and Cmax was not confirmed statistically. There was no correlation between plasma concentrations of propafenone and 5-OH-propafenone in these studies.

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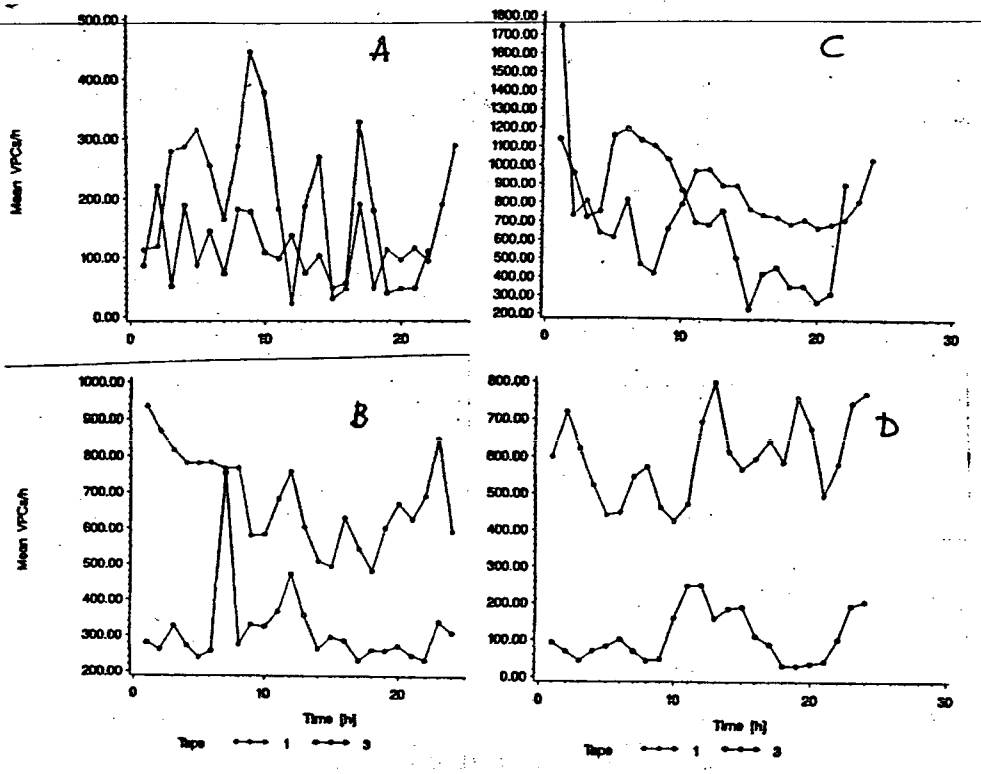

Figure 7.2.11. Mean VPC/hour(%) vs time for placebo (panel A), dose 225 mg (panel B), dose 325 mg (panel C), and dose 425 mg (panel D). Tape 1 – baseline, tape 3 – at steady state.

Summary statistics was calculated for relative reduction of VPCs and couplets pooled over studies (Table 7.2.10).

Table 7.2.10. Summary statistics for reductions of VPCs.

Variable	Dose (mg)	n	Mean	STD	CV(%)	Min	Median	Max
Relative	Placebo	3	17.8	47.9	268.7		32.2	
Reduction (%)	225	10	53.5	37.4	69.9		58.7	
VPCs/hr	325	5	8.57	86.7	1012.4		37.1	
	425	10	82.5	22.0	26.7		93.9	

Median VPCs per hour over 24 hours Holter interval were reduced by 59% and 94% in patients receiving 225 and 425 mg of propafenone SR. The data from the 325 mg dose group included only 5 patients and had high variability results and were difficult to interpret.

Individual values for the relative reduction of VPCs were plotted against the average propafenone concentration at steady state (Caverage).(Figure 7.2.12)

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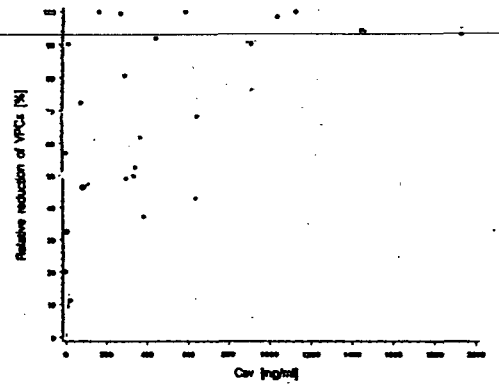

Figure 7.2.12. Relative reduction of VPCs vs Caverage of propafenone
The sponsor applied an Emax model to these data. The model fits these data poorly, R=0.16. The same analysis was also performed with the average concentrations of 5-0H-propafenone, and results were much better, R=0.87 (Figure 7.2.13)

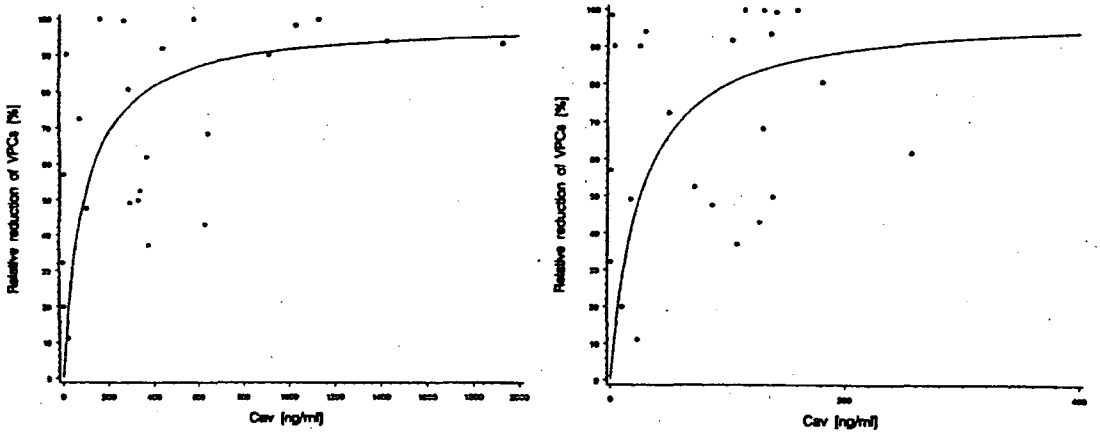

Figure 7.2.13. Relative reduction of VPCs vs Caverage of propafenone (left panel) and of 5-OH-propafenone (right panel). The lines are the model predictions.

The effect of propafenone and 5-OH-propafenone was analyzed simultaneously but the results were not improved. The results of the PK/PD modeling are shown in Table 7.2.11.

Table 7.2.11.Parameters estimated for the pharmacodynamic models
$y=100 \cdot C_{av}/(EC_{50}+C_{av})$

Model	Parameter	Estimate	Standard error	R
ΔVPCs/h[a] vs C_{av} propafenone	EC_{50}	90.7	38.7	-0.16
ΔVPCs/h vs C_{av} propafenone [b]	EC_{50}	60.4	44.9	-0.33
ΔVPCs/h vs C_{av} 5-OH-propafenone	EC_{50}	25.0	12.2	-0.87
ΔVPCs/h vs C_{av} 5-OH-propafenone [c]	EC_{50}	27.9	13.8	-0.02
ΔVPCs/h vs a*C_{av} propafenone+(1-a) C_{av} 5-OH-propafenone	EC_{50}	42.6	18.7	0.09
	a	0.15	0.15	

COMMENTS:

1. The pharmacokinetics of propafenone and its metabolites were satisfactorily described in 29 patients. Pharmacodynamics was assessed in the same patients as reduction in ventricular premature contractions. In patients receiving 225 and 425 mg of propafenone SR median VPCs per hour over 24 hours Holter interval were reduced by 59% and 94%. The number of patients in the group receiving 325 mg dose was small and the data uninterpretable.
2. [redacted]

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7.3.2 A study on the biopharmaceutical properties of three experimental sustained release preparations of propafenone (400 mg) during multiple dose administration (to healthy volunteers). (Protocol SR-HPD27/90EReport No. MPF/HP 9112E)

Volumes 26
Investigator/ Study Center

Objectives
To study the biopharmaceutical characteristics of three experimental sustained release capsules of propafenone during multiple dose administration for five days under fasting conditions.

Study Period
1990-1991

Design
The study was a multiple dose, open label, randomized, three period cross-over study in 18 male subjects. The male subjects were between 18 and 45 years of age, in good physical health, weight within 15% of normal range, and were normal metabolizers of dextromethorphan. Each of the three treatment formulations (Treatments A, B and C) was a hard gelatin capsule containing microtablets. The active compound in each capsule was 400 mg propafenone HCL. Treatments consisted of oral administration of 400 mg propafenone bid at 8:00 h and 20:00 hours for five days without wash-out between the three successive periods.

Treatment A: 0005-01-A1VS (reference)
Treatment B: 0005-02-A1VS (test)
Treatment C: 0005-03-A1VS (test)

A 12- lead ECG was recorded on each study day prior to the morning dose.
On Day 5 of each study period a 12-lead ECG was also taken at 1, 2, 3, 4, 6, 8, 10 and 12 hours after the morning dose. Blood pressure, heart rate, and body temperature were recorded between 7:00 and 8:30 h on each study day.
Blood samples were collected on Day 1 of the first study period just before the morning dose, on Days 3, 4 and 5 of each study period just before the morning dose, and on Day 5 of each study period at 1, 2, 3, 4, 6, 8 10, 12 (just before the evening dose), 13, 14, 15, 16, 18, 20, 22, and 24 hours after the morning dose. The pharmacokinetics of propafenone, 5-hydroxypropafenone and norpropafenone were determined. The pharmacokinetic parameters assessed for propafenone were Cmax, Cmin, Tmax, AUC, t75, PTF and AUCF. For the two metabolites, 5-hydroxypropafenone and norpropafenone, Cmax, Cmin, and AUC were assessed.

Results:

Individual plasma concentrations data for each of the assayed molecular entity show high interpatient variability. Mean plasma concentration profiles of the three treatments are compared in Figure 7.2.14.

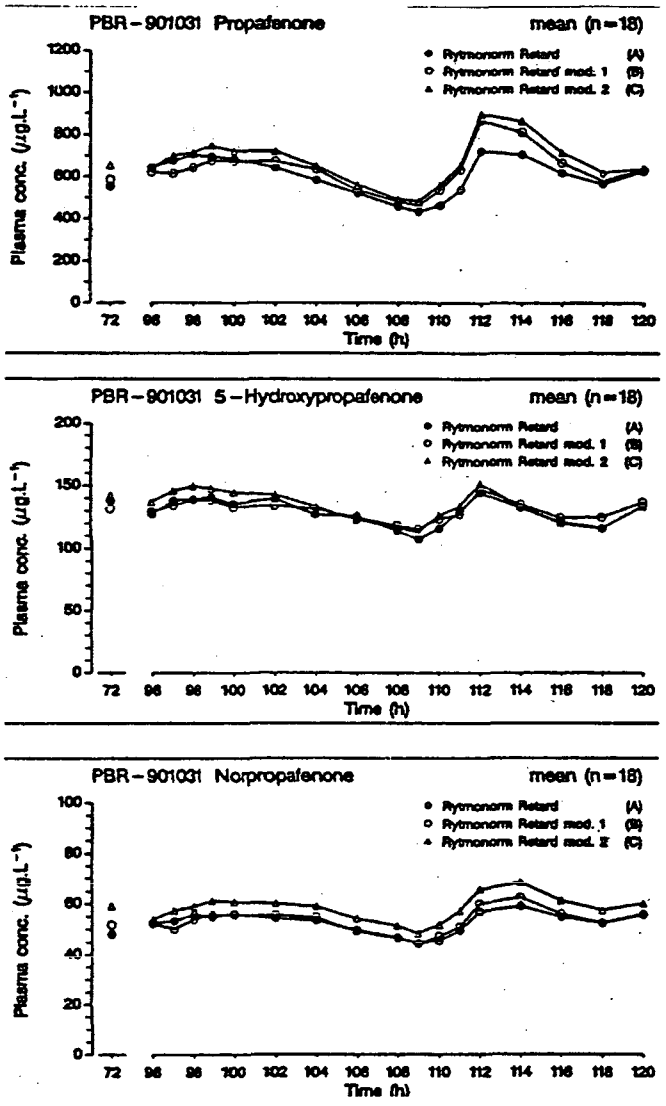

Figure 7.2.14. Plasma concentration vs time profiles of propafenone, 5-OH-propafenone and norpropafenone.

Pharmacokinetic parameters and summary statistics are shown in Tables 1.

This was not the bioequivalence study. However, the sponsor compared the three formulations based on the principle of bioequivalence.

Table 7.2.12. Pharmacokinetic parameters and summary statistics for propafenone (upper panel), 5-OH-propafenone and norpropafenone (lower panel).

Propafenone parameter		Treatment	Mean	SD	Range	90% confidence interval and point estimate of ratio (%)[a]	
C_{max}[a]	($\mu g \cdot L^{-1}$)	A	751				
		B	802			94 - 122	107
		C	895			105 - 136	119
C_{min}[a]	($\mu g \cdot L^{-1}$)	A	252				
		B	281			95 - 131	112
		C	270			91 - 126	108
t_{max}[b]	(h)	A	16				
		B	16				
		C	16				
AUC[a]	($\mu g \cdot L^{-1} \cdot h$)	A	11563				
		B	12191			95 - 117	105
		C	12770			100 - 122	110
$t_{1/2}$	(h)	A	9.92	6.91			
		B	8.92	5.20		70 - 110	90
		C	8.43	6.11		65 - 105	85
PTF	(%)	A	107.3	85.8			
		B	105.1	67.5		81 - 115	98
		C	121.1	81.5		96 - 130	113
AUCF	(%)	A	22.7	17.5			
		B	23.1	16.3		84 - 119	102
		C	25.3	15.8		94 - 129	111

Parameter		Treatment	Mean	Range	90% confidence interval and point estimate of ratio (%)[b]	
5-Hydroxypropafenone						
C_{max}[a]	($\mu g \cdot L^{-1}$)	A	136			
		B	141		98 - 109	103
		C	145		101 - 112	106
C_{min}[a]	($\mu g \cdot L^{-1}$)	A	87			
		B	90		86 - 112	104
		C	89		95 - 112	103
AUC[a]	($\mu g \cdot L^{-1} \cdot h$)	A	2673			
		B	2892		95 - 107	101
		C	2753		97 - 109	103
Norpropafenone						
C_{max}[a]	($\mu g \cdot L^{-1}$)	A	56			
		B	60		97 - 119	107
		C	64		103 - 127	114
C_{min}[a]	($\mu g \cdot L^{-1}$)	A	30			
		B	31		92 - 120	105
		C	31		92 - 121	106
AUC[a]	($\mu g \cdot L^{-1} \cdot h$)	A	1029			
		B	1087		97 - 115	106
		C	1123		100 -119	109

For both Cmax and AUC formulation B was bioequivalent to the reference formulation A, and formulation C was bioequivalent to the formulation A by AUC but not bioequivalent by Cmax.

There were differences between the first (day) and the second (night) dose interval. During the night, AUC, and Cmax were increased and in combination with lower Cmin, it led to an increase in fluctuation in plasma concentrations. The sponsor speculated that

possible explanation may be the change in posture during the night and therefore, increased absorption.
The effect of propafenone of the ECG parameters was assessed by comparison of PQ, QRS and QTc intervals at pre-dose, days 1-4 and on day 4 throughout the day
Mean parameter values all over the study similar at each time point for each treatment, however, statistical assessment of these parameters was not performed.

COMMENTS:

1. This study was designed to evaluate which of three formulations will be chosen for clinical development. Although this study was not designed as a bioequivalence study, the 90% confidence intervals constructed for the log-transformed parameters (AUC and Cmax) were calculated for propafenone, 5-OH-propafenone, and norpropafenone. For propafenone, formulation B was bioequivalent to the reference formulation A in regard to both Cmax and AUC. Formulation C was bioequivalent to the formulation A with regards to AUC but not to Cmax. Treatments B and C were bioequivalent to treatment A with regards to both metabolites (Cmax and AUC).

7.4 In vitro dissolution

Dissolution testing is performed in a medium simulating the conditions in the human gastrointestinal tract. After — dissolution in —— the pH of the dissolution medium is shifted to pH 6.8 —— Since physiological pH might vary, —— It was shown that drug release is independent of the pH of the dissolution medium. Dissolution of batch 282800A1 (325 mg) was investigated at different pHs (Figure 3). All dissolution curves lie within a small range and no trend with respect to pH could be observed.
Thus, drug release of Propafenone SR is independent of pH of the dissolution medium in the range investigated, representing physiological conditions.

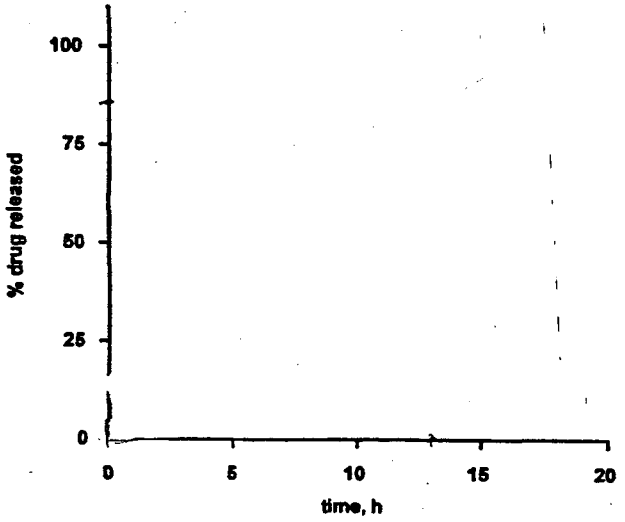

Figure 3.1. Influence of pH of the medium on dissolution rate (900 mL —— ph shift - —— 37°C, USP apparatus 2, 50 rpm, mean, N=6)

The conditions of the dissolution test (apparatus type and stirring speed, medium composition and pH, medium volume) have not changed during the development program.

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Dissolution test results for each dosage strengh are shown in the following Table 7.3.1.

Capsule 400mg

Batch Number	Single-Letter Code	Date of Manufacture of Granulation (month year)	Sample Times (h)	Mean Percent Label Claim Released	Range (%)
0005-01-A-1-VS	A	Jul 90	1	11	--
			2	19	
			3	30	
			4	37	
			5	43	
			6	48	
			7	52	
			8	56	
0005-02-A-1-VS	B	Jul 90	1	12	
			2	22	
			3	33	
			4	41	
			5	47	
			6	52	
			7	57	
			8	61	
0005-03-A-1-VS	C	Jul 90	1	18	
			2	29	
			3	43	
			4	52	
			5	59	
			6	65	
			7	70	
			8	74	

Capsule 425 mg

Batch Number	Single-Letter Code	Date of Manufacture (month year)	Sample Times (h)	Mean Percent Label Claim Released	Range (%)
101000A1	N	Jul 90	1	14	--
			2	26	
			3	37	
			4	46	
			5	58	
			6	65	
			7	72	
			8	78	
282100A1	O	Nov 91	1	10	
			4	43	
			15	93	
780101A0 (RYT-0367)	O	Mar 97	1	17	
			4	47	
			15	91	
780102A0	O	Mar 97	1	17	
			4	47	
			15	91	
980211A0 (RYT-0249)	O	Jan 99	1	14	
			4	49	
			15	94	
980212A0	O	Jan 99	1	14	
			4	49	
			15	94	

Capsule 325 mg

100900A1	I	Jul 90	1	13	--
			2	25	
			3	39	
			4	49	
			5	58	
			6	66	
			7	74	
			8	81	
282000A1	J	Nov 91	1	11	
			4	46	
			15	94	
780100A0 (RYT-0377)	J	Mar 97	1	13	
			4	49	
			15	96	
780200A0	J	Mar 97	1	14	
			4	48	
			15	95	
980311A0 (RYT-0239)	J	Jan 99	1	14	
			4	50	
			15	95	
980312A0	J	Jan 99	1	14	
			4	50	
			--	--	

Capsule 225 mg

100800A1	D	Jul 90	1	15	--
			2	29	
			3	43	
			4	54	
			5	63	
			6	72	
			7	80	
			8	86	
281900A1	E	Nov 91	1	10	
			4	45	
			15	90	
780101A0 (RYT-0507)	E	Mar 97	1	11	
			4	46	
			15	96	
780200A0 (RYT-0039)	E	Mar 97	1	15	
			4	48	
			15	99	
980310A0 (RYT-0229)	E	Jan 99	1	15	
			4	52	
			15	97	

The composition and dissolution of formulations used in clinical trials are identical to the to-be-marketed formulations. Dissolution data obtained from the Phase III clinical trials is similar in batch size to the proposed commercial scale up lots.

The sponsor's dissolution method:

Dosage Form, Strength	Capsules, 225, 325, 425 mg
Apparatus Type	Type 2 (Paddle), 50 RPM
Media	Phosphate buffer (pH 6.8)
Temperature, Volume	37°C, 900 mL
Specification	Q[ ]% at [ ]hour, Q[ ]% at 4 hours and Q[ ] at [ ]ours

The sampling frequency in the specification decreased in later studies, when —4, and — hours time points were selected.

There were three strengths of Rythmol (propafenone hydrochloride) SR Capsules -225 mg, 325 mg and 425 mg. The three strengths were manufactured by encapsulating a certain weight of microtablets (of a single formulation) into different size hard gelatin capsules. Three different capsule shell formulations have been used. Clinical trials were conduced with red-brown-white capsules, stability slides were conducted with blue/while capsules and the white/while capsules are proposed for marketing. To link the proposed market image (product and process) to the products used in the phase III clinical studies and to the formally reported stability data, 15-hour dissolution profiles of the three forms were compared. 15-Hour dissolution profiles of twelve capsules from one lot of each strength from each of the three formulation identification codes (nine samples) were generated. Comparative dissolution profiles of propafenone, consisting of one lot of each strength of capsules (N = 12 for all tests) are provided in Tables 7.3.2.-7.3.10 and Figures 7.3.1-7.3.4.

Table 7.3.2. Dissolution Data for Rythmol SR 225 mg Capsules, Formulation Identification Code 3060-K-53 (Capsules with light blue opaque cap and opaque white body).

KPC Lot RYT-0549, KAG Lot 980100A0, F.I.C. 3060-K-53 (light blue cap), 225 mg						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	9.08	22.50	48.58	80.83	97.17	103.00
SD	1.68	2.07	3.45	4.02	3.33	2.00
RSD	0.18	0.09	0.07	0.05	0.03	0.02
High						
Low						

Table 7.3.3. Dissolution Data for Rythmol SR 225 mg Capsules. Formulation Identification Code 3060-G-53 (Capsules with red-brown opaque cap and opaque white body).

KPC Lot RYT-0229, KAG Lot 980310A0, F. I. C. 3060-G-53 (red-brown capsules), 225 mg.						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	16.75	32.08	56.75	86.92	100.67	104.42
SD	0.75	3.18	2.63	3.12	3.39	3.29
RSD	0.05	0.10	0.05	0.04	0.03	0.03
High						
Low						

Table 7.3.4. Dissolution Data for Rythmol SR 225 mg Capsule, Formulation Identification Code 3060-N-53 (Capsules with white to off-white opaque cap and white to off-white body).

KPC Lot RYT-05700, KAG Lot 080100A0, F. I. C. 3060-N-53 (white to off-white cap), 225 mg

	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	14.83	29.00	52.67	83.50	98.33	103.42
SD	1.03	2.17	2.93	3.68	3.23	2.97
RSD	0.07	0.07	0.06	0.04	0.03	0.03
High						
Low						

Figure 7.3.1.

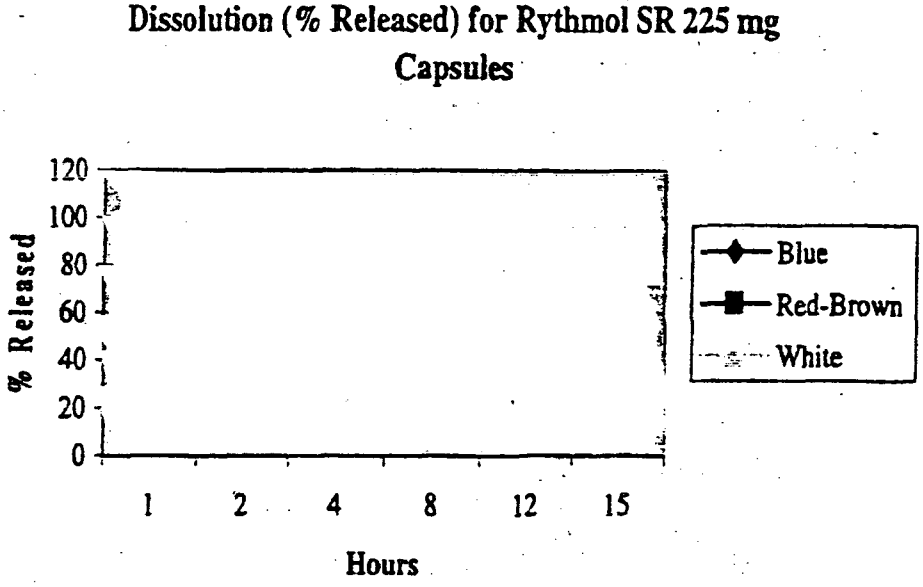


Table 7.3.5. Dissolution Data for Rythmol SR 325mg Capsules, Formulation Identification Code 3060- 5-53 (blue opaque cap with white opaque body).

KPC Lot RYT-0499, KAG Lot 980200A0, F.I.C. 3060-J-53 (blue cap), 325 mg						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	5.58	18.58	41.08	72.00	[illegible]	94.50
SD	4.08	7.32	8.70	8.70	6.87	5.82
RSD	0.73	0.39	0.21	0.12	0.08	0.06
High						
Low						

Table 7.3.6. Dissolution Data for Rythmol SR 325 mg Capsules, Formulation Identification Code 3060-F-53 (red-brown opaque cap with white opaque body).

KPC Lot RYT-0239, KAG Lot 980311A0, F. I. C. 3060-F-53 (red-brown cap), 325 mg						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	2.83	25.67	49.00	80.58	92.67	98.67
SD	1.40	2.19	3.02	6.47	2.93	3.73
RSD	0.11	0.09	0.06	0.08	0.03	0.04
High						
Low						

Table 7.3.7. Dissolution Data for Rythmol SR 325 mg Capsules, Formulation Identification Code 3060-M-53 (white to off-white opaque cap with white to off-white body).

KPC Lot-05600, KAG Lot 080100A0, F. I. C. 3060-M-53 (white to off-white cap), 325 mg.						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	15.58	28.33	51.33	81.58	95.17	99.42
SD	1.44	1.72	2.77	3.55	3.43	5.05
RSD	0.09	0.06	0.05	0.04	0.04	0.05
High						
Low						

Figure 7.3.2

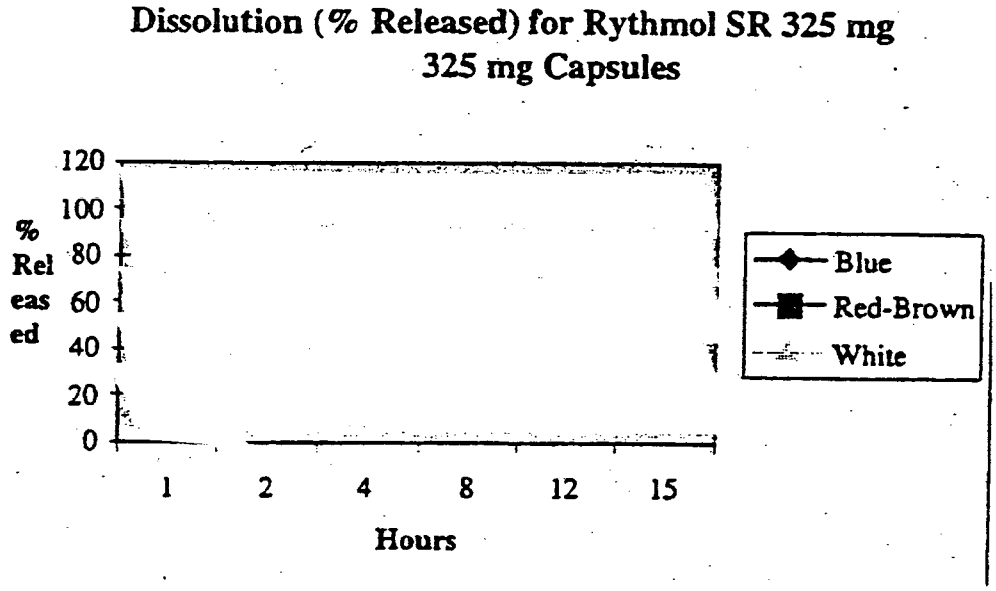


Table 7.3.8. Dissolution Data for Rythmol SR 425mg Capsules, Formulation Identification Code 3060-1-53 (Capsules with dark blue opaque cap and opaque white body).

KPC Lot RYT-0539, KAG Lot 980300A0, F. I. C. 3060-1-53 (dark blue cap), 425 mg						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	14.50	27.17	49.75	77.67	92.50	98.25
SD	1.78	1.64	3.41	3.82	3.37	2.93
RSD	0.12	0.06	0.07	0.05	0.04	0.03
High						
Low						

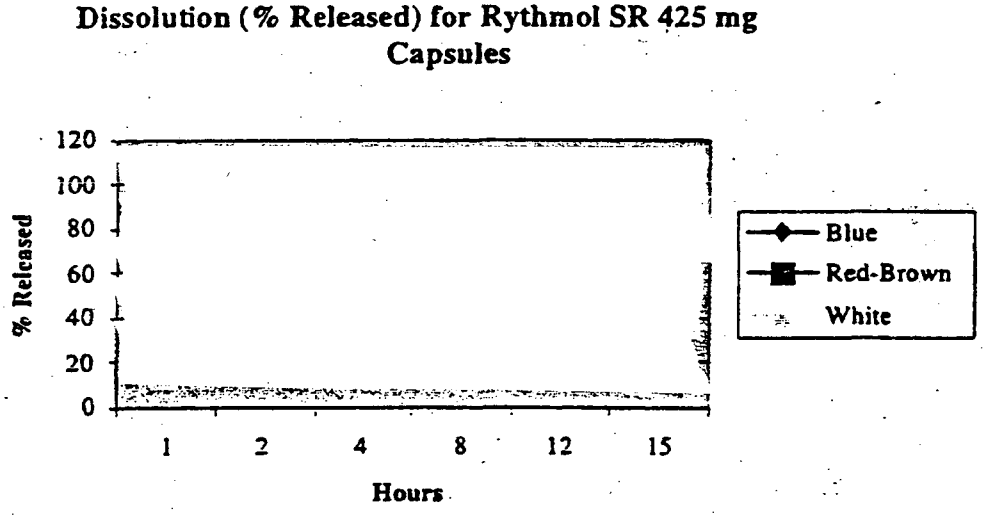
Table 7.3.9. Dissolution Data for Rythmol SR 425 mg Capsules, Formulation Identification Code 3060-E-53 (Capsules with red-brown opaque cap and opaque white body).

KPC Lot RYT-0249, KAG Lot 980211A0, F. I. C. 3060-E-53 (red-brown cap), 425 mg						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	13.67	26.58	47.75	76.33	88.33	96.75
SD	1.61	2.31	3.60	4.94	4.92	4.05
RSD	0.12	0.09	0.08	0.06	0.06	0.04
High						
Low						

Table 7.3.10. Dissolution Data for Rythmol SR 425 mg Capsules, Formulation Identification Code 3060-L-53 (Capsules with white to off-white cap and white to off-white body).

KPC Lot RYT-05500, KAG Lot 080100A0, F. I. C. 3060-L-53 (white to off-white cap), 425 mg						
	1-Hour	2-Hour	4-Hour	8-Hour	12-Hour	15-Hour
Mean	13.08	25.33	47.83	77.08	92.33	98.50
SD	1.68	1.15	1.99	2.94	3.39	3.58
RSD	0.13	0.05	0.04	0.04	0.04	0.04
High						
Low						

Figure 7.3.3.



These profiles are tested for similarity (f2). The f2 values ranged between — for the 225 capsules, — for the 325 capsules and — for the 425 capsules (Table 7.3.11.).

Table 7.3.11. Rythmol (propafenone hydrochloride) SR Capsules, f2 comparison values for
red-brown/white clinical products, blue/white registration stability product and white/white proposed market image product.

	225mg	325mg	425mg
Blue/white vs. red-brown/white opaque			
Red-brown/white vs. white/white opaque			
White/white vs. blue/white opaque			

COMMENTS:

The proposed dissolution method:

Apparatus Type	Type 2 (Paddle), 50 RPM
Media	Phosphate buffer (pH 6.8)
Temperature, Volume	37°C, 900 mL
Specification	Q[ ]% at – hour, Q[ ]% at 4 hours and Q[ ]% at – hours

is deemed acceptable.

However, since the drug is administered BID and according to the presented dissolution profiles, the specification should be corrected to Q[ ]% at 12 hours.

APPEARS THIS WAY
ON ORIGINAL

21 pages redacted from this section of the approval package consisted of draft labeling

7.6 Filing Memo

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-416	Brand Name	Rythmol SR
OCPB Division (I, II, III)	DIV-1	Generic Name	Propafenone HCL
Medical Division	CARDIORENAL	Drug Class	1C-ANTIARRYTHMIC AGENT
OCPB Reviewer	ELENA MISHINA	Indication(s)	VENTRICULAR ARRYTHMIA
OCPB Team Leader	GABRIEL ROBBIE	Dosage Form	225 mg, 325 mg, 425 mg CAPSULES
		Dosing Regimen	225 mg BID for the initial dose which may be titrated up to 425 mg BID
Date of Submission	MARCH 15, 2002	Route of Administration	ORAL
Estimated Due Date of OCPB Review	NOVEMBER 15, 2002	Sponsor	ABBOTT LABORATORIES
PDUFA Due Date	JANUARY 2003	Priority Classification	S
Division Due Date	JANUARY 2003		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		
multiple dose:	X	5		
Patients-				
single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				

PK/PD:				
Phase 1 and/or 2, proof of concept:	X	1		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:	X	1		
Bioequivalence studies -				
traditional design; single / multi dose:	X	2		
replicate design; single / multi dose:				
Food-drug interaction studies:	X	2		
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	6			

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	Are the extended release Rythmol capsules comparable with respect to PK and PD to immediate release propafenone?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-416, HFD-850(Lee), HFD-860(Marroum, Mehta, Mishina), Biopharm (CDER)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Elena Mishina
12/18/02 04:50:20 PM
BIOPHARMACEUTICS

Patrick Marroum
12/23/02 08:48:12 AM
BIOPHARMACEUTICS