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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-416

Pharmacology Review(s)

NDA 21-416 Rythmol® SR Capsules Abbott Laboratories

SUPERVISORY PHARMACOLOGIST'S REVIEW OF LABELING

C.A. Resnick, Ph.D.
11 August 2002

Documents Reviewed: Labeling dated 2 April 2002 submitted as amendment to NDA [N000(BL)]
Pharmacology/Toxicology review of NDA 21-416 by A.G. Proakis, Ph.D.

Sponsor's proposed labeling for Rythmol® SR Capsules is consistent with revised labeling we had requested for Rythmol® Tablets [see my reviews of NDA 19-151/S-005 dated 14 November 1998 (DDR stamp date 17 November 1998) and 22 June 1999 (DDR stamp date 30 June 1999) and our letters to Knoll Pharmaceutical Company dated 12 January 1999 and 28 August 2000]. Additional genetic toxicology studies have recently been performed and Dr. Proakis has addressed them in his review of NDA 21-416. Based on the results of those studies, Dr. Proakis has recommended revised wording for the **PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility** section of the labeling. I concur with his proposed revision and offer the following additional recommendations.

Under **PRECAUTIONS, Impaired Spermatogenesis,**

Under **PRECAUTIONS, Pregnancy,**

Non-teratogenic Effects:

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/s/

Charles Resnick
9/10/02 06:05:11 PM
PHARMACOLOGIST

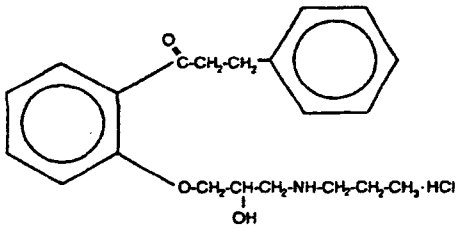
PHARMACOLOGY/TOXICOLOGY REVIEW COVER SHEET

NDA Number: 21,416
Review Number: 1
Date of Submission: 3/15/02 (Sponsor's letter date); 3/15/02 (Center receipt date)
Sponsor: Abbott Laboratories, Abbott Park , IL
Manufacturer for Drug Substance: Knoll GmbH, Ludwigshafen, Germany

Reviewer: Anthony G. Proakis, Ph.D.
Division: Cardio-Renal Drug Products (HFD-110)
Review Completion Date: 8/08/02

Drug Product: Rythmol® SR Capsules
Drug

Generic name: Propafenone HCl
Code name: BSF 29007
Chemical name: 2'-(2-hydroxy-3-propylaminopropoxy)-3-phenylpropiophenone hydrochloride
CAS registry number: 34183-22-7
Molecular formula; molecular weight: $C_{21}H_{27}NO_3.HCl$; 377.92
Structure:



Related NDA: 19,151 (Rythmol® Tablets)

Drug Class: Cardiac Antiarrhythmic

Indication:

Clinical Formulation: Rythmol® SR capsules are composed of prolonged release compressed microtablets of different dosage strengths containing the following:

	225 mg	325 mg	425 mg
Propafenone HCl Hypromellose Ph.Eur./ Hydroxypropyl methylcellulose USP Magnesium stearate PH.Eur./NF			
Filling weight	234 mg	338 mg	442 mg
Capsule size	1	0	0+

Route of Administration: Oral

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a preclinical perspective, this new drug application for Rythmol® SR Capsules (propafenone HCl) is approvable with the recommended changes in labeling.

B. Recommendations for Nonclinical Studies

None

C. Recommendations on Labeling

Statements in the sponsor's proposed labeling for Rythmol® SR Capsules that refer to non-clinical studies are the same as those for immediate release Rythmol® Tablets. Modification of the sponsor's proposed labeling is required to include the results of the additional genotoxicity studies covered by this review. Although the highest dose strength for Rythmol® SR Capsules (425mg) differs from that of Rythmol® Tablets (300 mg), the maximum recommended human daily dose [MRHD] is not substantially different for the two formulations (850 mg for the sustained release [425 mg BID] *vs* 900 mg for the immediate release [300 TID]). Thus, there is no need to correct the description of animal doses as multiples of the human dose. The human dose multiples noted in the non-clinical sections of the Rythmol® SR Capsule labeling should be identical to those that appear in the Rythmol® Tablet labeling.

Under the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the sponsor's proposed text for genotoxicity results reads as follows:

In order to include results from the additional genotoxicity studies, the text should be revised to read as follows:

Propafenone HCl tested negative for mutagenicity in the Ames (salmonella) test and the *in vivo* mouse dominant lethal test. It tested negative for clastogenicity in the human lymphocyte chromosome aberration assay *in vitro* and in rat and Chinese hamster micronucleus tests, and other *in vivo* tests for chromosomal aberrations in rat bone marrow and Chinese hamster bone marrow and spermatogonia.

II. Brief Overview of Nonclinical Findings

The sponsor refers to the preclinical pharmacology and toxicology studies previously used to support the safety of Rythmol® Tablets (NDA # 19,151) as support for the approval of Rythmol® SR Capsules. The sponsor further provides 3 additional genotoxicity studies (Ames test, human lymphocyte chromosome aberration assay and a rat bone marrow micronucleus test) conducted subsequent to the establishment of GLP regulations, which show propafenone HCl to be void of genotoxic potential.

Studies of the preclinical pharmacodynamics, drug disposition and toxicology of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84). The following is a brief summary of the most relevant findings.

Propafenone HCl is a cardiac antiarrhythmic and shares cardiac cell ion channel properties common to other Class I antiarrhythmic agents. In cardiac Purkinje fibers and cells, propafenone reduces the fast inward current carried by sodium ions and, thus induces delay in cardiac conduction and prolongs the effective refractory period. At very high concentrations, propafenone inhibits slow inward calcium current, but this action is weak (100-fold less potent than verapamil) and does not appear to contribute to the antiarrhythmic effect. Studies in anesthetized dogs and isolated organ preparations show that propafenone, with structural similarity to propranolol, possesses beta receptor blocking activity that is less pronounced than that of other beta blockers (about 1/50 the potency of propranolol).

Propafenone is almost completely (>80%) absorbed and extensively metabolized following oral administration to rats and dogs, with elimination primarily as metabolites in the urine, bile and feces. Propafenone is highly bound to rat and dog plasma (~ 98% with concentrations ≤ 2 mcg/ml).

Renal lesions were observed in the rat following 6 months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about 2 and 4 times, respectively, the maximum recommended human daily dose [MRHD] on a mg/m^2 basis). Both inflammatory and non-inflammatory effects in the renal tubules, with accompanying interstitial nephritis, were observed. These renal effects were reversible, as they were not found in rats allowed to recover for 6 weeks. No renal lesions were observed in rats given a dose of 90 mg propafenone HCl/kg/day.

Fatty degenerative lesions of the liver were found in rats following oral administration of propafenone HCl at a dose of 360 mg/kg/day for 6 months and at a dose of 270 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis) for 2 years.

No histopathological lesions were observed in dogs receiving oral doses of propafenone HCl up to 120 mg/kg/day (about 4 times the MRHD on a mg/m^2 basis) for 1 year.

Propafenone HCl, administered intravenously to rabbits, dogs and monkeys has been shown to decrease spermatogenesis. These effects were reversible with drug withdrawal, were not found following oral dosing of propafenone HCl, were seen at lethal or near lethal dose levels and were not seen in rats treated orally or intravenously. Treatment of male rabbits for 10 weeks prior to mating at an oral dose of 120 mg/kg/day (about 2.4 times the MRHD on a mg/m^2 basis) or an intravenous dose of 3.5 mg/kg/day (a spermatogenesis-impairing dose) did not result in evidence of impaired fertility. Nor was there evidence of impaired fertility when propafenone HCl was administered orally to male and female rats at dose levels up to 270 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis).

Propafenone has been shown to be embryotoxic (decreased survival) in rabbits and rats when given in oral maternally toxic doses of 150 mg/kg/day (about 3 times the MRHD on a mg/m^2 basis) and 600 mg/kg/day (about 6 times the MRHD on a mg/m^2 basis) respectively. Although maternally tolerated doses (up to 270 mg/kg/day, about 3 times the MRHD on a mg/m^2 basis) produced no evidence of embryotoxicity in rats, post-implantation loss was elevated in all rabbit treatment groups (doses as low as 15 mg/kg/day, about 1/3 the MRHD on a mg/m^2 basis). In a

study in which female rats received daily oral doses of propafenone HCl from mid-gestation through weaning of their offspring, doses as low as 180 mg/kg/day (about 2 times the MRHD on a mg/m^2 basis) produced increases in maternal deaths. Doses ≥ 360 mg/kg/day (4 or more times the MRHD on a mg/m^2 basis) resulted in reductions in neonatal survival, body weight gain and physiological development.

Propafenone was not carcinogenic when given orally to mice or rats for 2 years at maximally tolerated doses (2x and 3x the MRHD on a mg/m^2 basis). Nor was it genotoxic in a number of *in vitro* and *in vivo* assays for mutagenic and clastogenic activity.

III. Administrative

Reviewer signature: _____

Supervisor signature: Concurrence - _____

Non-Concurrence - _____
(see memo attached)

cc:
Orig: HFD-110
HFD-110/ Proj. Mgr.
HFD-110/AProakis
HFD-110/CResnick

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY

Studies of the preclinical cardiac antiarrhythmic and other pharmacodynamic actions of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84)

II. SAFETY PHARMACOLOGY

Studies of the preclinical safety pharmacology of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84)

I. PHARMACOKINETICS/TOXICOKINETICS

Studies of the preclinical pharmacokinetics and toxicokinetics of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84)

IV. GENERAL TOXICOLOGY

Studies of the preclinical toxicology of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84)

V. GENETIC TOXICOLOGY

Genetic toxicology studies were previously reviewed under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84). These studies (Ames test, dominant lethal test in mice, micronucleus assay in Chinese hamster bone marrow and rat bone marrow chromosome analysis) were conducted prior to GLP regulations and, for the purpose of this application, the sponsor has submitted the following genotoxicity studies that were conducted in compliance with GLP regulations.

Bacterial Mutagen (Ames) Assay (Vol 12, pg 5-252)

Study Facility: [redacted]
Study No: 381/55
Study Date: 2/08/01

GLP Compliance: Compliance with GLP regulations attested.
QA Report: Yes

Bacterial Strains: *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537.

Procedure: Propafenone HCl (BSF 29007; Batch # 67070 was dissolved in DMSO and added to triplicate cultures containing the bacterial tester strains in the presence and absence of S-9 fraction obtained from the livers of Aroclor-1254 treated rats. An initial experiment assessed the effects of propafenone HCl at concentrations up to 5000 ug/plate. In a repeat experiment, the maximum test dose for each tester strain

was selected based on toxic signs from the initial experiment (5000 ug/plate for TA 1535, 1000 ug/plate for TA 98, TA 100 and TA 1537 and 400 ug/plate for TA 102). DMSO was used as the negative (solvent) control. Positive controls included 2-nitrofluorene (2 NF; 5 ug/plate), sodium azide (NaN3; 2 ug/plate), 9-aminoacridine (AAC; 50 ug/plate), glutaraldehyde (GLU; 25 ug/plate), benzo[a]pyrene (B[a]P), 10 ug/plate and 2-aminoanthracene (AAN; 20 ug/plate). Following the addition of the test article, positive control or negative control, the plates were incubated at 37°C in the dark for 3 days. Following incubation, the plates were examined for evidence of cytotoxicity and the number of revertant colonies counted. The test article was considered to be positive for mutagenicity if it caused a significant dose-related and reproducible (in a repeat assay) increase ($p<0.01$; Dunnett's test) in the number of revertant colonies.

Results: In the initial experiment, propafenone HCl did not cause an increase in the number of revertant colonies for any tester strain in the absence or presence of metabolic activation (Tables 1 & 2). Cytotoxicity was evident in strain TA98, TA 1537 and TA 102 with propafenone HCl concentrations of 1000 and 5000 ug/plate. In strain TA 1535, cytotoxicity was seen with the 5000 ug/plate concentration.

In experiment 2, the tester strains were exposed to propafenone HCl concentrations that were selected based on cytotoxicity observed in the initial experiment. For TA 1535, 2000 ug/plate (with S-9) or 5000 ug/plate (without S-9) was used as the maximum test dose. The maximum test dose employed for the remaining strains was reduced to either 1000 ug/plate (for TA 98, TA 100 or TA 1537) or 400 ug/plate (for TA 102). In this experiment, propafenone HCl tested negative for mutagenicity, both in the absence and presence of metabolic activation (Tables 3 & 4). In both experiments, the positive controls caused significant increases in the number of revertant colonies.

Table 1

BSF 29007: summary of mean revertant colonies (-S-9) - Experiment 1

Substance	Dose Level µg/plate	TA98	TA100	TA1535	TA1537	TA102
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
DMSO	0 (100 µl)	46 ± 8	125 ± 11	20 ± 3	7 ± 5	334 ± 29
BSF 29007	1.6	42 ± 8	117 ± 4	21 ± 11	8 ± 1	370 ± 2
	8	55 ± 6	125 ± 11	19 ± 3	7 ± 3	358 ± 27
	40	54 ± 3	116 ± 17	17 ± 5	9 ± 5	342 ± 12
	200	45 ± 6	117 ± 3	25 ± 5	6 ± 4	267 ± 11 (S)
	1000	4 ± 4 (V)	10 ± 4 (S)	22 ± 11	- (T)	- (T)
	5000	- (T)	- (T)	- (T)	- (T)	- (T)
Positive controls	Compound	2NF	NaN3	NaN3	AAC	GLU
	Dose Level	5 µg	2 µg	2 µg	50 µg	25 µg
	Mean ± SD	733 ± 45	720 ± 48	442 ± 30	205 ± 19	680 ± 44

SD Standard deviation

2NF 2-Nitrofluorene
NaN3 Sodium azide
AAC 9-Aminoacridine
GLU Glutaraldehyde

S : Slight thinning of background lawn
T : Toxic, no revertant colonies
V : Very thin background lawn

Table 2.

BSF 29007: summary of mean revertant colonies (+S-9) - Experiment 1

Substance	Dose Level µg/plate	TA98	TA100	TA1535	TA1537	TA102
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
DMSO	0 (100 µl)	49 ± 10	117 ± 17	20 ± 4	10 ± 2	352 ± 26
BSF 29007	1.6	48 ± 6	147 ± 9	22 ± 6	10 ± 1	344 ± 24
	8	48 ± 12	143 ± 16	19 ± 2	9 ± 5	348 ± 16
	40	57 ± 8	141 ± 10	20 ± 7	16 ± 8	355 ± 16
	200	51 ± 3	135 ± 5	22 ± 6	8 ± 1	273 ± 13 (S)
	1000	9 ± 3 (S)	36 ± 4 (S)	15 ± 7	0 ± 0 (M)	27 ± 13 (M+V)
	5000	- (T)	- (T)	- (T)	- (T)	- (T)
Positive controls	Compound	B[a]P	AAN	AAN	AAN	AAN
	Dose Level	10 µg	5 µg	5 µg	5 µg	20 µg
	Mean ± SD	354 ± 13	2347 ± 437	185 ± 7	242 ± 12	1856 ± 214

SD Standard deviation

B[a]P Benzo[a]pyrene
AAN 2-Aminoanthracene

S : Slight thinning of background lawn
T : Toxic, no revertant colonies
V : Very thin background lawn
M : Plate counted manually

Table 3.

BSF 29007: summary of mean revertant colonies (-S-9) - Experiment 2

Substance	Dose Level µg/plate	TA98	TA100	TA1537	TA102	Dose Level µg/plate	TA1535
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD
DMSO	0 (100 µl)	44 ± 5	99 ± 6	8 ± 2 (M)	327 ± 40	0 (100 µl)	18 ± 4
BSF 29007	4.096	nt	nt	nt	270 ± 26	20.48	16 ± 6
	10.24	33 ± 1	96 ± 11	11 ± 4 (M)	251 ± 18	51.2	19 ± 5
	25.6	42 ± 17	94 ± 20	11 ± 3 (M)	295 ± 25	128	21 ± 9
	64	36 ± 6	103 ± 6	12 ± 6 (M)	292 ± 12	320	24 ± 6
	160	44 ± 3	101 ± 11	9 ± 4 (M)	263 ± 12	800	25 ± 7
	400	37 ± 10	105 ± 7	7 ± 2 (M)	133 ± 23	2000	14 ± 3 (S)
	1000	11 ± 1 (S)	19 ± 5 (S)	- (T)	nt	5000	- (T)
Positive controls	Compound	2NF	NaN3	AAC	GLU	Compound	NaN3
	Dose Level	5 µg	2 µg	50 µg	25 µg	Dose Level	2 µg
	Mean ± SD	916 ± 63	588 ± 32	49 ± 11 (M)	610 ± 73	Mean ± SD	484 ± 23

SD Standard deviation

GLU Glutaraldehyde
2NF 2-Nitrofluorene
NaN3 Sodium azide
AAC 9-Aminoacridine

nt : Not tested
S : Slight thinning of background lawn
T : Toxic, no revertant colonies
M : Plate counted manually

Table 4.

BSF 29007: summary of mean revertant colonies (+S-9) - Experiment 2

Substance	Dose Level µg/plate	TA98	TA100	TA1537	TA102	Dose Level µg/plate	TA1535
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD
DMSO	0 (50 µl)	53 ± 7	127 ± 8	14 ± 4 (M)	364 ± 20	0 (50 µl)	20 ± 3
BSF 29007	4.096	nt	nt	nt	388 ± 23	20.48	19 ± 10
	10.24	45 ± 6	118 ± 9	15 ± 4 (M)	372 ± 33	51.2	24 ± 7
	25.6	47 ± 6	111 ± 14	15 ± 4 (M)	373 ± 28	128	21 ± 1
	64	45 ± 10	123 ± 11	17 ± 6 (M)	329 ± 17	320	19 ± 6 (S)
	160	38 ± 10	114 ± 13	11 ± 4 (M)	278 ± 12 (S)	800	15 ± 5 (V)
	400	21 ± 3 (V)	89 ± 8	4 ± 2 (M+V)	67 ± 10 (M+V)	2000	- (T)
	1000	- (T)	- (T)	- (T)	nt	5000	nt
Positive controls	Compound	B[a]P	AAN	AAN	AAN	Compound	AAN
	Dose Level	10 µg	5 µg	5 µg	20 µg	Dose Level	5 µg
	Mean ± SD	348 ± 10	1315 ± 83	150 ± 9	2202 ± 107	Mean ± SD	115 ± 7

SD Standard deviation

AAN 2-Aminoanthracene
B[a]P Benzo[a]pyrene
nt Not tested

S : Slight thinning of background lawn
T : Toxic, no revertant colonies
V : Very thin background lawn
M : Plate counted manually

Human Peripheral Blood Lymphocyte Chromosome Aberration Assay (Vol 12, pg 5-198)

Study Facility: [redacted]
Study No: 381/58
Study Date: 7/26/00

GLP Compliance: Compliance with GLP regulations attested.
QA Report: Yes

Cell Culture: Human blood lymphocytes

Procedure: Propafenone HCl (BSF 29007; Batch # 67070) was dissolved in DMSO and added to duplicate cell cultures in the presence and absence of the S-9 fraction obtained from the livers of Aroclor-1254 treated rats. DMSO was used as the vehicle control. Cyclophosphamide (CPA) and 4-nitroquinolone (NQO) were used as the positive controls. In experiment 1, the cell cultures were exposed to propafenone HCl, solvent or positive controls in the absence and presence of metabolic activation for 3 hours followed by a 17 hr recovery period. The concentration levels of propafenone HCl for the test were selected by evaluating the drug's effect on mitotic index. The highest concentration of propafenone HCl chosen for assessment of chromosome aberration was 122.2 ug/ml, which induced 66% and 52% mitotic inhibition in the absence and presence of S-9, respectively (ICH guideline recommends at least 50% mitotic inhibition). In experiment 2, exposure of lymphocyte cells to the test agent was continuous for 20 hours in the absence of S-9. In the presence of S-9, treatment was for 3 hours followed by a 17 hr recovery period. The highest concentration of propafenone HCl for assessment of chromosome damage was 33.48 ug/ml in the absence of S-9 and 122.2 ug/ml in the presence of S-9; these concentrations induced 62% and 47% mitotic inhibition, respectively. (Although the mitotic inhibition in the presence of S-9 was slightly less than the ICH requirement of 50%, this same concentration produced >50% mitotic inhibition in the first experiment.) Approximately 2 hours prior to harvest, colchicine was added to the cell cultures to arrest the dividing cells in metaphase. The cells were fixed onto slides and one hundred metaphases from the vehicle control, positive control and each dose of test agent were analyzed for the presence of chromosome aberrations. The test agent was judged to be positive if the proportion of cells with structural aberrations at one or more concentrations was significantly higher than vehicle control (evidence of dose-related increase was considered useful but not essential).

Results: Treatment of the cell cultures with propafenone HCl in the absence and presence of S-9 in both experiments resulted in frequencies of cells with structural aberrations that were similar to those observed in concurrent vehicle control cultures (Tables 5-8). The positive controls induced significant increases above control frequencies of cells with chromosome aberrations.

Table 5.

3 hour treatment -S-9, 17 hour recovery (3+17), Experiment 1

Donor sex: male

Treatment (µg/mL)	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	Mitotic Index (mean)
0 (Solvent)	A	100	1	0	6.8
	B	100	5	2	8.2
	C	ND	ND	ND	8.5
	D	ND	ND	ND	8.0
	Totals	200	6	2	(7.9)
85.32	A	100	2	1	6.3
	B	100	2	0	6.7
	Totals	200	4	1	(6.5)
104.8	A	100	2	2	5.2
	B	100	1	1	5.5
	Totals	200	3	3	(5.4)
116.1	A	100	0	0	3.0
	B	100	3	3	6.0
	Totals	200	3	3	(4.5)
122.2	A	100	3	0	3.8
	B	94	6	3	1.6
	Totals	194	9	3	(2.7)
*NQO, 2.5	A	100	14	13	
	B	100	20	18	
	Totals	200	34	31[a]	

* 4-Nitroquinoline 1-oxide (NQO)
Binomial Dispersion Test $\chi^2 = 9.65$, not significant ($p \leq 0.05$ = significant)
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

Table 6.

3 hour treatment +S-9, 17 hour recovery (3+17), Experiment 1

Donor sex: male

Treatment (µg/mL.)	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	Mitotic Index (mean)
0 (Solvent)	A	100	2	1	9.9
	B	100	2	1	8.0
	C	ND	ND	ND	9.6
	D	ND	ND	ND	7.8
	Totals	200	4	2	(8.8)
81.05	A	100	0	0	7.3
	B	100	4	2	8.6
	Totals	200	4	2	(8.0)
104.8	A	100	4	2	5.9
	B	100	1	1	6.6
	Totals	200	5	3	(6.3)
122.2	A	100	1	0	4.2
	B	100	5	2	4.2
	Totals	200	6	2	(4.2)
*CPA, 12.5	A	100	45	41	
	B	100	29	19	
	Totals	200	74	60[a]	

* Cyclophosphamide (CPA)
Binomial Dispersion Test χ^2= 4.38, not significant ($p \leq 0.05$ = significant).
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

Table 7.

20 hour treatment -S-9, 0 hour recovery (20+0), Experiment 2

Donor sex: male

Treatment (µg/mL)	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	Mitotic Index (mean)
0 (Solvent)	A	100	0	0	8.5
	B	100	1	1	7.0
	C	ND	ND	ND	7.4
	D	ND	ND	ND	7.9
	Totals	200	1	1	(7.7)
24.41	A	100	1	1	7.7
	B	100	1	0	6.0
	Totals	200	2	1	(6.9)
27.12	A	100	3	0	5.0
	B	100	3	0	5.5
	Totals	200	6	0	(5.3)
33.48	A	100	2	1	3.2
	B	100	6	3	2.7
	Totals	200	8	4	(3.0)
*NQO, 5.0	A	71	41	35	
	B	100	52	43	
	Totals	171	93	78[a]	

* 4-Nitroquinoline 1-oxide (NQO)
Binomial Dispersion Test χ^2= 3.03, not significant ($p \leq 0.05$ = significant)
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

Table 8.

3 hour treatment +S-9, 17 hour recovery (3+17), Experiment 2
Donor sex: male

Treatment (µg/mL)	Replicate	Cells Scored	Cells with Aberrations Including Gaps	Cells with Aberrations Excluding Gaps	Mitotic Index (mean)
0 (Solvent)	A	100	0	0	5.2
	B	100	1	0	4.4
	C	ND	ND	ND	4.5
	D	ND	ND	ND	3.9
	Totals	200	1	0	(4.5)
81.05	A	100	1	1	3.9
	B	100	5	0	3.9
	Totals	200	6	1	(3.9)
104.8	A	100	3	3	3.7
	B	100	1	1	3.2
	Totals	200	4	4	(3.5)
122.2	A	100	4	2	2.4
	B	100	1	0	2.4
	Totals	200	5	2	(2.4)
*CPA, 6.25	A	100	17	14	
	B	100	14	9	
	Totals	200	31	23[a]	

* Cyclophosphamide (CPA)
Binomial Dispersion Test $\chi^2 = 4.05$, not significant ($p \leq 0.05$ = significant)
Note: solvent replicates C and D scored for mitotic index only
[a] Statistical significance $p \leq 0.001$
ND = not determined
Numbers highlighted exceed historical negative control range (Appendix 5)

Rat Micronucleus Assay (Vol 12, pg 5-306)

Study Facility: [redacted]
Study No: 381/57
Study Date: 6/22/00 – 8/14/00

GLP Compliance: Compliance with GLP regulations attested.
QA Report: Yes

Animals: Male Crl:HanWist (Glx:BRL) rats (241-281 gm) were housed in groups of no more than 4 rats/cage and maintained on rodent [redacted] Diet [redacted] and tap water *ad libitum.*

Drug Administration: Propafenone HCl (Batch # 67070) was suspended in 0.5% hydroxypropyl methylcellulose and administered orally by gavage. Cyclophosphamide (CPA) was used as the positive control.

Dose Levels: 0(vehicle), 50, 100 and 200 mg/kg (6 rats/group); Dose selection was based on a dose-rangefinding study which showed lethality at doses ≥ 350 mg/kg; clinical signs of toxicity after the 200 mg/kg dose included piloerection, lethargy, abnormal gait and protruding eyes.

Procedure: Rats were dosed once daily for 2 consecutive days with the test article or vehicle. The positive control, cyclophosphamide (CPA) was given as a single dose of 20 mg/kg on the 2nd day of dosing (6 rats). The animals were observed for clinical signs of toxicity during the treatment period. Twenty-four hours after CPA and the 2nd dose of test article or vehicle, the rats were killed by asphyxiation. A single femur from each animal was removed and the bone marrow extracted. The bone marrow suspension was placed onto slides, air dried and fixed. The number of polychromatic erythrocytes (PCEs) and normochromatic erythrocytes (NCEs) were counted from a total of at least 1000 cells to determine the PCE/NCE ratio to assess if there was any decrease in treated groups that could be taken as evidence of bone marrow toxicity. The number of PCEs with micronuclei was counted from at least 2000 PCEs. The group mean frequencies of micronucleated PCEs in each treated group was compared to the number of micronucleated PCEs in the vehicle control group. The test agent was considered to be positive in this assay if a statistically significant increase in the frequency of micronucleated PCEs occurred at one or more doses and if the frequency exceeded the historical vehicle control range.

Results: Propafenone HCl did not produce an increase above control frequency of micronucleated PCEs of the bone marrow of male rats treated with up to 200 mg/kg/day, a dose at which clinical signs of toxicity were seen (Table 9). The positive control, CPA, elicited a significant increase in the frequency of micronucleated PCEs compared to vehicle control. Thus, propafenone HCl was not clastogenic in this test system.

Table 9

Data for BSF 29007

Treatment group (mg/kg/day)	Time of sacrifice (hours)*	Mean ratio PCE/NCE	Group mean frequency of micronucleated PCE ± SD (per 1000 cells)
0 (Vehicle)	24	0.69	0.33 ± 0.41
50	24	0.76	0.17 ± 0.26
100	24	0.85	0.25 ± 0.27
200	24	0.89	0.21 ± 0.26
CPA, 20+	24	0.49	9.00 ± 2.51

+ Administered as a single oral dose
SD standard deviation, n=6
* Following the last dose administration

Genetic Toxicology Conclusions

The current submission for Rythmol® SR Capsules contains reports of recent genotoxicity studies in which propafenone HCl tested negative for mutagenicity (Ames test) and clastogenicity (human peripheral blood lymphocyte chromosome aberration assay and rat micronucleus assay). The findings from these studies (conducted in compliance with GLP regulations) are consistent with results of genotoxicity studies conducted with propafenone HCl prior to GLP regulations and described in the approved labeling for Rythmol® Tablets.

VI. CARCINOGENICITY

Rodent carcinogenicity studies of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84).

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Studies of the reproductive and developmental toxicology of propafenone HCl were reviewed previously under NDA # 19,151 for the currently approved Rythmol® Tablets (Review and Evaluation of Pharmacology and Toxicology Data, M.A. Commarato, 7/24/84)

VIII. SPECIAL TOXICOLOGY STUDIES: None

IX. CONCLUSIONS AND RECOMMENDATIONS

~~From a preclinical perspective, this new drug application for Rythmol® SR Capsules (propafenone HCl)~~ is approvable with the following changes in labeling.

Statements in the sponsor's proposed labeling for Rythmol® SR Capsules that refer to non-clinical studies are the same as those for immediate release Rythmol® Tablets. Modification of the sponsor's proposed labeling is required to include the results of the additional genotoxicity studies covered by this review. Although the highest dose strength for Rythmol® SR Capsules (425mg) differs from that of Rythmol® Tablets (300 mg), the maximum recommended human daily dose [MRHD] is not substantially different for the two formulations (850 mg for the sustained release [425 mg BID] *vs* 900 mg for the immediate release [300 TID]). Thus, there is no need to correct the description of animal doses as multiples of the human dose. The human dose multiples noted in the non-clinical sections of the Rythmol® SR Capsule labeling should be identical to those that appear in the Rythmol® Tablet labeling.

Under the **PRECAUTIONS** section, **Carcinogenesis, Mutagenesis, Impairment of Fertility** subsection, the sponsor's proposed text for genotoxicity results reads as follows:

In order to include results from the additional genotoxicity studies, the text should be revised to read as follows:

> Propafenone HCl tested negative for mutagenicity in the Ames (salmonella) test and the *in vivo* mouse dominant lethal test. It tested negative for clastogenicity in the human lymphocyte chromosome aberration assay *in vitro* and in rat and Chinese hamster micronucleus tests, and other *in vivo* tests for chromosomal aberrations in rat bone marrow and Chinese hamster bone marrow and spermatogonia.

X. APPENDICES/ATTACHMENTS: None

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/s/

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