CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-540

Name: Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg

Sponsor: Par Pharmaceutical, Inc.

Approval Date: October 18, 2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

CONTENTS

Reviews / Information Included in this Review

Approval Letter	**X**
Tentative Approval Letter	
Labeling	**X**
Labeling Reviews	**X**
Medical Reviews	
Chemistry Reviews	**X**
Bioequivalence Reviews	**X**
Statistical Reviews	
Microbiology Reviews	
Other Reviews	
Administrative & Correspondence Documents	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 078540

Par Pharmaceutical, Inc.
Attention: Julia Szozda
Submissions Manager, Regulatory Affairs
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated October 10, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg.

Reference is also made to your amendments dated January 10, February 7, June 1, and November 28, 2007; July 30, 2008; May 19, June 25, and July 16, 2009; and March 16, June 4, June 7, June 22, July 26, August 17, August 25, and September 8, 2010.

In addition, we acknowledge receipt of your correspondences dated November 9, 2006; February 22, July 19, 2007; and April 23, 2009, addressing the patent issues associated with this ANDA.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Rythmol SR Capsules 225 mg, 325 mg and 425 mg, respectively, of GlaxoSmithKline, LLC.

Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA. The "interim" dissolution specifications are as follows:

> The dissolution testing should be conducted in 900 mL of 0.08 M HCl for the first two (2) hours, followed by 1000 mL of pH 6.8 Phosphate Buffer for 2-12 hours, at 37°C ± 0.5°C using USP Apparatus II (paddle) @ 50 rpm (The second medium is obtained by adding a buffer concentrate to the initial HCl medium). The test product should meet the following "interim" specifications:

Time (Hours)	Percent Dissolved
1	(b) (4)
4	
12	

These "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement – Changes Being Effected" if there are no revisions to be made to the "interim" specifications, or if the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The RLD upon which you have based your ANDA, GSK's (formerly Reliant Pharmaceuticals Inc.) Rythmol SR Capsules, 225 mg, 325 mg, and 425 mg, is subject to a period of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent No. 5,681,588 (the '588 patent), is scheduled to expire on October 28, 2014.

Your ANDA contains a paragraph IV certification to the '588 patent under section 505(j)(2)(A)(vii)(IV) of the Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately, unless an action was brought against Par Pharmaceutical, Inc. (Par) for infringement of the listed '588 patent. You have notified the agency that Par complied with the requirements of section 505(j)(2)(B) of the Act, and that litigation for infringement of the '588 patent was brought against Par within the statutory 45-day period in the United

States District Court for the District of Delaware [Reliant Pharmaceuticals, Inc., v. Par Pharmaceutical, Inc., Civil Action No. 06-774]. You have also notified the agency that the litigation was dismissed; therefore, under section 505(j)(5)(B)(iii) your ANDA is eligible for approval.

With respect to 180-day generic drug exclusivity for Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg, we note that Par was the first ANDA applicant to submit a substantially complete ANDA for Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg with a paragraph IV certification to the '588 patent. Therefore, with this approval, Par may be eligible for 180-days of generic drug exclusivity for Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg. This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, begins to run from the date of commercial marketing identified in section 505(j)(5)(B)(iv). Please submit correspondence to this ANDA informing the agency of the date commercial marketing begins. The agency notes that Par failed to obtain tentative approval of this ANDA within 30 months after the date on which the ANDA was filed. See section 505(j)(5)(D)(i)(IV) of the Act. However, the agency is not making a formal determination at this time of Par's eligibility for 180-day generic drug exclusivity. It will do so only if another applicant becomes eligible for approval within 180 days after Par begins commercial marketing of Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed

launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

{See appended electronic signature page}

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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

/s/

ROBERT L WEST

10/18/2010

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

LABELING

NDC 49884-209-02

Propafenone Hydrochloride Extended Release Capsules

225 mg

Rx only

60 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 225 mg

Contains FD&C Yellow No.5 (tartrazine) as a color additive.

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.: LA209-02-1-01

Exp. Date: 05/07

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

3 49884-209-02 5

NDC 49884-209-01

Propafenone Hydrochloride Extended Release Capsules

225 mg

Rx only

100 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 225 mg

Contains FD&C Yellow No.5 (tartrazine) as a color additive.

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.: LA209-01-1-01

Exp. Date: 105/07

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-209-01 8

NDC 49884-209-05

Propafenone Hydrochloride Extended Release Capsules

225 mg

Rx only

500 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 225 mg

Contains FD&C Yellow No.5 (tartrazine) as a color additive.

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

LA209-05-1-01

Control No.:

Exp. Date:

105/07

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-209-05 6

NDC 49884-209-10

Propafenone Hydrochloride Extended Release Capsules

225 mg

Rx only

1000 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 225 mg

Contains FD&C Yellow No.5 (tartrazine) as a color additive.

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.: LA209-10-1-01

Exp. Date: 105/07

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

NDC 49884-210-02

Propafenone Hydrochloride Extended Release Capsules

325 mg

Rx only

60 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 325 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.: LA210-02-1-01

Exp. Date: 05/07

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-210-02 1

NDC 49884-210-01

Propafenone Hydrochloride Extended Release Capsules

325 mg

Rx only

100 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 325 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.:

Exp. Date:

I05/07

LA210-01-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-210-01 4

NDC 49884-210-05

Propafenone Hydrochloride Extended Release Capsules

325 mg

Rx only

500 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 325 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.:

Exp. Date:

105/07

LA210-05-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

3 49884-210-05 2

NDC 49884-210-10

Propafenone Hydrochloride Extended Release Capsules

325 mg

Rx only

1000 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 325 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.:

Exp. Date:

105/07

LA210-10-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-210-10 6

NDC 49884-211-02

Propafenone Hydrochloride Extended Release Capsules

425 mg

Rx only

60 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 425 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.: LA211-02-1-01

Exp. Date: 05/07

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-211-02 8

NDC 49884-211-01

Propafenone Hydrochloride Extended Release Capsules

425 mg

Rx only

100 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 425 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.:

Exp. Date:

I05/07

LA211-01-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-211-01 1

NDC 49884-211-05

Propafenone Hydrochloride Extended Release Capsules

425 mg

Rx only

500 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 425 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.:

Exp. Date:

I05/07

LA211-05-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

N 3 49884-211-05 9

NDC 49884-211-10

Propafenone Hydrochloride Extended Release Capsules

425 mg

Rx only

1000 Capsules

PAR PHARMACEUTICAL

Each capsule contains:
Propafenone hydrochloride ..... 425 mg

USUAL DOSAGE:
One capsule every 12 hours. See accompanying prescribing information.

KEEP THIS AND ALL DRUGS OUT OF REACH OF CHILDREN.

Do not accept if seal over bottle opening is broken or missing.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Control No.:

Exp. Date:

105/07

LA211-10-1-01

Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

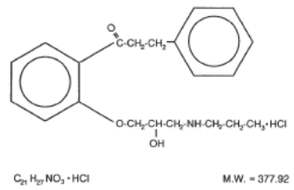
PROPAFENONE HYDROCHLORIDE EXTENDED RELEASE CAPSULES

Rx only

DESCRIPTION

Propafenone hydrochloride is an antiarrhythmic drug supplied in extended-release capsules of 225 mg, 325 mg and 425 mg for oral administration.

The structural formula of propafenone HCl is given below:



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

2'-[2-Hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride

Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone HCl occurs as colorless crystals or white crystalline powder with a very bitter taste. It is slightly soluble in water (20ºC), chloroform and ethanol. Propafenone extended release are capsules filled with granules containing the following inactive ingredients: ethylcellulose, lactose anhydrous, magnesium stearate and povidone. The capsules consist of D&C Red #28, FD&C Blue #1, FD&C Red #40, FD&C Yellow #5, FD&C Yellow #6, gelatin and titanium dioxide. In addition the ink consists of D&C Yellow #10 aluminum lake, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, FD&C Blue #1 aluminum lake and shellac glaze~45% (20% esterfied) in ethanol.

CLINICAL PHARMACOLOGY

Mechanism of Action:
Propafenone is a Class 1C antiarrhythmic drug with local anesthetic effects, and a direct stabilizing action on myocardial membranes. The electrophysiological effect of propafenone 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, propafenone reduces the fast inward current carried by sodium ions. Diastolic excitability threshold is increased and effective refractory period prolonged. Propafenone reduces spontaneous automaticity and depresses triggered activity.

Studies in anesthetized dogs and isolated organ preparations show that propafenone has beta-sympatholytic activity at about 1/50 the potency of propranolol. Clinical studies employing isoproterenol challenge and exercise testing after single doses of propafenone indicate a beta-adrenergic blocking potency (per mg) about 1/40 that of propranolol in man. In clinical trials with the immediate release formulation, resting heart rate decreases of about 8% were noted at the higher end of the therapeutic plasma concentration range. At very high concentrations *in vitro*, propafenone can inhibit the slow inward current carried by calcium, but this calcium antagonist effect probably does not contribute to antiarrhythmic efficacy. Moreover, propafenone inhibits a variety of cardiac potassium currents in *in vitro* studies (i.e. the transient outward, the delayed rectifier, and the inward rectifier current). Propafenone has local anesthetic activity approximately equal to procaine. Compared to propafenone, the main metabolite, 5-hydroxypropafenone, has similar sodium and calcium channel activity, but about 10 times less beta-blocking activity (N-depropylpropafenone has weaker sodium channel activity but equivalent affinity for beta-receptors).

Electrophysiology:
Electrophysiology studies in patients with ventricular tachycardia (VT) have shown that propafenone prolongs atrioventricular (AV) conduction while having little or no effect on sinus node function. Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone has little or no effect on the atrial functional refractory period, but AV nodal functional and effective refractory periods are prolonged. In patients with Wolff-Parkinson-White (WPW) syndrome, propafenone hydrochloride immediate release tablets reduce conduction and increase the effective refractory period of the accessory pathway in both directions (see **ADVERSE REACTIONS/ Electrocardiograms**).

Hemodynamics:
Studies in humans have shown that propafenone exerts a negative inotropic effect on the myocardium. Cardiac catheterization studies in patients with moderately impaired ventricular function (mean C.I.=2.61 L/min/m^2), utilizing intravenous propafenone infusions (loading dose of 2 mg/kg over 10 min+ followed by 2 mg/min for 30 min) that gave mean plasma concentrations of 3.0 mcg/mL (a dose that produces plasma levels of propafenone greater than does recommended oral dosing), showed significant increases in pulmonary capillary wedge pressure, systemic and pulmonary vascular resistances and depression of cardiac output and cardiac index.

Pharmacokinetics and Metabolism:
Absorption/Bioavailability
Maximal plasma levels of propafenone are reached between three to eight hours following the administration of propafenone extended release capsules. Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose and dosage form dependent absolute bioavailability; e.g., a 150 mg immediate release tablet had an absolute bioavailability of 3.4%, while a 300 mg immediate release tablet had an absolute bioavailability of 10.6%. Absorption from a 300 mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate release tablets increased still further.

Relative bioavailability assessments have been performed between propafenone ER capsules and propafenone HCl immediate release tablets. In extensive metabolizers, the bioavailability of propafenone from the ER formulation was less than that of the immediate release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase of overall first pass metabolism (see **Metabolism**). As a result of the increased first pass effect, higher daily doses of propafenone were required from the ER formulation relative to the immediate release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 mg twice daily regimens of propafenone ER approximates that of propafenone HCl immediate release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20-25% higher after ER capsule administration than after immediate-release tablet administration.

Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of propafenone ER capsules. However, in the multiple dose study (425 mg dose BID), the difference between the fed and fasted state was not significant.

Distribution
Following intravenous administration of propafenone, plasma levels decline in a bi-phasic manner consistent with a two compartment pharmacokinetic model. The average distribution half-life corresponding to the first phase was about five minutes. The volume of the central compartment was about 88 liters (1.1 L/kg) and the total volume of distribution about 252 liters.

In serum, propafenone is greater than 95% bound to proteins within the concentration range of 0.5 - 2 mcg/mL. Protein binding decreases to about 88% in patients with severe hepatic dysfunction.

Metabolism
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 from 2-10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10-32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers.

As a consequence of the observed differences in metabolism, administration of propafenone ER capsules to slow and extensive metabolizers results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about three to four times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of propafenone ER capsules. In slow metabolizers, propafenone pharmacokinetics are linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady state conditions are achieved after four to five days of dosing in all patients, the recommended dosing regimen of propafenone ER capsules is the same for all patients. The large inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity (see **DOSAGE AND ADMINISTRATION**).

The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone *in vitro*. In man after administration of propafenone ER capsules, the 5-hydroxypropafenone metabolite is usually present in concentrations less than 40% of propafenone. The norpropafenone metabolite is usually present in concentrations less than 10% of propafenone.

Inter-Subject Variability:
With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of propafenone ER capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.

The clearance of propafenone is reduced and the elimination half-life increased in patients with significant hepatic dysfunction (see **PRECAUTIONS**). Decreased liver function also increases the bioavailability of propafenone. Absolute bioavailability assessments have not been determined for the propafenone ER capsule formulation. Absolute bioavailability of propafenone HCl immediate release tablets has been demonstrated to be inversely related to indocyanine green clearance, reaching 60-70% at clearances of 7 mL/min and below.

Stereochemistry:
Propafenone ER capsule 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 ß-antagonist than the R-enantiomer. Following administration of propafenone HCl immediate release tablets or propafenone ER capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R ratios of propafenone obtained after administration of 225, 325 and 425 mg propafenone ER capsules are independent of dose. In addition, no difference in the average values of the S/R ratios is evident between genotypes or over time.

Clinical Trials:
Propafenone ER capsules has been evaluated in patients with a history of electrocardiographically documented recurrent episodes of symptomatic atrial fibrillation in two randomized, double-blind, placebo controlled trials.

RAFT
In one U.S. multicenter study (propafenone ER capsules Atrial Fibrillation Trial, RAFT), three doses of propafenone ER capsules (225 mg BID, 325 mg BID and 425 mg BID) and placebo were compared in 523 patients with symptomatic, episodic atrial fibrillation. The patient population in this trial was 59% male with a mean age of 63 years, 91% White and 6% Black. The patients had a median history of atrial fibrillation of 13 months, and documented symptomatic atrial fibrillation within 12 months of study entry. Over 90% were NYHA Class I, and 21% had a prior electrical cardioversion. At baseline, 24% were treated with calcium channel blockers, 37% with beta blockers, and 38% with digoxin. Symptomatic arrhythmias after randomization were documented by transtelephonic electrocardiogram and centrally read and adjudicated by a blinded adverse event committee. Propafenone ER capsules administered for up to 39 weeks was shown to prolong significantly the time to the first recurrence of symptomatic atrial arrhythmia, predominantly atrial fibrillation, from Day 1 of randomization (primary efficacy variable) compared to placebo, as shown in **Table 1**.

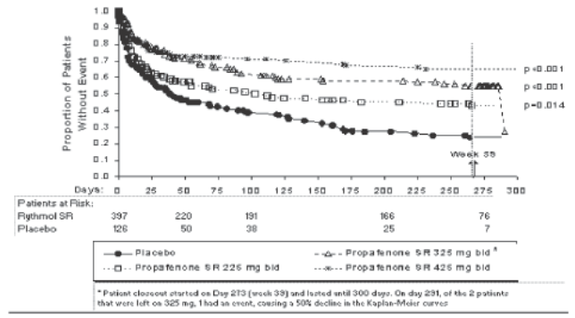
Table 1: Analysis of tachycardia-free period (days) from Day 1 randomization

	Propafenone ER Dose			
Parameter	225 mg BID (N = 126) n (%)	325 mg BID (N = 135) n (%)	425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
Patients completing with terminating event†	66 (52)	56 (41)	41 (30)	87 (69)
Comparison of tachycardia-free periods				
Kaplan-Meier Median	112	291	*	41
Range	0–285	0–293	0–300	0–289
p-Value (Log-rank test)	0.014	<0.0001	<0.0001	--
Hazard Ratio compared to placebo	0.67	0.43	0.35	--
95% CI for Hazard Ratio	(0.49, 0.93)	(0.31, 0.61)	(0.24, 0.51)	--

*Fewer than 50% of the patients had events. The median time is not calculable.
†Terminating events comprised 91% atrial fibrillation, 5% atrial flutter, and 4% PSVT.

There was a dose response for propafenone ER for the tachycardia-free period as shown in the proportional hazard analysis and the Kaplan-Meier curves presented in **Figure 1**.

Figure 1: RAFT Kaplan-Meier Analysis for the Tachycardia-free period from Day 1 of randomization:



In additional analyses, propafenone ER capsules (225 mg BID, 325 mg BID, and 425 mg BID) was also shown to prolong time to the first recurrence of symptomatic atrial fibrillation from Day 5 (steady state pharmacokinetics were attained). The antiarrhythmic effect of propafenone ER capsules was not influenced by age, gender, history of cardioversion, duration of atrial fibrillation, frequency of atrial fibrillation or use of medication that lowers heart rate. Similarly, the antiarrhythmic effect of propafenone ER capsules was not influenced by the individual use of calcium channel blockers, beta-blockers or digoxin. Too few non-White patients were enrolled to assess the influence of race on effects of propafenone ER capsules (propafenone hydrochloride).

No difference in the average heart rate during the first recurrence of symptomatic arrhythmia between propafenone ER capsules and placebo was observed.

ERAFT
In a European multicenter trial [(European Rythmonorm SR Atrial Fibrillation Trial (ERAFT)], two doses of propafenone ER capsules (325 mg BID and 425 mg BID) and placebo were compared in 293 patients. The patient population in this trial was 61% male, 100% White with a mean age of 61 years. Patients had a median duration of atrial fibrillation of 3.3 years, and 61% were taking medications that lowered heart rate. At baseline, 15% of the patients were treated with calcium channel blockers (verapamil and diltiazem), 42% with beta-blockers and 8% with digoxin. During a qualifying period of up to 28 days, patients had to have one ECG-documented incident of symptomatic atrial fibrillation. The double-blind treatment phase consisted of a four day loading period followed by a 91-day efficacy period. Symptomatic arrhythmias were documented by electrocardiogram monitoring.

In ERAFT, propafenone ER capsules were shown to prolong the time to the first recurrence of symptomatic atrial arrhythmia from Day 5 of randomization (primary efficacy analysis). The proportional hazard analysis revealed that both propafenone ER capsules doses were superior to placebo. The antiarrhythmic effect of propafenone ER was not influenced by age, gender, duration of atrial fibrillation, frequency of atrial fibrillation or use of medication that lowers heart rate. It was also not influenced by the individual use of calcium channel blockers, beta-blockers or digoxin. Too few non-White patients were enrolled to assess the influence of race on the effects of propafenone ER capsules. There was a slight increase in the incidence of centrally diagnosed asymptomatic atrial fibrillation or atrial flutter in each of the two propafenone ER capsules treatment groups compared to placebo.

INDICATIONS AND USAGE

Propafenone Extended Release Capsules are indicated to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease.

The use of propafenone ER capsules in patients with permanent atrial fibrillation or in patients exclusively with atrial flutter or PSVT has not been evaluated. Propafenone ER capsules should not be used to control ventricular rate during atrial fibrillation.

The effect of propafenone ER capsules on mortality has not been determined (see black box **WARNINGS**).

CONTRAINDICATIONS

Propafenone ER capsules are contraindicated in the presence of congestive heart failure, cardiogenic shock, sinoatrial, atrioventricular and intraventricular disorders of impulse generation or conduction (e.g., sick sinus node syndrome, atrioventricular block) in the absence of an artificial pacemaker, bradycardia, marked hypotension, bronchospastic disorders, electrolyte imbalance, or hypersensitivity to the drug.

WARNINGS

Mortality:
In the National Heart, Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term, multi-center, randomized, double-blind study in patients with asymptomatic non-life-threatening ventricular arrhythmias who had a myocardial infarction more than six days but less than two years previously, an increased rate of death or reversed cardiac arrest rate (7.7%; 56/730) was seen in patients treated with encainide or flecainide (Class 1C antiarrhythmics) compared with that seen in patients assigned to placebo (3.0%; 22/725). The average duration of treatment with encainide or flecainide in this study was ten months.

The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) or other antiarrhythmic drugs is uncertain, but at present, it is prudent to consider any 1C antiarrhythmic to have a significant risk in patients with structural heart disease. Given the lack of any evidence that these drugs improve survival, antiarrhythmic agents should generally be avoided in patients with non-life-threatening ventricular arrhythmias, even if the patients are experiencing unpleasant, but not life-threatening, symptoms or signs.

Proarrhythmic Effects:
Propafenone has caused new or worsened arrhythmias. Such proarrhythmic effects include sudden death and life-threatening ventricular arrhythmias such as ventricular fibrillation, ventricular tachycardia, asystole and Torsade de Pointes. It may also worsen premature ventricular contractions or supraventricular arrhythmias, and it may prolong the QT interval. It is therefore essential that each patient given propafenone ER capsules be evaluated electrocardiographically prior to and during therapy, to determine whether the response to propafenone ER capsules supports continued treatment. Because propafenone prolongs the QRS interval in the electrocardiogram, changes in the QT interval are difficult to interpret.

In a 474 patient U.S. uncontrolled, open label multicenter trial using the immediate release formulation in patients with symptomatic SVT, 1.9% (9/474) of these patients experienced ventricular tachycardia (VT) or ventricular fibrillation (VF) during the study. However, in four of the nine patients, the ventricular tachycardia was of atrial origin. Six of the nine patients that developed ventricular arrhythmias did so within 14 days of onset of therapy. About 2.3% (11/474) of all patients had recurrence of SVT during the study which could have been a change in the patients' arrhythmia behavior or could represent a proarrhythmic event. Case reports in patients treated with propafenone HCl for atrial fibrillation/flutter have included increased PVCs, VT, VF, Torsade de Pointes, asystole, and death.

In the RAFT study, there were five deaths, three in the pooled propafenone ER capsules group (0.8%) and two in the placebo group (1.6%). In the overall propafenone ER capsules and propafenone HCl immediate release database of eight studies, the mortality rate was 2.5% per year on propafenone HCl and 4% per year on placebo. Concurrent use of propafenone with other antiarrhythmic agents has not been well studied.

Use with Drugs that Prolong the QT Interval and Antiarrhythmic Agents:
The use of propafenone ER capsules (propafenone hydrochloride) in conjunction with other drugs that prolong the QT interval has not been extensively studied and is not recommended. Such drugs may include many antiarrhythmics, some phenothiazines, cisapride, bepridil, tricyclic antidepressants and oral macrolides. Class Ia and III antiarrhythmic agents should be withheld for at least five half-lives prior to dosing with propafenone ER capsules. The use of propafenone with Class Ia and III antiarrhythmic agents (including quinidine and amiodarone) is not recommended. There is only limited experience with the concomitant use of Class Ib or Ic antiarrhythmics.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema):
Patients with bronchospastic disease should not, in general, receive propafenone or other agents with beta-adrenergic-blocking activity.

Congestive Heart Failure:
Propafenone exerts a negative inotropic activity on the myocardium as well as beta-blockade effects and may provoke overt congestive heart failure. In the U.S. trial (RAFT) in patients with symptomatic atrial fibrillation, congestive heart failure was reported in four (1%) patients receiving propafenone ER capsules (all doses), compared to one (0.8%) patient receiving placebo. Proarrhythmic effects are more likely to occur when propafenone is administered to patients with congestive heart failure (NYHA III and IV) or severe myocardial ischemia (see **CONTRAINDICATIONS**).

Conduction Disturbances:
Propafenone causes dose-related first degree AV block. Average PR interval prolongation and increases in QRS duration are also dose-related.

Propafenone should not be given to patients with atrioventricular and intraventricular conduction defects in the absence of a pacemaker (see **CONTRAINDICATIONS**).

In a U.S. trial (RAFT) in 523 patients with a history of symptomatic atrial fibrillation treated with propafenone ER capsules, electrocardiograms obtained in response to symptoms were associated with no patients having sinus rhythm with Mobitz Type I (Wenckenbach) second degree AV block, sinus rhythm with Mobitz Type II second degree AV block, or third degree AV block. Sinus bradycardia (rate <50 beats/min) was reported with the same frequency with propafenone ER capsules and placebo.

Effects on Pacemaker Threshold:
Propafenone may alter both pacing and sensing thresholds of artificial pacemakers. Pacemakers should be monitored and programmed accordingly during therapy.

Hematologic Disturbances:
Agranulocytosis (fever, chills, weakness, and neutropenia) has been reported in patients receiving propafenone. Generally, the agranulocytosis occurred within the first two months of propafenone therapy and upon discontinuation of therapy, the white count usually normalized by 14 days. Unexplained fever and/or decrease in white cell count, particularly during the initial three months of therapy, warrant consideration of possible agranulocytosis or granulocytopenia. Patients should be instructed to report promptly the development of any signs of infection such as fever, sore throat, or chills.

PRECAUTIONS

Hepatic Dysfunction:
Propafenone is highly metabolized by the liver and should, therefore, be administered cautiously to patients with impaired hepatic function. Severe liver dysfunction increases the bioavailability of propafenone to approximately 70% compared to 3-40% in patients with normal liver function when given propafenone HCl immediate release tablets. In eight patients with moderate to severe liver disease administered propafenone HCl immediate release tablets, the mean half-life was approximately nine hours. No studies are currently available comparing bioavailability of propafenone from propafenone ER capsules in patients with normal and impaired hepatic function. Increased bioavailability of propafenone in these patients may result in excessive accumulation. Careful monitoring for excessive pharmacological effects (see **OVERDOSAGE**) should be performed for patients with impaired hepatic function.

Renal Dysfunction:
Approximately 50% of propafenone metabolites are excreted in the urine following administration of propafenone HCl immediate release tablets. No studies have been performed to assess the percentage of metabolites eliminated in the urine following the administration of propafenone ER capsules.

Until further data are available, propafenone ER capsules should be administered cautiously to patients with impaired renal function. These patients should be carefully monitored for signs of overdosage (see **OVERDOSAGE**).

Information for Patients:
Medications and Supplements:
Assessment of patients' medication history should include all over-the-counter, prescription and herbal/natural preparations with emphasis on preparations that may affect the pharmacodynamics or kinetics of propafenone ER capsules (see **WARNINGS/Use with Drugs that Prolong QT Interval and Antiarrhythmic Agents**). Patients should be instructed to notify their health care providers of any change in over-the-counter, prescription and supplement use. If a patient is hospitalized or is prescribed new medication for any condition, the patient must inform the health care provider of ongoing propafenone ER capsules therapy. Patients should also check with their health care providers prior to taking a new over-the-counter medicine.

Electrolyte Imbalance:
If patients experience symptoms that may be associated with altered electrolyte balance, such as excessive or prolonged diarrhea, sweating, vomiting, or loss of appetite or thirst, these conditions should be immediately reported to their health care provider.

Dosing Schedule:
Patients should be instructed NOT to double the next dose if a dose is missed. The next dose should be taken at the usual time.

Elevated ANA Titers:
Positive ANA titers have been reported in patients receiving propafenone. They have been reversible upon cessations of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosus (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

The 225 mg capsules contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No.5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Impaired Spermatogenesis:
Reversible disorders of spermatogenesis have been demonstrated in monkeys, dogs and rabbits after high dose intravenous administration of propafenone. Evaluation of the effects of short-term propafenone HCl administration on spermatogenesis in 11 normal subjects suggested that propafenone produced a reversible, short-term drop (within normal range) in sperm count. Subsequent evaluations in 11 patients receiving propafenone HCl chronically have found no effect of propafenone on sperm count.

Neuromuscular Dysfunction:
Exacerbation of myasthenia gravis has been reported during propafenone HCl immediate release tablet therapy.

Drug Interactions:
Propafenone is metabolized by CYP2D6 (major pathway) and CYP1A2 and CYP3A4. Drugs that inhibit CYP2D6 (such as desipramine, paroxetine, ritonavir, sertraline), CYP1A2 (such as amiodarone), and CYP3A4 (such as ketaconazole, ritonavir, saquinavir, erythromycin, and grapefruit juice) can be expected to cause increased plasma levels of propafenone. Appropriate monitoring is recommended when propafenone ER capsules are used together with such drugs. In addition, propafenone is an inhibitor of CYP2D6. Coadministration of propafenone with drugs metabolized by CYP2D6 (such as desipramine, imipramine, haloperidol, venlafaxine) might lead to increased plasma concentrations of these drugs. The effect of propafenone on the P-Glycoprotein transporter has not been studied.

Quinidine: Small doses of quinidine completely inhibit the CYP2D6 hydroxylation metabolic pathway, making all patients, in effect, slow metabolizers (see **CLINICAL PHARMACOLOGY**). Concomitant administration of quinidine (50 mg TID) with 150 mg immediate release propafenone TID decreased the clearance of propafenone by 60% in EM, making them PM. Steady state plasma concentrations increased by more than 2-fold for propafenone, and decreased 50% for 5-OH-propafenone. A 100 mg dose of quinidine increased steady state concentrations of propafenone 3-fold. Concomitant use of propafenone and quinidine is not recommended.

Digoxin: Concomitant use of propafenone and digoxin increased steady state serum digoxin exposure (AUC) in patients by 60 to 270%, and decreased the clearance of digoxin by 31 to 67%. Plasma digoxin levels of patients receiving propafenone should be monitored and digoxin dosage adjusted as needed.

Lidocaine: No significant effects on the pharmacokinetics of propafenone or lidocaine have been seen following their concomitant use in patients. However, concomitant use of propafenone and lidocaine have been reported to increase the risks of central nervous system side effects of lidocaine.

Beta-Antagonists: Concomitant use of propafenone and propranolol in healthy subjects increased propranolol plasma concentrations at steady state by 113%. In 4 patients, administration of metoprolol with propafenone increased the metoprolol plasma concentrations at steady state by 100-400%. The pharmacokinetics of propafenone was not affected by the coadministration of either propranolol or metoprolol. In clinical trials using propafenone immediate release tablets, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects.

Warfarin: The concomitant administration of propafenone and warfarin increased warfarin plasma concentrations at steady state by 39% in healthy volunteers and prolonged the prothrombin time in patients taking warfarin. Adjustment of the warfarin dose should be guided by monitoring of the prothrombin time.

Cimetidine: Concomitant administration of propafenone immediate release tablets and cimetidine in 12 healthy subjects resulted in a 20% increase in steady state plasma concentrations of propafenone.

Rifampin: Concomitant administration of rifampin and propafenone in extensive metabolizers decreased the plasma concentrations of propafenone by 67% with a corresponding decrease of 5OH-propafenone by 65%. The concentrations of norpropafenone increased by 30%. In poor metabolizers, there was a 50% decrease in propafenone plasma concentrations and increased the AUC and C_{max} of norpropafenone by 74 and 20%, respectively. Urinary excretion of propafenone and its metabolites decreased significantly. Similar results were noted in elderly patients: Both the AUC and C_{max} propafenone decreased by 84%, with a corresponding decrease in AUC and C_{max} of 5OH-propafenone by 69 and 57%.

Fluoxetine: Concomitant administration of propafenone and fluoxetine in extensive metabolizers increased the S propafenone C_{max} and AUC by 39 and 50% and the R propafenone C_{max} and AUC by 71 and 50%.

Amiodarone: Concomitant administration of propafenone and amiodarone can affect conduction and repolarization and is not recommended.

Post Marketing Reports: Orlistat may limit the fraction of propafenone available for absorption. In post marketing reports, abrupt cessation of orlistat in patients stabilized on propafenone has resulted in severe adverse events including convulsions, atrioventricular block and acute circulatory failure.

Renal and Hepatic Toxicity in Animals:
Renal changes have been observed in the rat following six months of oral administration of propafenone HCl at doses of 180 and 360 mg/kg/day (about two and four times, respectively, the maximum recommended human daily dose [MRHD] on a mg/m^2 basis). Both inflammatory and non-inflammatory changes in the renal tubules, with accompanying interstitial nephritis, were observed. These changes were reversible, as they were not found in rats allowed to recover for six weeks. Fatty degenerative changes of the liver were found in rats following longer durations of administration of propafenone HCl at a dose of 270 mg/kg/day (about three times the MRHD on a mg/m^2 basis). There were no renal or hepatic changes at 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis).

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Lifetime maximally tolerated oral dose studies in mice (up to 360 mg/kg/day, about twice the maximum recommended human oral daily dose [MRHD] on a mg/m^2 basis) and rats (up to 270 mg/kg/day, about three times the MRHD on a mg/m^2 basis) provided no evidence of a carcinogenic potential for propafenone HCl.

Propafenone HCl tested negative for mutagenicity in the Ames (salmonella) test and in 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.

Propafenone HCl, administered intravenously to rabbits, dogs, and monkeys, has been shown to decrease spermatogenesis. These effects were reversible, 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 either orally or intravenously (see **PRECAUTIONS, Impaired Spermatogenesis**). 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).

Pregnancy
Teratogenic Effects: Pregnancy Category C. Propafenone HCl 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 three times the maximum recommended human dose [MRHD] on a mg/m^2 basis) and 600 mg/kg/day (about six times the MRHD on a mg/m^2 basis), respectively. Although maternally tolerated doses (up to 270 mg/kg/day, about three 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). There are no adequate and well-controlled studies in pregnant women. Propafenone ER capsules (propafenone hydrochloride) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-Teratogenic Effects: 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 90 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis) produced increases in maternal deaths. Doses of 360 or more mg/kg/day (four or more times the MRHD on a mg/m^2 basis) resulted in reductions in neonatal survival, body weight gain and physiological development.

Labor and Delivery:
It is not known whether the use of propafenone during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetrical intervention.

Nursing Mothers:
Propafenone is excreted in human milk. Caution should be exercised when propafenone ER capsules are administered to a nursing mother.

Pediatric Use:
The safety and effectiveness of propafenone in pediatric patients have not been established.

Geriatric Use:
Of the total number of subjects in Phase III clinical studies of propafenone ER capsules (propafenone hydrochloride) 45.7 percent were 65 and over, while 15.7 percent were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals at higher doses cannot be ruled out. The effect of age on the pharmacokinetics and pharmacodynamics of propafenone has not been studied.

ADVERSE REACTIONS

The data described below reflect exposure to propafenone ER capsules 225 mg BID in 126 patients, to propafenone ER capsules 325 mg BID in 135 patients, to propafenone ER capsules 425 mg BID in 136 patients, and to placebo in 126 patients for up to 39 weeks in a placebo-controlled trial (RAFT) conducted in the U.S. The most commonly reported adverse events in the trial included dizziness, chest pain, palpitations, taste disturbance, dyspnea, nausea, constipation, anxiety, fatigue, upper respiratory tract infection, influenza, first degree heart block and vomiting. The frequency of discontinuation due to adverse events was highest during the first 14 days of treatment. The majority of the patients with serious adverse events who withdrew or were discontinued recovered without sequelae.

Adverse events occurring in 2% or more of the patients in any of the RAFT propafenone ER capsules treatment groups and more common with propafenone than with placebo, excluding those that are common in the population and those not plausibly related to drug therapy, are listed in **Table 2**.

Table 2: Most common adverse events (≥2% in any RAFT propafenone ER treatment group and more common on propafenone than on placebo)

Propafenone ER Capsules				
MeDRA Body System/Preferred Term	225 mg BID (N = 126) n (%)	325 mg BID (N = 135) n (%)	425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
Mean exposure (days)	124	149	141	91
Cardiac disorders				
Angina pectoris	0 (0)	0 (0)	3 (2)	0 (0)
Atrial flutter	3 (2)	2 (1)	0 (0)	1 (1)
AV block first degree	3 (2)	3 (2)	4 (3)	0 (0)
Bradycardia	4 (3)	4 (3)	6 (4)	1 (1)
Cardiac failure congestive	0 (0)	1 (1)	3 (2)	1 (1)
Cardiac murmur	2 (2)	3 (2)	6 (4)	0 (0)
Edema	6 (5)	18 (13)	10 (7)	8 (6)
Eye disorders				
Vision blurred	1 (1)	1 (1)	5 (4)	0 (0)
Gastrointestinal disorders				
Constipation	10 (8)	19 (14)	16 (12)	3 (2)
Diarrhea	2 (2)	3 (2)	5 (4)	3 (2)
Dry mouth	1 (1)	1 (1)	5 (4)	1 (1)
Flatulence	3 (2)	3 (2)	1 (1)	0 (0)
Nausea	11 (9)	15 (11)	23 (17)	11 (9)
Vomiting	1 (1)	0 (0)	8 (6)	3 (2)
General disorder and administration site				
Fatigue	14 (11)	17 (13)	17 (13)	7 (6)
Weakness	4 (3)	6 (4)	6 (4)	3 (2)
Infections and Infestations				
Upper respiratory tract infection	11 (9)	16 (12)	11 (8)	7 (6)
Propafenone ER Capsules (continued)				
MeDRA Body System/Preferred Term	225 mg BID (N = 126) n (%)	325 mg BID (N = 135) n (%)	425 mg BID (N = 136) n (%)	Placebo (N = 126) n (%)
Mean exposure (days)	124	149	141	91
Investigations				
Blood alkaline phosphatase increased	0 (0)	0 (0)	4 (3)	0 (0)
Cardioactive drug level above therapeutic	1 (1)	1 (1)	3 (2)	1 (1)
Hematuria	2 (2)	2 (1)	4 (3)	3 (2)
Musculoskeletal, connective tissue and bone				
Muscle weakness	1 (1)	5 (4)	1 (1)	0 (0)
Nervous system disorders				
Dizziness (excluding vertigo)	29 (23)	28 (21)	29 (21)	18 (14)
Headache	8 (6)	12 (9)	14 (10)	11 (9)
Taste disturbance	7 (6)	18 (13)	30 (22)	1 (1)
Tremor	2 (2)	0 (0)	3 (2)	1 (1)
Somnolence	1 (1)	1 (1)	4 (3)	0 (0)
Psychiatric disorders				
Anxiety	12 (10)	17 (13)	16 (12)	13 (10)
Depression	1 (1)	4 (3)	0 (0)	2 (2)
Respiratory, thoracic and mediastinal disorder				
Dyspnea	16 (13)	23 (17)	17 (13)	9 (7)
Rales	2 (2)	1 (1)	3 (2)	0 (0)
Wheezing	0 (0)	0 (0)	3 (2)	0 (0)
Skin & subcutaneous tissue disorders				
Ecchymosis	2 (2)	3 (2)	5 (4)	0 (0)

No clinically important differences in incidence of adverse reactions were noted by age, or gender. Too few non-White patients were enrolled to assess adverse events according to race. Adverse events occurring in 2% or more of the patients in any of the ERAFT propafenone ER treatment groups and not listed in Table 2 include the following: bundle branch block left, bundle branch block right, conduction disorders, sinus bradycardia and hypotension.

Other adverse events reported with propafenone clinical trials not already listed in Table 2 include the following adverse events by body and preferred term.

Blood and lymphatic system disorders: anemia; lymphadenopathy; spleen disorder; thrombocytopenia; *Cardiac disorders:* angina unstable; arrhythmia; atrial hypertrophy; atrioventricular block; bundle branch block left; bundle branch block right; cardiac arrest; cardiac disorder; conduction disorder; coronary artery disease; extrasystoles; myocardial infarction; nodal arrhythmia; palpitations; pericarditis; sinoatrial block; sinus arrest; sinus arrhythmia; sinus bradycardia; supraventricular extrasystoles; supraventricular tachycardia; ventricular arrhythmia; ventricular extrasystoles; ventricular hypertrophy; *Ear and labyrinth disorders:* hearing impaired; tinnitus; vertigo; *Eye disorders:* eye hemorrhage; eye inflammation; eyelid ptosis; miosis; retinal disorder; visual acuity reduced; *Gastrointestinal disorders*: abdominal distension; abdominal pain; dry throat; duodenitis; dyspepsia; dysphagia; eructation; gastritis; gastroesophageal reflux disease; gingival bleeding; glossitis; glossodynia; gum pain; halitosis; intestinal obstruction; melena; mouth ulceration; pancreatitis; peptic ulcer; rectal bleeding; sore throat; *General disorders and administration site conditions:* chest pain; feeling hot; hemorrhage; malaise; pain; pyrexia; *Hepato-biliary disorders:* hepatomegaly; *Investigations:* abnormal electrocardiogram; abnormal heart sounds; abnormal liver function tests; abnormal pulse; carotid bruit; decreased blood chloride; decreased blood pressure; decreased blood sodium; decreased hemoglobin; decreased neutrophil count; decreased platelet count; decreased prothrombin level; decreased red blood cell count; decreased weight; electrocardiogram QT prolonged; glycosuria present; heart rate irregular; increased alanine aminotransferase; increased aspartate aminotransferase; increased blood bilirubin; increased blood cholesterol; increased blood creatinine; increased blood glucose; increased blood lactate dehydrogenase; increased blood pressure; increased blood prolactin; increased blood triglycerides; increased blood urea; increased blood uric acid; increased eosinophil count; increased gamma-glutamyltransferase; increased monocyte count; increased prostatic specific antigen; increased prothrombin level; increased weight; increased white blood cell count; ketonuria present; proteinuria present; *Metabolism and nutrition disorders:* anorexia; dehydration; diabetes mellitus; gout; hypercholesterolemia; hyperglycemia; hyperlipidemia; hypokalemia; *Musculoskeletal, connective tissue and bone disorders:* arthritis; bursitis; collagen-vascular disease; costochondritis; joint disorder; muscle cramps; muscle spasms; myalgia; neck pain; pain in jaw; sciatica; tendonitis; *Nervous system disorders:* amnesia; ataxia; balance impaired; brain damage; cerebrovascular accident; dementia; gait abnormal; hypertonia; hypothesia; insomnia; paralysis; paresthesia; peripheral neuropathy; speech disorder; syncope; tongue hypoesthesia; *Psychiatric disorders:* decreased libido; emotional disturbance; mental disorder; neurosis; nightmare; sleep disorder; *Renal and urinary disorders:* dysuria; nocturia; oliguria; pyuria; renal failure; urinary casts; urinary frequency; urinary incontinence; urinary retention; urine abnormal; *Reproductive system and breast disorders:* breast pain; impotence; prostatism; *Respiratory, thoracic and mediastinal disorders:* atelectasis; breath sounds decreased; chronic obstructive airways disease; cough; epistaxis; hemoptysis; lung disorder; pleural effusion; pulmonary congestion; rales; respiratory failure; rhinitis; throat tightness; *Skin and subcutaneous tissue disorders:* alopecia; dermatitis; dry skin; erythema; nail abnormality; petechiae; pruritis; sweating increased; urticaria; *Vascular disorders:* arterial embolism limb; deep limb venous thrombosis; flushing; hematoma; hypertension; hypertensive crisis; hypotension; labile blood pressure; pallor; peripheral coldness; peripheral vascular disease; thrombosis.

Laboratory: Electrocardiograms
Propafenone prolongs the PR and QRS intervals in patients with atrial and ventricular arrhythmias. Prolongation of the QRS interval makes it difficult to interpret the effect of propafenone on the QT interval.

Table 3: Mean Change in 12-Lead Electrocardiogram Results (RAFT)

	Propafenone ER Capsules BID dosing			
	225 mg	325 mg	425 mg	Placebo
	n=126	n=135	n=136	n=126
PR (ms)	9±22	12±23	21±24	1±16
QRS (ms)	4±14	6±15	6±15	-2±12
QTc* (ms)	2±30	5±36	6±37	5±35

*Calculated using Bazett's correction factor.

In RAFT, the distribution of the maximum changes in QTc compared to baseline over the study in each patient was similar in the propafenone ER capsules 225 mg BID, 325 mg BID, and 425 mg BID and placebo dose groups. Similar results were seen in the ERAFT study.

Table 4: Number of patients according to the range of maximum QTc change compared to baseline over the study in each dose group (RAFT study)

Range of maximum QTc change	Propafenone ER Capsules			Placebo
	225 mg BID	325 mg BID	425 mgBID	
	N=119	N=129	N=123	N=100
	n (%)	n (%)	n (%)	n (%)
>20%	1 (1%)	6 (5%)	3 (2%)	5 (4%)
10-20%	19 (16%)	28 (22%)	32 (26%)	24 (20%)
≤10%	99 (83%)	95 (74%)	88 (72%)	91 (76%)

OVERDOSAGE

The symptoms of overdosage may include hypotension, somnolence, bradycardia, intra-atrial and intraventricular conduction disturbances, and rarely convulsions and high grade ventricular arrhythmias. Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling abnormal ventricular rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam. General supportive measures such as mechanical respiratory assistance and external cardiac massage may be necessary.

The hemodialysis of propafenone in patients with an overdose is expected to be of limited value in the removal of propafenone as a result of both its high protein binding (>95%) and large volume of distribution.

DOSAGE AND ADMINISTRATION

The dose of propafenone ER capsules must be individually titrated on the basis of response and tolerance. Therapy should be initiated with propafenone ER capsules 225 mg given every twelve hours. Dosage may be increased at a minimum of five day interval to 325 mg given every twelve hours. If additional therapeutic effect is needed, the dose of propafenone ER capsules may be increased to 425 mg given every twelve hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

Propafenone ER capsules can be taken with or without food. Do not crush or further divide the contents of the capsule.

HOW SUPPLIED

Propafenone Extended Release Capsules, 225 mg are available as hard gelatin capsules containing 225 mg of propafenone HCl. The capsule is a peach opaque cap printed "par/209" in black ink and white opaque body printed "par/209" in black ink.

NDC 49884-209-02 Bottles of 60 capsules
NDC 49884-209-01 Bottles of 100 capsules
NDC 49884-209-05 Bottles of 500 capsules
NDC 49884-209-10 Bottles of 1000 capsules

Propafenone Extended Release Capsules, 325 mg are available as hard gelatin capsules containing 325 mg of propafenone HCl. The capsule is an orange opaque cap printed "par/210" in black ink and white opaque body printed "par/210" in black ink.

NDC 49884-210-02 Bottles of 60 capsules
NDC 49884-210-01 Bottles of 100 capsules
NDC 49884-210-05 Bottles of 500 capsules
NDC 49884-210-10 Bottles of 1000 capsules

Propafenone Extended Release Capsules, 425 mg are available as hard gelatin capsules containing 425 mg of propafenone HCl. The capsule is a red opaque cap printed "par/211" in black ink and white opaque body printed "par/211" in black ink.

NDC 49884-211-02 Bottles of 60 capsules
NDC 49884-211-01 Bottles of 100 capsules
NDC 49884-211-05 Bottles of 500 capsules
NDC 49884-211-10 Bottles of 1000 capsules

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Dispense in a tight container as defined in the USP.

Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

Issued: 05/07 OS209-02-1-01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

LABELING REVIEWS

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

ANDA Number: **78-540** Dates of Submissions: **October 10 and November 6, 2006**

Applicant's Name: **Par Pharmaceutical, Inc.**

Established Name: **Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg and 425 mg**

Labeling Deficiencies:

1. CONTAINER 60s, 100s, 500s and 1000s

    a. Established name

        i. Increase the prominence of the established name and strength so that they appear as the most prominent information on the label.

        ii. Decrease the prominence of "PAR".

        Iii. "Hydrochloride" rather than "HCl"

    b. Differentiate your product strengths by boxing, contrasting colors, or some other means.

    c. Storage temperature recommendation

        i. "15^{o} to" rather than "15^{o}to"

        ii. "Controlled Room Temperature" [upper case "C", "R" and "T"]

    d. 225 mg LABELS – "Contains FD&C Yellow No.5 (tartrazine) as a color additive." or "Contains color additives including FD&C Yellow No.5 (tartrazine)."

    e. 425 mg LABELS – 100s, 500s and 1000s

        i. "Each capsule contains" – "hydrochloride … 425 mg"

        ii. USUAL DOSAGE – "One capsule every 12 hours. See …"

2. INSERT

    a. GENERAL COMMENTS

        i. "Propafenone ER capsules" rather than "Propafenone HCl ER" and "Propafenone HCl ER capsules" throughout the text of the insert.

        ii. "mcg" rather than "µg" throughout the insert

b. TITLE:

Place “Rx only” beneath the title.

c. CLINICAL PHARMACOLOGY

i. Hemodynamics, second line –

A). Place “2.61” and “L/min/m^2” on same line of text.

B). “L/min/m^2” rather than “L/min/m2”

ii. Pharmacokinetics and Metabolism

A). Absorption/Bioavailability, second paragraph

1). “ER” rather than (b) (4)[three instances

2). Fourth line – “… an increase of overall …” rather than “an increase in overall …”

B). Distribution, second paragraph – Place “0.5 – 2” and “mcg/mL” on same line of text.

C). Metabolism, first paragraph

1). Third line – “5-hydroxypropafenone” [spelling]

2). Sixth line – Place “10-32” and “hours” on the same line of text.

iii. Clinical Trials

A). RAFT

1). First paragraph, seventh line – “beta-blockers” [add hyphen]

2). Improve the clarity/legibility of the graph

B). ERAFT, second paragraph, last sentence – “propafenone” [lower case “p”]

d. WARNINGS

i. Proarrhythmic Effects, last paragraph, second sentence – “4%” [delete the terminal zero]

ii. Congestive Heart Failure

A). First sentence – “beta-blockade” [add hyphen]

B). Second sentence – “1%” [delete the terminal zero]

iii. Conduction Disturbances, last paragraph, last sentence – Place “(rate <50” and “beats/min)” on the same line of text.

e. PRECAUTIONS

i. Hepatic Dysfunction

A). Place the subsection title immediately beneath the section title.

B). "… propafenone HCl immediate release tablets …" [delete (b) (4) – two instances]

ii. Information for Patients

A). Add the following sub-subsection immediately beneath the "Dosing Schedule" sub-subsection:

Elevated ANA Titers:
Positive ANA titers have been reported in patients receiving propafenone. They have been reversible upon cessation of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosus (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

B) Add the following to the end of this subsection:

"The 225 mg capsules contain FD&C Yellow No.5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No.5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity>"

iii. Drug Interactions

A). Rifampin – "C_{max}" rather than "Cmax" [three instances]

B). Fluoxetine - "C_{max}" rather than "Cmax" [two instances]

f. ADVERSE REACTIONS

i. First paragraph, first sentence – "U.S." rather than "US."

ii. Table 2

A). Title – "(≥ 2%" rather than (b) (4)

B). "MeDRA" rather than "MedDRA"

C). First column – Place the title "**Investigations**" immediately above the "Blood alkaline phosphatase increased" row.

iii. Cardiac disorders, second line "…block; bundle branch block left; …"

iv. "*Investigations:*" [*italics*]

v. Table 3 – “**Propafenone ER**” [**bold print**]

vi. Table 4, last column – “N=100” rather than (b) (4)

g. HOW SUPPLIED

i. Place "225" and “mg” on the same line of text.

ii. Place "325" and “mg” on the same line of text.

iii. Place "425" and “mg” on the same line of text.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA". The immediate container labels may be submitted either electronically or in hard copy. However, for ease of review, we ask that you submit electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

	SUBMIT	ACTION
LABELS		
225 mg		
60s	11-6-06	REVISE
100s	11-6-06	REVISE
500s	11-6-06	REVISE
1000s	11-6-06	REVISE
325 mg		
60s	11-6-06	REVISE
100s	11-6-06	REVISE

500s	11-6-06	REVISE
1000s	11-6-06	REVISE
425 mg		
60s	11-6-06	REVISE
100s	11-6-06	REVISE
500s	11-6-06	REVISE
1000s	11-6-06	REVISE
Insert	11-6-06	REVISE

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Rythmol SR®
NDA Number: 21-416
NDA Drug Name: Rythmol SR® (propafenone hydrochloride) Extended-Release Capsules, 225 mg, 325 mg and 425 mg
NDA Firm: Reliant Pharmaceuticals
Date of Approval of NDA Insert and supplement #: 9-13-04 (S-001)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? NO
Other Comments

_____
_____

FOR THE RECORD:

1. Review based on the labeling of Rythmol SR® (NDA 21-416/S-001); approved 9-13-04.

2. Patent/ Exclusivities

Patent Data – 21-416

No	Expiration	Use Code	Use	File
5681588	10-28-14			PIV

Exclusivity Data – 21-416

Code/sup	Expiration	Use Code	Description		Labeling Impact
None			There is no unexpired exclusivity for this product		

3. Storage Conditions:
NDA – Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP controlled room temperature.]
ANDA – Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].
USP – not USP

4. Product Line:
The innovator markets their product in bottles of 100s.
The applicant proposes to market their product in bottles of 60s, 100s, 500s and 1000s.

5. The capsule descriptions have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

225 mg	Peach opaque cap printed “par/209” in black ink/white opaque body printed “par/209” in black ink
325 mg	Orange opaque cap printed “par/210” in black ink/ (b) (4) opaque body printed “par/210” in black ink
425 mg	Red opaque cap printed “par/211” in black ink/ (b) (4) opaque body printed “par/211” in black ink

6. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition

7. Par Pharmaceutical is the manufacturer.

8. This is a FIRST GENERIC.

9. The date of the original submission was October 10, 2006 in which the 225 mg and 425 mg labeling was submitted. The labeling for the 325 mg was submitted November 6, 2006 but was not "tagged" as a labeling amendment and so does not appear on my queue.

Date of Review: 5-3-07 Dates of Submission: 10-10-06 and 11-6-06

Primary Reviewer: Adolph Vezza Date:

Team Leader: Captain Lillie Golson Date:

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cc: ANDA: 78-540
DUP/DIVISION FILE
HFD-613/AVezza/LGolson (no cc)
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Review.

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

/s/

Adolph Vezza
5/9/2007 02:08:29 PM
MEDICAL OFFICER

Lillie Golson
5/9/2007 03:10:08 PM
MEDICAL OFFICER

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

ANDA Number: **78-540** Date of Submission: **January 10 and June 1, 2007**

Applicant's Name: **Par Pharmaceutical, Inc.**

Established Name: **Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg and 425 mg**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

	SUBMIT	ACTION
LABELS		
225 mg		
60s	6-1-07	APPROVE
100s	6-1-07	APPROVE
500s	6-1-07	APPROVE
1000s	6-1-07	APPROVE
325 mg		
60s	6-1-07	APPROVE
100s	6-1-07	APPROVE
500s	6-1-07	APPROVE
1000s	6-1-07	APPROVE
425 mg		
60s	6-1-07	APPROVE
100s	6-1-07	APPROVE
500s	6-1-07	APPROVE
1000s	6-1-07	APPROVE
Insert	6-1-07	APPROVE

Revisions needed post-approval: PI – PRECAUTIONS, Information for Patients, Elevated ANA Titers, first paragraph, second line – “cessation” [singular]

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Rythmol SR®
NDA Number: 21-416
NDA Drug Name: Rythmol SR® (propafenone hydrochloride) Extended-Release Capsules, 225 mg, 325 mg and 425 mg
NDA Firm: Reliant Pharmaceuticals
Date of Approval of NDA Insert and supplement #: 9-13-04 (S-001)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? NO
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must he package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of he statement been confirmed? PER FIRM - THERE IS SOME IN THE IMPRINTING INK	X		
Do any of the inac ives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommenda ions fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification			

of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Rythmol SR® (NDA 21-416/S-001); approved 9-13-04.

2. Patent/ Exclusivities

Patent Data – 21-416

No	Expiration	Use Code	Use	File
5681588	10-28-14			PIV

Exclusivity Data – 21-416

Code/sup	Expiration	Use Code	Description		Labeling Impact
None			There is no unexpired exclusivity for this product		

3. Storage Conditions:
NDA – Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP controlled room temperature.]
ANDA – Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].
USP – not USP

4. Product Line:
The innovator markets their product in bottles of 100s.
The applicant proposes to market their product in bottles of 60s, 100s, 500s and 1000s.

5. The capsule descriptions have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

225 mg	Peach opaque cap printed “par/209” in black ink/white opaque body printed “par/209” in black ink
325 mg	Orange opaque cap printed “par/210” in black ink/ (b) (4) opaque body printed “par/210” in black ink
425 mg	Red opaque cap printed “par/211” in black ink/ (b) (4) opaque body printed “par/211” in black ink

6. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition

7. Par Pharmaceutical is the manufacturer.

8. This is a FIRST GENERIC.

9. The date of the original submission was October 10, 2006 in which the 225 mg and 425 mg labeling was submitted. The labeling for the 325 mg was submitted November 6, 2006 but was not “tagged” as a labeling amendment and so did not appear on my queue.

Date of Review: 6-11-07 Date of Submission: 1-10-07 and 6-1-07

Primary Reviewer: Adolph Vezza Date:

Team Leader: Captain Lillie Golson Date:

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cc: ANDA: 78-540
DUP/DIVISION FILE
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Review.

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

/s/

Adolph Vezza
6/18/2007 01:07:54 PM
LABELING REVIEWER

Lillie Golson
6/19/2007 12:42:55 PM
LABELING REVIEWER

(this supersedes the Approval Summary done on the 6-1-07 submission)
APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **78-540** Date of Submission: **March 16, 2010**

Applicant's Name: **Par Pharmaceutical, Inc.**

Established Name: **Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg and 425 mg**

BASIS OF APPROVAL:

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? No - ELECTRONIC

	SUBMIT	ACTION
LABELS		
225 mg		
60s	3-16-10	APPROVE
100s	3-16-10	APPROVE
500s	3-16-10	APPROVE
1000s	3-16-10	APPROVE
325 mg		
60s	3-16-10	APPROVE
100s	3-16-10	APPROVE
500s	3-16-10	APPROVE
1000s	3-16-10	APPROVE
425 mg		
60s	3-16-10	APPROVE
100s	3-16-10	APPROVE
500s	3-16-10	APPROVE
1000s	3-16-10	APPROVE
Insert	3-16-10	APPROVE

Revisions needed post-approval: PI – DESCRIPTION – Indicate that the FD&C Yellow No.5 is only in the 225 mg capsule shell - PRECAUTIONS, Information for Patients, Elevated ANA Titers, first paragraph, second line – “cessation” [singular]

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Rythmol SR®
NDA Number: 21-416
NDA Drug Name: Rythmol SR® (propafenone hydrochloride) Extended-Release Capsules, 225 mg, 325 mg and 425 mg
NDA Firm: Reliant Pharmaceuticals
Date of Approval of NDA Insert and supplement #: 9-13-04 (S-001)
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? NO
Other Comments

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured.		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any o her safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger han 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed? PER FIRM - THERE IS SOME IN THE IMPRINTING INK	X		
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list he coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprin ing inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommenda ions supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of he unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet hem?			X
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility informa ion? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (portions taken from previous review)

1. Review based on the labeling of Rythmol SR® (NDA 21-416/S-001); approved 9-13-04.

2. Patent/ Exclusivities

Patent Data – 21-416

No	Expiration	Use Code	Use	File
5681588	10-28-14			PIV

Exclusivity Data – 21-416

Code/sup	Expiration	Use Code	Description		Labeling Impact
None			There is no unexpired exclusivity for this product		

The RLD company – RELIANT – sued PAR but the suit action has been dropped so this drug product can be approved.

3. Storage Conditions:
NDA – Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP controlled room temperature.]
ANDA – Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room temperature].
USP – not USP

4. Product Line:
The innovator markets their product in bottles of 100s.
The applicant proposes to market their product in bottles of 60s, 100s, 500s and 1000s.

5. The capsule descriptions have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

225 mg	Peach opaque cap printed “par/209” in black ink/white opaque body printed “par/209” in black ink
325 mg	Orange opaque cap printed “par/210” in black ink/ (b) (4) opaque body printed “par/210” in black ink
425 mg	Red opaque cap printed “par/211” in black ink/ (b) (4) opaque body printed “par/211” in black ink

6. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition

7. Par Pharmaceutical is the manufacturer.

8. This is a FIRST GENERIC.

9. The date of the original submission was October 10, 2006 in which the 225 mg and 425 mg labeling was submitted. The labeling for the 325 mg was submitted November 6, 2006 but was not “tagged” as a labeling amendment and so did not appear on my queue.

10. I called the firm on 3-17-10 and spoke to Julia Szozda about the tartrazine and how someone reading the DESCRIPTION section might think that it was in all three of the capsule shells and not just the 225 mg strength – she said the firm would change it at their next printing. I suggested that they could also just use a different dye rather than tartrazine.

Date of Review: 3-17-10 Date of Submission: 3-16-10

Primary Reviewer: Adolph Vezza Date:

Team Leader: Koung Lee Date:

---

cc: ANDA: 78-540
DUP/DIVISION FILE
HFD-613/AVezza/KLee (no cc)
aev/3/17/10|C:\OldComputer\cdw5106378\C-drive\FIRMSNZ\PAR\LTRS&REV\78540AP2.LABELING.doc
Review.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78540	ORIG-1	PAR PHARMACEUTICAL	PROPAFENONE HYDROCHLORIDE

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

/s/

ADOLPH E VEZZA
03/17/2010

KOUNG U LEE
03/24/2010
For Wm Peter Rickman - Labeling reviewer will inform the firm to replace "ER" with "extended-release" in the insert labeling.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

CHEMISTRY REVIEWS

ANDA 78-540

Propafenone Hydrochloride Extended release Capsules 225 mg, 325 mg, and 425 mg

Par Pharmaceutical, Inc.

Shankar Saha
OGD/Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-540

2. REVIEW #: 1

3. REVIEW DATE: February 22, 2007; 06-Jul-2007

4. REVIEWER: Shankar Saha

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission for 225 mg and 425 mg	October 10, 2006
Electronic QOS	November 6, 2006
Amendment for 325 mg	November 6, 2006

7. NAME & ADDRESS OF APPLICANT:

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

U.S. Representative (Contact person)
Janis Picurro, Director
Regulatory Affairs
Telephone: (845) 639-5121
Fax: (845) 639-5201

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):

Propafenone Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Rythmol SR® Extended Release Capsules, 225 mg and 425 mg held by Reliant Pharmaceuticals Inc. The NDA number is 21416.

Patent and exclusivity:

Application Number	Patent Number	Patent Expiration
021416	5681588	October 28, 2014

Patent Certification:

The firm filed Paragraph IV Certification for U.S. Patent 5681588 and submitted the following exclusivity statement.

According to information published in the "Electronic Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations), Rythmol SR® , is identified as the RLD and Reliant Pharmaceuticals Inc, is no longer entitled to a period of marketing exclusivity under section 505 (j) (4) (D) of the Federal, Food, Drug and Cosmetic Act for New dosage Form. The above exclusivity expired on September 4, 2006.

Par Pharmaceutical will market Propafenone HCl ER Capsules, 225 mg and 425 mg upon approval of this abbreviated new drug application.

10. PHARMACOL. CATEGORY: Anti-arrhythmic

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 225 mg, 325 mg, and 425 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

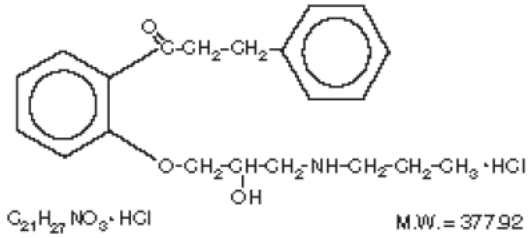
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2'-[2-Hydroxy-3-(propylamino-propoxyl]-3-phenylpropiophenone hydrochloride.

Molecular formula: $C_{21}H_{27}NO_3$. HCl

Molecular Weight: 377.92



2'-[2-Hydroxy-3-(propylamino)-propoxy]-
3-phenylpropiophenone hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	3/28/2007	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

		Company					

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Pending, dissolution deficiency letter in DFS	2/1/2007	
EA	N/A		
Radiopharmaceutical	N/A		
Toxicology consult	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
_X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-540

The QoS provided was in the QbR format and the application was thus treated as a QbR application and reviewed in accordance with the current QbR templates by using the QoS as written and adding reviewer commentary in boxed sections. Any additional information added to the QoS text from module 3 is referred accordingly.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Par Pharmaceutical, Inc. request a waiver of the in-vivo bioequivalence study requirements for Propafenone Hydrochloride ER Capsules, 225 mg on the basis of proportionality similar quantitative formulations, in vitro dissolution results and in-vivo bioavailability studies performed under fasting and fed conditions comparing Par's Propafenone Hydrochloride ER Capsules, 425 mg with RLD, Rythmol® SR, 425 mg, manufactured by Reliant Pharmaceuticals.

The ANDA is recommended for not approvable for the following:

CMC Review: Deficient
Labeling: Pending
Bioequvalence: Dissolution method deficient and overall bio review pending.
DMF: Deficient
EES: Pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Propafenone hydrochloride is an antiarrhythmic drug supplied as extended-release capsules of 225 mg, 325 mg and 425 mg for oral administration. Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone hydrochloride extended release capsules are filled with granules containing the following inactive ingredients: ethylcellulose, lactose anhydrous, magnesium stearate and povidone. The capsules consist of D&C Red #28, (b) (4) (b) (4), FD&C Blue #1, FD&C Red #40, FD&C Yellow #5, FD&C Yellow #6, gelatin and titanium dioxide. In addition the ink consists of D&C Yellow #10 aluminum lake, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, FD&C Blue #1 aluminum lake and shellac glaze~45% (20% esterified) in ethanol. The formulation suggests possible API-Lactose interaction.

Packaging:
Propafenone HCl Extended Release Capsules, 225 mg are available as hard gelatin capsules containing 225 mg of propafenone HCl. The capsule is a peach opaque cap printed "par/209" in black ink and white opaque body printed "par/209" in black ink.

NDC 49884-209-02 Bottles of 60 capsules
NDC 49884-209-01 Bottles of 100 capsules
NDC 49884-209-05 Bottles of 500 capsules
NDC 49884-209-10 Bottles of 1000 capsules

Propafenone HCl Extended Release Capsules, 325 mg are available as hard gelatin capsules containing 325 mg of Propafenone HCl. The capsule is an orange opaque cap printed "par/210" in black ink and white opaque body printed "par/210" in black ink.

NDC 49884-210-02 Bottles of 60 capsules
NDC 49884-210-01 Bottles of 100 capsules
NDC 49884-210-05 Bottles of 500 capsules
NDC 49884-210-10 Bottles of 1000 capsules

Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Dispense in a tight container as defined in the USP.

B. Drug Substance

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

C. **Description of How the Drug Product is Intended to be Used**

The dose of Propafenone HCl ER must be individually titrated based on response and tolerance. Therapy should be initiated with Propafenone HCl ER 225 mg given every twelve hours. Dosage may be increased at a minimum of five day interval to 325 mg given every twelve hours. If additional therapeutic effect is needed, the dose of Propafenone HCl ER may be increased to 425 mg given every twelve hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

Propafenone HCl ER can be taken with or without food. Do not crush or further divide the contents of the capsule.

D. **Basis for Approvability or Not-Approval Recommendation**

The ANDA is recommended not approvable for the following:

CMC Review: Deficient
Labeling: Pending
Bioequvalence: Dissolution method deficient and overall bio review pending
EES: Pending

Following this page, 49 pages withheld in full - (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540 APPLICANT: Par Pharmaceuticals, Inc

DRUG PRODUCT: Propafenone HCl Extended Release Capsules, 225 mg, 325 mg, and 425 mg

Chemistry Deficiencies:

1. (b) (4)

2.

3.

4.

(b) (4)

5.

6.

7.

8.

9. The specification for dissolution in the release and stability of the finished product is not consistent with the recommended specification by the Division of Bioequivalence. Please submit updated specifications. Submit data to support the 24 months expiration dating.

10. Please submit available controlled room temperature stability data.

Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Shankar Saha
7/25/2007 11:29:24 AM
CHEMIST

Ubrani Venkataram
7/25/2007 11:47:30 AM
CHEMIST

Ted Palat
7/25/2007 02:43:23 PM
CSO

ANDA 78-540

Propafenone Hydrochloride Extended release Capsules 225 mg, 325 mg, and 425 mg

Par Pharmaceutical, Inc.

Shankar Saha
OGD/Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-540

2. REVIEW #: 2

3. REVIEW DATE: May 28, 2008

4. REVIEWER: Shankar Saha

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission for 225 mg and 425 mg	October 10, 2006
Electronic QOS	November 6, 2006
Amendment for 325 mg	November 6, 2006
Deficiency Letter	July 26, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
First Minor Amendment	November 28, 2007

7. NAME & ADDRESS OF APPLICANT:

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

U.S. Representative (Contact person)
Janis Picurro, Director
Regulatory Affairs
Telephone: (845) 639-5121
Fax: (845) 639-5201

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):

Propafenone Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Rythmol SR® Extended Release Capsules, 225 mg and 425 mg held by Reliant Pharmaceuticals Inc. The NDA number is 21416.

Patent and exclusivity:

Application Number	Patent Number	Patent Expiration
021416	5681588	October 28, 2014

Patent Certification:

The firm filed Paragraph IV Certification for U.S. Patent 5681588 and submitted the following exclusivity statement.

According to information published in the "Electronic Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations), Rythmol SR® , is identified as the RLD and Reliant Pharmaceuticals Inc, is no longer entitled to a period of marketing exclusivity under section 505 (j) (4) (D) of the Federal, Food, Drug and Cosmetic Act for New dosage Form. The above exclusivity expired on September 4, 2006.

Par Pharmaceutical will market Propafenone HCl ER Capsules, 225 mg and 425 mg upon approval of this abbreviated new drug application.

10. PHARMACOL. CATEGORY: Anti-arrhythmic

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 225 mg, 325 mg, and 425 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

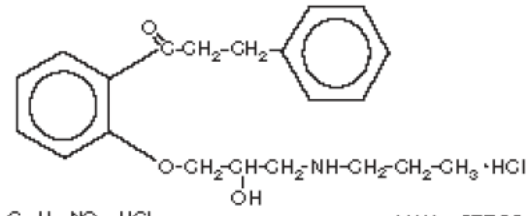
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2'-[2-Hydroxy-3-(propylamino-propoxyl]-3-phenylpropiophenone hydrochloride.

Molecular formula: $C_{21}H_{27}NO_3$. HCl

Molecular Weight: 377.92



2'-[2-Hydroxy-3-(propylamino)-propoxy]-
3-phenylpropiophenone hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	3/28/2007	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

		(b) (4)				

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/15/2007	
Methods Validation	Not requested per OGD policy		
Labeling	Acceptable	6/19/2007	
Bioequivalence	Acceptable	6/15/2007	
EA	Categorical Exclusion		21 CFR 25.31 (a)
Radiopharmaceutical	N/A		
Toxicology consult	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
_X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-540

The QoS provided was in the QbR format and the application was thus treated as a QbR application and reviewed in accordance with the current QbR templates by using the QoS as written and adding reviewer commentary in boxed sections. Any additional information added to the QoS text from module 3 is referred accordingly.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Par Pharmaceutical, Inc. request a waiver of the in-vivo bioequivalence study requirements for Propafenone Hydrochloride ER Capsules, 225 mg on the basis of proportionality similar quantitative formulations, in vitro dissolution results and in-vivo bioavailability studies performed under fasting and fed conditions comparing Par's Propafenone Hydrochloride ER Capsules, 425 mg with RLD, Rythmol® SR, 425 mg, manufactured by Reliant Pharmaceuticals.

The ANDA is recommended for not approvable for the following:

CMC Review: Deficient

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Propafenone hydrochloride is an antiarrhythmic drug supplied as extended-release capsules of 225 mg, 325 mg and 425 mg for oral administration. Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone hydrochloride extended release capsules are filled with granules containing the following inactive ingredients: ethylcellulose, lactose anhydrous, magnesium stearate and povidone. The capsules consist of D&C Red #28, (b) (4) (b) (4), FD&C Blue #1, FD&C Red #40, FD&C Yellow #5, FD&C Yellow #6, gelatin and titanium dioxide. In addition the ink consists of D&C Yellow #10 aluminum lake, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, FD&C Blue #1 aluminum lake and shellac glaze~45% (20% esterified) in ethanol. The formulation suggests possible API-Lactose interaction.

Packaging:

Propafenone HCl Extended Release Capsules, 225 mg are available as hard gelatin capsules containing 225 mg of propafenone HCl. The capsule is a peach opaque cap printed "par/209" in black ink and white opaque body printed "par/209" in black ink.

NDC 49884-209-02 Bottles of 60 capsules
NDC 49884-209-01 Bottles of 100 capsules
NDC 49884-209-05 Bottles of 500 capsules
NDC 49884-209-10 Bottles of 1000 capsules

Propafenone HCl Extended Release Capsules, 325 mg are available as hard gelatin capsules containing 325 mg of Propafenone HCl. The capsule is an orange opaque cap printed "par/210" in black ink and white opaque body printed "par/210" in black ink.

NDC 49884-210-02 Bottles of 60 capsules
NDC 49884-210-01 Bottles of 100 capsules
NDC 49884-210-05 Bottles of 500 capsules
NDC 49884-210-10 Bottles of 1000 capsules

Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Dispense in a tight container as defined in the USP.

B. Drug Substance

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

C. **Description of How the Drug Product is Intended to be Used**

The dose of Propafenone HCl ER must be individually titrated based on response and tolerance. Therapy should be initiated with Propafenone HCl ER 225 mg given every twelve hours. Dosage may be increased at a minimum of five day interval to 325 mg given every twelve hours. If additional therapeutic effect is needed, the dose of Propafenone HCl ER may be increased to 425 mg given every twelve hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

Propafenone HCl ER can be taken with or without food. Do not crush or further divide the contents of the capsule.

D. **Basis for Approvability or Not-Approval Recommendation**

The ANDA is recommended not approvable for the following:

CMC Review: Deficient

Following this page, 57 pages withheld in full - (b)(4)

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540 APPLICANT: Par Pharmaceuticals, Inc

DRUG PRODUCT: Propafenone HCl Extended Release Capsules, 225 mg, 325 mg, and 425 mg

A. Chemistry Deficiencies

1. (b) (4)

2.

3.

4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or

Tentative Approval. Please refer to the letter posted on the Office of Generic Drugs website for further information and submit the necessary revisions to your application.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 78-540
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/S. Saha/05/31/2008

HFD-647/U. Venkataram/05-Jun-2008

HFD-617/N. Patel/12-Jun-2008

F/T by np

V:\Division of Chemistry II\Team 8\Final version for DFS\78540N02_RSS

TYPE OF LETTER: NOT APPROVABLE (Minor)

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

/s/

Shankar Saha
6/13/2008 01:39:43 PM
CHEMIST

Ubrani Venkataram
6/13/2008 02:00:01 PM
CHEMIST

Nitin Patel
6/13/2008 02:20:55 PM
CSO

ANDA 78-540

Propafenone Hydrochloride Extended release Capsules 225 mg, 325 mg, and 425 mg

Par Pharmaceutical, Inc.

Shankar Saha
OGD/Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-540

2. REVIEW #: 3

3. REVIEW DATE: March 28, 2009

4. REVIEWER: Shankar Saha

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission for 225 mg and 425 mg	October 10, 2006
Electronic QOS	November 6, 2006
Amendment for 325 mg	November 6, 2006
Deficiency Letter	July 26, 2007
First Minor Amendment	November 28, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Second Minor Amendment	July 30, 2008
Telephone Deficiency	April 28, 2009
First Telephone Amendment	May 19, 2009
Telephone Amendment	25 June, 2009
Telephone Amendment	July 16, 2009

7. NAME & ADDRESS OF APPLICANT:

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

U.S. Representative: N/A

Contact Person:
Julie Szozda
Submission Manager, Regulatory Affairs
Telephone: (845) 573-5780

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):

Propafenone Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Rythmol SR® Extended Release Capsules, 225 mg and 425 mg held by Reliant Pharmaceuticals Inc. The NDA number is 21416.

Patent and exclusivity:

Application Number	Patent Number	Patent Expiration
021416	5681588	October 28, 2014

Patent Certification: Paragraph IV Certification is submitted.

Exclusivity statement: Exclusivity expire on September 4, 2006

10. PHARMACOL. CATEGORY: Anti-arrhythmic

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 225 mg, 325 mg, and 425 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

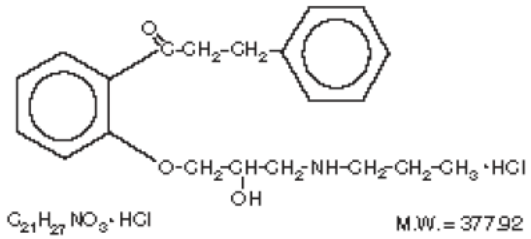
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2'-[2-Hydroxy-3-(propylamino-propoxyl]-3-phenylpropiophenone hydrochloride.

Molecular formula: $C_{21}H_{27}NO_3$. HCl

Molecular Weight: 377.92



2'-[2-Hydroxy-3-(propylamino)-propoxy]-
3-phenylpropiophenone hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	4/22/2009	**S.Saha**
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/15/2007	
Methods Validation	Not requested per OGD policy		
Labeling	Acceptable	6/19/2007	
Bioequivalence	Acceptable	6/15/2007	
EA	Categorical Exclusion		21 CFR 25.31 (a)
Radiopharmaceutical	N/A		
Toxicology consult	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
_X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-540

The QoS was provided in the QbR format and the application was thus treated as a QbR application and reviewed in accordance with the current QbR templates by using the QoS as written and adding reviewer comments in boxed sections. Any additional information added to the QoS text from Module 3 is referred accordingly.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC section is satisfactory; the EER is acceptable; the reviews from DBE and labeling are acceptable. We recommend approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Propafenone hydrochloride is an antiarrhythmic drug supplied as extended-release capsules of 225 mg, 325 mg and 425 mg for oral administration. Propafenone HCl has some structural similarities to beta-blocking agents. Propafenone hydrochloride extended release capsules are filled with granules containing the following inactive ingredients: ethylcellulose, lactose anhydrous, magnesium stearate and povidone. The capsules consist of D&C Red #28, (b) (4) (b) (4) FD&C Blue #1, FD&C Red #40, FD&C Yellow #5, FD&C Yellow #6, gelatin and titanium dioxide. In addition the ink consists of D&C Yellow #10 aluminum lake, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, FD&C Blue #1 aluminum lake and shellac glaze~45% (20% esterified) in ethanol. The formulation suggests possible API-Lactose interaction.

Packaging:
Propafenone HCl Extended Release Capsules, 225 mg are available as hard gelatin capsules containing 225 mg of propafenone HCl. The capsule is a peach opaque cap printed "par/209" in black ink and white opaque body printed "par/209" in black ink. They are available in bottles of 60, 100, 500 and 1000 capsules.

Propafenone HCl Extended Release Capsules, 325 mg are available as hard gelatin capsules containing 325 mg of Propafenone HCl. The capsule is an orange opaque cap printed "par/210" in black ink and white opaque body printed "par/210" in black ink. They are available in bottles of 60, 100, 500 and 1000 capsules.

Propafenone HCl Extended Release Capsules, 425 mg are available as hard gelatin capsules containing 425 mg of Propafenone HCl. The capsule is a red opaque cap printed "par/211" in black ink and white opaque body printed "par/211" in black ink. They are available in bottles of 100, 500 and 1000 capsules.

Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Dispense in a tight container as defined in the USP.

B. Drug Substance

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

C. **Description of How the Drug Product is Intended to be Used**

The dose of Propafenone HCl ER must be individually titrated based on response and tolerance. Therapy should be initiated with Propafenone HCl ER 225 mg given every twelve hours. Dosage may be increased at a minimum of five-day interval to 325 mg given every twelve hours. If additional therapeutic effect is needed, the dose of Propafenone HCl ER may be increased to 425 mg given every twelve hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

Propafenone HCl ER can be taken with or without food. Do not crush or further divide the contents of the capsule. MDD: 850 mg

D. **Basis for Approvability or Not-Approval Recommendation**

ANDA is satisfactory in CMC, EER, labeling and BA/BE evaluations; We recommend the application for approval.

Following this page, 40 pages withheld in full - (b)(4)

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested.

Evaluation:
The drug product has the same indications and usage as the reference listed drug and will not be administered at a higher dosage level or for a longer duration than were previously in effect. As per 21 CFR 25.31(a), the categorical exclusion should be granted.

III. List of Deficiencies to be communicated:

NONE

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540 APPLICANT: Par Pharmaceuticals, Inc

DRUG PRODUCT: Propafenone HCl Extended Release Capsules, 225 mg, 325 mg, and 425 mg

The CMC review is acceptable.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 78-540
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/S. Saha, PH. D./05/19/2009; 7/17/2009

HFD-647/U. Venkataram, Ph. D./21-Jul-2009

HFD-617/N. Patel/28-Jul-2009

F/T by np

V:\Division of Chemistry II\Team 8\Final version for DFS\78540N03_RSS

TYPE OF LETTER: APPROVABLE

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
ANDA 78540	ORIG 1	PAR PHARMACEUTICAL	PROPAFENONE HYDROCHLORIDE

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

/s/

SHANKAR L SAHA
07/31/2009

UBRANI V VENKATARAM
07/31/2009

NITIN K PATEL
07/31/2009

ANDA 78-540

Propafenone Hydrochloride Extended release Capsules 225 mg, 325 mg, and 425 mg

Par Pharmaceutical, Inc.

Shankar Saha
OGD/Chemistry II

Table of Contents

Chemistry Review Data Sheet

1. ANDA 78-540

2. REVIEW #: 4

3. REVIEW DATE: August 30, 2010; 10-Sep-2010

4. REVIEWER: Shankar Saha

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission for 225 mg and 425 mg	October 10, 2006
Electronic QOS	November 6, 2006
Amendment for 325 mg	November 6, 2006
Deficiency Letter	July 26, 2007
First Minor Amendment	November 28, 2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Second Minor Amendment	July 30, 2008
Telephone Deficiency	April 28, 2009
First Telephone Amendment	May 19, 2009
Telephone Amendment	25 June, 2009
Telephone Amendment	July 16, 2009
Telephone Amendments	June 04, 2010; June 07, 2010; June 22, 2010; July 27, 2010; August 17, 2010 and August 25, 2010. September 08, 2010

7. NAME & ADDRESS OF APPLICANT:

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977

U.S. Representative: N/A

Contact Person:
Julie Szozda
Submission Manager, Regulatory Affairs
Telephone: (845) 573-5780

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A

b) Non-Proprietary Name (USAN):

Propafenone Hydrochloride Extended Release Capsules

9. LEGAL BASIS FOR SUBMISSION:

The RLD is Rythmol SR® Extended Release Capsules, 225 mg and 425 mg held by Reliant Pharmaceuticals Inc. The NDA number is 21416.

Patent and exclusivity:

Application Number	Patent Number	Patent Expiration
021416	5681588	October 28, 2014

Patent Certification: Paragraph IV Certification is submitted

Exclusivity statement: Exclusivity expire on September 4, 2006

10. PHARMACOL. CATEGORY: Anti-arrhythmic

11. DOSAGE FORM: Extended Release Capsules

12. STRENGTH/POTENCY: 225 mg, 325 mg, and 425 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

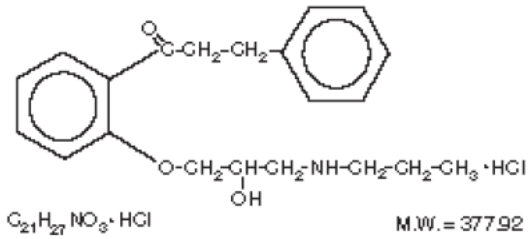
__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 2'-[2-Hydroxy-3-(propylamino-propoxyl]-3-phenylpropiophenone hydrochloride.

Molecular formula: $C_{21}H_{27}NO_3$. HCl

Molecular Weight: 377.92



2'-[2-Hydroxy-3-(propylamino)-propoxy]-3-phenylpropiophenone hydrochloride

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)		1	Adequate	4/22/2009	**S.Saha**
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)	III	(b) (4)	4			
	III		4			

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
None		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	8/15/2007	
Methods Validation	Not requested per OGD policy		
Labeling	Acceptable	6/19/2007	
Bioequivalence	Acceptable	6/15/2007	
EA	Categorical Exclusion		21 CFR 25.31 (a)
Radiopharmaceutical	N/A		
Toxicology consult	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-540

The QoS was provided in the QbR format and the application was thus treated as a QbR application and reviewed in accordance with the current QbR templates by using the QoS as written and adding reviewer comments in boxed sections. Any additional information added to the QoS text from Module 3 is referred to accordingly.

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The CMC section is satisfactory; the EER is acceptable; the reviews from DBE and labeling are acceptable. We recommend approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Propafenone hydrochloride is an antiarrhythmic drug supplied as extended-release capsules of 225 mg, 325 mg and 425 mg for oral administration. Propafenone HCI has some structural similarities to beta-blocking agents. Propafenone hydrochloride extended release capsules are filled with granules containing the following inactive ingredients: ethylcellulose, lactose anhydrous, magnesium stearate and povidone. The capsules consist ofD&C Red #28, (b) (4) (b) (4), FD&C Blue #1, FD&C Red #40, FD&C Yellow #5, FD&C Yellow #6, gelatin and titanium dioxide. In addition the ink consists ofD&C Yellow #10 aluminum lake, iron oxide black, n-butyl alcohol, propylene glycol, FD&C Blue #2 aluminum lake, FD&C Red #40 aluminum lake, FD&C Blue #1 aluminum lake and shellac glaze~45% (20% esterified) in ethanol.

Packaging:
Propafenone HCI Extended Release Capsules, 225 mg are available as hard gelatin capsules containing 225 mg of propafenone HCl. The capsule is a peach opaque cap printed "parI209" in black ink and white opaque body printed "parI209" in black ink. They are available in bottles of 60, 100, 500 and 1000 capsules.

Propafenone HCI Extended Release Capsules, 325 mg are available as hard gelatin capsules containing 325 mg of Propafenone HCl. The capsule is an orange opaque cap printed "parI210" in black ink and white opaque body printed "parl21 0" in black ink. They are available in bottles of 60, 100, 500 and 1000 capsules.

Propafenone HCl Extended Release Capsules, 425 mg are available as hard gelatin capsules containing 425 mg of Propafenone HCl. The capsule is a red opaque cap printed "par/211" in black ink and white opaque body printed "par/211" in black ink. They are available in bottles of 100, 500 and 1000 capsules.

Storage:
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]. Dispense in a tight container as defined in the USP.

B. Drug Substance

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

C. **Description of How the Drug Product is Intended to be Used**

The dose of Propafenone HCl ER must be individually titrated based on response and tolerance. Therapy should be initiated with Propafenone HCl ER 225 mg given every twelve hours. Dosage may be increased at a minimum of five-day interval to 325 mg given every twelve hours. If additional therapeutic effect is needed, the dose of Propafenone HCl ER may be increased to 425 mg given every twelve hours.

In patients with hepatic impairment or having significant widening of the QRS complex or second or third degree AV block, dose reduction should be considered.

Propafenone HCl ER can be taken with or without food. Do not crush or further divide the contents of the capsule. MDD: 850 mg

D. **Basis for Approvability or Not-Approval Recommendation**

ANDA is satisfactory in CMC, EER, labeling and BA/BE evaluations; we recommend the application for approval.

Following this page, 46 pages withheld in full - (b)(4)

A APPENDICES
A.1 Facilities and Equipment (biotech only) – N/A
A.2 Adventitious Agents Safety Evaluation – N/A
A.3 Novel Excipients-N/A

R REGIONAL INFORMATION
R1 Executed Batch Records

The information on executive batches are provided. See section P.3.5 for details and comparison with proposed commercial batches. Information is noted in the text of the review.

R2 Information on Components

The firm provides vendor statements of compliance with OVI/residual solvent and animal sourcing requirements for the excipients used.

R3 Methods Validation Package

Provided; No FDA validation of the methods is requested per policy.

II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Chemical Name: Satisfactory

Chemical Structure: ,,
Empirical Formula: ,,
Molecular Weight: ,,
Description including
List of excipients: ,,

Professional Labeling Review: Pending

Conclusion: Satisfactory from chemistry perspective

B. Environmental Assessment Or Claim Of Categorical Exclusion

Categorical exclusion from the requirement to prepare an Environmental Assessment is requested.

Evaluation:
The drug product has the same indications and usage as the reference listed drug and will not be administered at a higher dosage level or for a longer duration than were previously in effect. As per 21 CFR 25.31(a), the categorical exclusion should be granted.

III. List of Deficiencies to be communicated:

NONE

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540 APPLICANT: Par Pharmaceuticals, Inc

DRUG PRODUCT: Propafenone HCl Extended Release Capsules, 225 mg, 325 mg, and 425 mg

The CMC review is acceptable.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA # 78-540
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-647/S. Saha, PH. D./05/19/2009; 7/17/2009; 9-10-2010

HFD-647/U. Venkataram, Ph. D./21-Jul-2009; 15-Sep-2010

HFD-617/Tina Nhu/16-Sep-2010

F/T by TN

V:\Division of Chemistry II\Team 8\Final version for DFS\78540_N04_RSS

TYPE OF LETTER: APPROVABLE

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

/s/

SHANKAR L SAHA
09/30/2010

UBRANI V VENKATARAM
10/01/2010

TINA T NHU
10/01/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE DISSOLUTION REVIEW

ANDA No.	78-540
Drug Product Name	Propafenone Hydrochloride Extended-Release Tablets
Strength	225 mg, 325 mg, and 425 mg
Applicant Name	Par Pharmaceutical, Inc.
Applicant Address	One Ram Ridge Road, Spring Valley, NY 10977
Contact Information	Janis Picurro, PH 845-639-5121 and Fax 845-639-5201
Clinical Site	Fasting BE Study No. BA0667005 and Fed BE Study No. BA0667006 BA Research India Ltd., BA Research House, Opp. Pushparaj Towers, Nr. Judges Bungalows, Bodakdev, Ahmedabad-380 054, India
Analytical Site	Fasting BE Study No. BA0667005 and Fed BE Study No. BA0667006 (b) (4)
Submission Date	October 10, 2006
Amendment Date	November 06, 2006 (325 mg New Strength)
Reviewer	April C. Braddy, Ph.D.
First Generic	**Yes**

EXECUTIVE SUMMARY

This is a review of the dissolution testing data only.

There is no USP method for this product but there is an FDA-recommended method. The firm also conducted comparative *in vitro* dissolution testing in three (3) different media at varying pHs: (1) SGF without enzyme, pH 1.2, (2) acetate buffer, pH 4.5, and (3) phosphate buffer, pH 6.8. The other dissolution parameters remained the same. The data showed no evidence of dose dumping. The firm's dissolution testing data with the FDA-recommended method is acceptable. However, the firm did not propose any specifications for its test product. Therefore, based on the submitted data, the FDA-recommends the following specifications:

1 hr:	(b) (4)
4 hrs:	%
12 hrs:	NLT (b) (4) %

The firm should acknowledge and accept the FDA-recommended method and specifications.

The DBE will review the fasted and fed BE studies and waiver requests at a later date.

TABLE 1. SUBMISSION CONTENT CHECKLIST

Information			YES	NO	N/A
Did the firm use the FDA-recommended dissolution method			☒	☐	☐
Did the firm use the USP dissolution method			☐	☐	☒
Did the firm use 12 units of both test and reference in dissolution testing			☒	☐	☐
Did the firm provide complete dissolution data (all raw data, range, mean, % CV, dates of dissolution testing)			☒	☐	☐
Did the firm conduct dissolution testing with its own proposed method			☐	☒	☐
Is FDA method in the public dissolution database (on the web)			☐	☐	☐
SAS datasets submitted to the electronic document room (edr)	Fasting BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Fed BE study	PK parameters	☒	☐	☐
		Plasma concentrations	☒	☐	☐
	Other study	PK parameters	☐	☐	☒
		Plasma concentrations	☐	☐	☒
Are all eight electronic summary biotables present			☒	☐	☐
Are electronic summary biotables in pdf format			☒	☐	☐

If the answer to either of the last two questions is no, indicate which summary biotables are

- Not present:
- Not in pdf format:

FDA-Recommended Dissolution Method		
Medium	0-2 hours	0.08N HCl, 900 mL
	2-12 hours	Phosphate buffer, pH 6.8
	The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours	
Temperature (˚C)	37˚C ± 0.5˚C	
Apparatus	II (Paddle)	
Rotational Speed (rpm)	50 rpm	
Sampling Times (min)	1, 2, 4 and every 2 hours thereafter	
Specifications	Q = (b) (4) % at 1 hr	
	Q = % at 4 hrs	
	Q ≥ (b) (4) % (Q) in 12 hours	
Dosage Units	12	

TABLE 2: IN VITRO DISSOLUTION DATA, FDA-RECOMMENDED METHOD

A. 425 mg Propafenone Hydrochloride Extended-Release Tablets[1]

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV]								Study Report Location
					1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	
Comparative Study Report # CS06.010.0	Test product Propafenone HCl ER Capsules Lot No. 595551	425 mg Capsules	Conditions of Dissolution Testing: Apparatus: II (Paddle) Speed of Rotation: 50 rpm Medium: 0-2 hrs: 900 mL 0.08N HCl 2-12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours Temperature: 37 C+ 0.5 C	12	18 %RSD = 5.2	28 % RSD = 6.1	49 % RSD = 8.1	63 %RSD = 9.6	73 %RSD = 8.7	83 % RSD = 6.8	90 %RSD = 4.8	95 (b) (4) %RSD = 3.5	HP Bio
	Rythmol® (propafenone HCl) ER Capsules 2BC0072			12	12 %RSD = 3.9	22 %RSD = 4.7	43 %RSD = 6.1	57 %RSD = 8.0	69 %RSD = 7.5	78 %RSD = 6.7	85 %RSD = 5.9	90 (b) (4) %RSD = 5.0	

[1] The in vitro dissolution summary table contains the data submitted by the firm. The dissolution reviewer put the data into the table.

B. 325 mg Propafenone Hydrochloride Extended-Release Tablets[1]

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV]								Study Report Location
					1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	
Comparative Study Report # CS06.014.0	Test product Propafenone HCl ER Capsules Lot No. 604728	325 mg Capsules	Conditions of Dissolution Testing: Apparatus: II (Paddle) Speed of Rotation: 50 rpm Medium: 0-2 hrs: 900 mL 0.08N HCl 2-12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours Temperature: 37 C+ 0 5 C	12	18 %RSD = 9.6	30 %RSD = 10.4	53 %RSD = 11.0	68 %RSD = 12.1	79 %RSD = 11.2	87 %RSD = 10.1	91 %RSD = 9.3	93 (b) (4) %RSD = 8.4	HP Bio
	Rythmol® (propafenone HCl) ER Capsules 2BE0118			12	14 %RSD = 10.8	25 %RSD = 7.4	49 %RSD = 5.7	65 %RSD = 8.6	78 %RSD = 8.5	87 %RSD = 7.2	93 %RSD = 5.0	97 (b) (4) %RSD = 4.1	

[1] The in vitro dissolution summary table contains the data submitted by the firm. The dissolution reviewer put the data into the table.

C. 225 mg Propafenone Hydrochloride Extended-Release Tablets[1]

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV] 1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	Study Report Location
Comparative Study Report # CS06.013.0	Test product Propafenone HCl ER Capsules Lot No. 598399	225 mg Capsules	Conditions of Dissolution Testing: Apparatus: II (Paddle) Speed of Rotation: 50 rpm Medium: 0-2 hrs: 900 mL 0.08N HCl 2-12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours Temperature: 37 C+ 0 5 C	12	19 %RSD = 5.4	30 %RSD = 5.8	54 %RSD = 8.9	69 %RSD = 10.3	80 %RSD = 8.5	88 %RSD = 6.1	93 %RSD = 4.1	95 (b) (4) %RSD = 3.2	HP Bio
	Rythmol® (propafenone HCl) ER Capsules Lot No. 2BE0065			12	15 %RSD = 6.1	26 %RSD = 8.8	48 %RSD = 7.3	63 %RSD = 5.8	78 %RSD = 5.5	88 %RSD = 5.3	94 %RSD = 4.9	98 (b) (4) %RSD = 4.5	

[1] The in vitro dissolution summary table contains the data submitted by the firm. The dissolution reviewer put the data into the table.

SOURCE OF FDA METHOD: [OCPB –Clinical Pharmacology & Biopharmaceutics Review, NDA # 21-416 SE5 029, Submission date: January 31, 2003, Rythmol® (propafenone hydrochloride) Extended Release Tablets by Abbott Laboratories (in DFS)]

TABLE 3: IN VITRO DISSOLUTION DATA, IN 3 DIFFERENT MEDIAS AT VARYING pHs[1]

A. Dissolution Profile in pH 1.2 SGF without enzyme, pH 1.2 buffer

1. 425 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 425 mg, Par Pharmaceutical, Inc., Batch# 595551

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	16	27	41	52	60	68	73	78
% RSD	4.5	6.5	7.9	7.8	6.8	6.4	5.9	5.3
High								(b) (4)
Low								

Reference: (b) (6), R06-113, page 1

Rythmol SR 425 mg, Reliant, Lot # 2BC0072

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	14	24	42	56	67	75	83	90
% RSD	5.6	7.6	6.9	5.8	5.9	3.7	3.4	4.1
High								(b) (4)
Low								

Reference: (b) (6), R06-093, page 174

2. 325 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 325 mg, Par Pharmaceutical, Inc., Batch# 604728

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	13	22	34	44	51	58	64	69
% RSD	6.6	5.1	6.1	8.1	8.4	8.6	8.4	7.6
High								(b) (4)
Low								

Reference: (b) (6), R06-125, page 106

Rythmol SR 325 mg, Reliant, Lot # 2BE0118

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	11	20	36	47	57	65	72	78
% RSD	21.9	24.0	23.7	20.4	17.3	15.2	12.7	10.6
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 112

3. 225 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 225 mg, Par Pharmaceutical, Inc., Batch# 598399

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	16	26	39	50	59	67	73	79
% RSD	17.4	16.1	10.9	11.5	11.3	11.0	10.0	9.4
High								(b) (4)
Low								

Reference: (b) (6), R06-125, page 98, 100

Rythmol SR 225 mg, Reliant, Lot # 2BE0065

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	10	19	35	48	60	71	80	87
% RSD	10.0	11.5	13.5	13.6	11.9	9.9	8.1	6.6
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 103

B. Dissolution Profile in Acetate Buffer, pH 4.5

1. 425 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 425 mg, Par Pharmaceutical, Inc., Batch# 595551

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	36	60	77	88	95	98	99	99
% RSD	7.5	9.0	7.9	5.4	3.7	3.0	3.1	3.1
High								
Low								

(b) (4)

Reference: (b) (6), R06-084, page 180

Rythmol SR 425 mg, Reliant, Lot # 2BC0072

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	33	57	73	84	91	96	99	100
% RSD	18.6	17.0	13.2	9.3	5.6	3.0	2.1	2.1
High								
Low								

(b) (4)

Reference: (b) (6) R06-086, page 182

2. 325 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 325 mg, Par Pharmaceutical, Inc., Batch# 604728

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	36	59	74	84	91	95	97	98
% RSD	6.5	6.9	6.9	5.4	4.0	3.0	3.1	3.4
High	(b) (4)							
Low								

Reference: (b) (6) R06-125, page 121

Rythmol SR 325 mg, Reliant, Lot # 2BE0118

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	35	58	74	86	92	97	99	99
% RSD	3.8	6.2	6.3	4.9	3.7	3.1	2.7	2.7
High	(b) (4)							
Low								

Reference: (b) (6) R06-131, page 111

3. 225 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 225 mg, Par Pharmaceutical, Inc., Batch# 598399

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	37	57	72	84	91	95	98	99
% RSD	8.2	8.7	8.4	7.4	5.7	4.2	3.9	3.0
High								(b) (4)
Low								

Reference: (b) (6) R06-115 page 144

Rythmol SR 225 mg, Reliant, Lot # 2BE0065

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	38	60	76	83	97	101	102	103
% RSD	6.7	6.0	5.2	10.2	3.9	3.7	3.7	3.9
High								(b) (4)
Low								

Reference: (b) (6) R06-131, page 97; Kalpana Singh R06-123, page 105

C. Dissolution Profile in Phosphate Buffer, pH 6.8

1. 425 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 425 mg, Par Pharmaceutical, Inc., Batch# 595551

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	38	63	79	90	96	98	98	98
% RSD	6.5	6.1	4.6	3.6	3.4	3.4	3.6	3.3
High								
Low								

(b) (4)

(b) (4)

Reference: (b) (6) R06-101, page 96

Rythmol SR 425 mg, Reliant, Lot # 2BC0072

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	39	64	80	90	97	99	99	99
% RSD	6.4	4.5	4.0	2.9	2.0	2.0	1.7	1.8
High								
Low								

(b) (4)

(b) (4)

Reference: (b) (6) R06-115, page 36

2. 325 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 325 mg, Par Pharmaceutical, Inc., Batch# 604728

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	40	63	81	91	96	97	98	97
% RSD	8.0	5.1	3.8	2.5	2.3	2.6	2.5	2.7
High								(b) (4)
Low								

Reference: (b) (6), R06-135, page 21, 26

Rythmol SR 325 mg, Reliant, Lot # 2BE0118

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	40	65	81	92	98	100	100	100
% RSD	4.3	3.8	3.7	3.3	2.8	2.5	2.4	2.2
High								(b) (4)
Low								

Reference: (b) (6) R06-115, page 157

3. 225 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 225 mg, Par Pharmaceutical, Inc., Batch# 598399

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	40	66	84	95	99	100	100	100
% RSD	7.0	4.8	2.3	0.9	1.2	1.4	1.4	1.4
High								(b) (4)
Low								

Reference: (b) (6), R06-135, page 18

Rythmol SR 225 mg, Reliant, Lot # 2BE0065

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	39	53	79	91	96	98	99	99
% RSD	9.0	26.9	3.8	3.3	3.4	3.2	4.3	3.3
High								(b) (4)
Low								

Reference: (b) (6) R06-135, page 14

[1]These tables were provided by the firm

COMMENTS:

1. The firm's comparative *in vitro* dissolution testing on its test product, Propafenone Hydrochloride (HCl) Extended-Release Capsules, 225 mg (Lot No. 598399), 325 mg (Lot No. 604728), and 425 mg (Lot No. 595551) using the FDA-recommended dissolution method is acceptable.

2. The firm's additional comparative *in vitro* dissolution testing on its test product, Propafenone Hydrochloride (HCl) Extended-Release Capsules, 225 mg (Lot No. 598399), 325 mg (Lot No. 604728), and 425 mg (Lot No. 595551) in the (3) different media at varying pHs: (1) SGF without enzyme, pH 1.2, (2) acetate buffer, pH 4.5, and (3) phosphate buffer, pH 6.8 is acceptable. The dissolution profiles for all strengths of the test product showed no evidence of dose dumping.

3. The firm did not propose specifications for its test product. Therefore, based on the submitted data, the DBE recommends the following specifications:

1 hr:	(b) (4)
4 hrs:	%
12 hrs:	NLT (b) (4) %

4. The FDA-recommended dissolution method is not currently available in the public dissolution database.

5. The reviewer inputted the dissolution testing data using the FDA-recommended method into the summary tables.

DEFICIENCY COMMENTS:

1. The firm should acknowledge and accept the FDA-recommended dissolution method and specifications for its test product, Propafenone Hydrochloride Extended-Release Capsules.

Medium:	0 to 2 hours: 900 mL of 0.08N HCl 2 to 12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	1, 2, 4, and every 2 hours thereafter
Specifications:	1 hr: (b) (4) 4 hrs: % 12 hrs: NLT (b) (4) %

2. In order to improve the review process, the Division of Bioequivalence requests that you provide the *in vitro* dissolution studies summary table using the format provided in Attachment 1 (**Table 4. Summary of In Vitro Dissolution Studies**). We request that you provide the study summary table in this template in an electronic file. We hope to improve the efficiency of our review process and your cooperation is greatly appreciated.

3. The firm should clearly define the SAS data files (.xpt) so that they correspond to the appropriate bioequivalence study. The SAS data files provided by the firm are labeled Propafenone HCL 425mg ER Cap **Fast**-D-1.XPT, Propafenone HCL 425mg ER Cap **Fast**-M-1.XPT, and Propafenone HCL 425mg ER Cap **Fast**-D-2.XPT, Propafenone HCL 425mg ER Cap **Fast**-M-2.XPT. According to the file name, it is unclear to the reviewer which datasets are for the fasting BE study No. BA0667005 and fed BE study No. BA0667006. The DATADEF .pdf file does not provide sufficient information to clear up this discrepancy.

RECOMMENDATIONS:

1. The *in vitro* dissolution testing conducted by Par Pharmaceutical, Inc. on its Propafenone Hydrochloride Extended-Release Capsules, 225, 325, and 425 mg is acceptable.

2. The firm should acknowledge and accept the FDA-recommended dissolution method and specifications for its test product, Propafenone Hydrochloride Extended-Release Capsules, 225, 325, and 425 mg.

3. For future applications, the firm should provide the *in vitro* dissolution summary tables containing the dissolution data as shown in Attachment 1.

4. For this application, the firm should clearly label the SAS data files (.xpt) so that they correspond to the appropriate bioequivalence study.

The firm should be informed of the above deficiency comments and recommendations.

DISSOLUTION CONSULT

From: Seo, Paul
Sent: Thursday, January 25, 2007 2:03 PM
To: Braddy, April
Cc: Seo, Paul
Subject: RE: Additional Dissolution Question for ANDA 78-540: Propafenone HCl ER Tablets

Hi April,

There is no need to request repeat dissolution testing in the pH1.2 media, since the dissolution data submitted by the firm using the "FDA-recommended" is sufficient. Typically, when we request extra dissolution in various media for ER products, it serves as FYI type of info to (1) see if the product may dose dump and (2) provide an idea of how the product performs in alternate media in case the FDA-rec media doesn't work.

That being said, after looking at the current submitted data, I recommend that the firm continue to use the FDA-recommended method of: 900 mL 0.08M HCl (0-2hrs), 900 mL pH 6.8 phosphate buffer (2-12hrs) using paddles at 50 rpm with specs of:

1hr: (b) (4)
4hr: %
12 hrs: NLT (b) (4) %

This is just a recommendation, please consult your TL as well.

Thanks,
Paul

From: Braddy, April
Sent: Thursday, January 25, 2007 1:47 PM
To: Seo, Paul
Subject: Additional Dissolution Question for ANDA 78-540: Propafenone HCl ER Tablets

Good afternoon,

In addition, to the issue concerning the specification for the FDA-recommended method for propafenone HCl ER Tablets, I have another question. The firm conducted additional dissolution testing in 3 different media at 3 different pHs. At the lowest pH of 1.2, the% dissolved is < 80% for all strengths of the tablets after 14 hours. The % dissolved values may range between the (b) (4) (mean < 80%). Should I ask the firm to conduct additional dissolution testing using the medium at pH 1.2 w/ a surfactant? The sampling times recommended are 1, 2, 4, and every 2 hours until at 80% is dissolved.

The dissolution profiles for the test product (all strengths) are acceptable in the other 2 media, w/ a pH 4.5 and pH 6.8 and there appears to be no dose dumping.

Thanks,

April

April C. Braddy, Ph.D.
Pharmacologist

FDA/CDER/OPS/OGD/DBE
PH 301.827.7369
FAX 301.594.0181
April.Braddy@fda.hhs.gov

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-540 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Propafenone Hydrochloride Extended-Release Capsules, 225, 325, and 425 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies and waiver requests will be conducted later. The following deficiencies have been identified:

1. Please provide acknowledgement for your acceptance of the following dissolution method and specifications:

Medium:	0 to 2 hours: 900 mL of 0.08N HCl 2 to 12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	1, 2, 4, and every 2 hours thereafter

The test product should meet the following specifications:

1 hr:	(b) (4)
4 hrs:	%
12 hrs:	NLT (b) (4) %

2. For future applications, please provide the *in vitro* dissolution summary table as shown in Attachment 1 in a word file (.doc) and pdf format.

3. For this application, please clearly define the SAS data files (.xpt) so that they correspond to the appropriate bioequivalence study. The SAS data files provided by the firm are labeled Propafenone HCL 425mg ER Cap **Fast**-D-1.XPT, Propafenone HCL 425mg ER Cap **Fast**-M-1.XPT, and Propafenone HCL 425mg ER Cap **Fast**-D-2.XPT, Propafenone HCL 425mg ER Cap **Fast**-M-2.XPT. According to the file name, it is unclear to the DBE as to which datasets are for the fasting BE study No. BA0667005 and fed BE study No. BA0667006. The DATADEF .pdf file does not provide sufficient information to clear up this discrepancy.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment 1

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV]				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Conditions of Dissolution Testing: Apparatus: Speed of Rotation: rpm Medium: Volume: mL Temperature: °C+ Proposed Specification:	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

CC: ANDA NO. 78-540

BIOEQUIVALENCE - INCOMPLETE Submission date: October 10, 2006

[NOTE: The in vitro testing is incomplete. The fasting and fed BE studies and waiver requests are pending review]

1. DISSOLUTION (Dissolution Data)	Strengths:	225, 325, and 425mg
	Outcome:	**IC**

Outcome Decisions: IC –Incomplete
WinBio Comments: IC

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

/s/

April Braddy
1/31/2007 01:58:55 PM
BIOPHARMACEUTICS

Moheb H. Makary
1/31/2007 02:00:16 PM
BIOPHARMACEUTICS

Dale Conner
1/31/2007 03:13:03 PM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-540
Drug Product Name	Propafenone HCl ER Capsules
Strength(s)	425 mg, 325 mg & 225 mg
Applicant Name	Par Pharmaceutical
Address	One Ram Ridge Road Spring Valley, NY 10977
Applicant's Point of Contact	Janis A. Picurro
Contact's Telephone Number	(845) 425-7100
Contact's Fax Number	(845) 425-7907
Original Submission Date(s)	October 10, 2006
Submission Date(s) of Amendment(s) Under Review	February 7, 2007
Reviewer	Hoainhon Nguyen
Study Number (s)	Study No. BA0667005
Study Type (s)	Fasting Study
Strength (s)	425 mg
Clinical Site	BA Research India Ltd.
Clinical Site Address	BA Research House, Opp. Pushparaj Towers, Nr. Judges Bungalows, Bodakdev Ahmedabad-380 054, India
Analytical Site	(b) (4)
Analytical Site Address	
Study Number (s)	Study No. BA0667006
Study Type (s)	Nonfasting Study
Strength (s)	425 mg
Clinical Site	BA Research India Ltd.
Clinical Site Address	BA Research House, Opp. Pushparaj Towers, Nr. Judges Bungalows, Bodakdev Ahmedabad-380 054, India
Analytical Site	(b) (4)
Analytical Site Address	

1. EXECUTIVE SUMMARY

This submission consisted of two bioequivalence (BE) studies, one under fasting and one under nonfasting conditions, on the firm's Propafenone HCl ER Capsules, 425 mg, comparing it with the RLD product, Rythmol SR® Capsules, 425 mg (propafenone), manufactured by Reliant Pharmaceuticals. The submission also included dissolution data for all strengths of the test and reference products, and waiver requests for the lower strengths, 225 mg and 325 mg.

The fasting BE study was conducted in healthy male subjects, using a dose of 1x425 mg and a two-way crossover study design. The study results are summarized below:

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals – Propafenone				
Fasting Bioequivalence Study (N=78)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/mL)	142.4	140.2	1.016	92.82 – 111.2
AUC∞ (ng hr/mL)	148.0	148.1	0.999	90.54 – 110.2
Cmax (ng/mL)	9.088	8.671	1.048	94.48 – 116.3

Although the results of the metabolite, 5-Hydroxypropafenone, did not meet the confidence interval criteria with respect to log-transformed Cmax, the point estimate for the log-transformed Cmax of the metabolite was within 0.80-1.25 limits. The results of log-transformed AUCt and AUCinfinity of the metabolite met the confidence interval criteria. Currently, the DBE does not apply the confidence interval criteria to the metabolite data. The fasting study is **acceptable.**

The nonfasting BE study was conducted in healthy male subjects, using a dose of 1x425 mg, and a two-way crossover study design. The study results are summarized below:

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals - Propafenone				
Nonfasting Bioequivalence Study (N=71)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/mL)	730.8	735.3	0.994	92.38 – 106.9
AUC∞ (ng hr/mL)	738.9	750.3	0.985	91.36 – 106.2
Cmax (ng/mL)	96.39	96.88	0.995	89.53 – 110.6

In addition, the results of the metabolite also met the confidence interval criteria. The nonfasting study is **acceptable.**

The dissolution testing of the test and RLD products using the FDA-recommended method is **acceptable**. The firm acknowledged the FDA-recommended dissolution method and specifications. The dissolution testing is **complete**.

The waiver requests for the lower strengths, 225 mg and 325 mg, are granted.

The application is **complete.**

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Propafenone HCl ER Capsules, 425 mg, 325 mg & 225 mg
Reference Product	Rythmol SR® (propafenone) Capsules, 425 mg, 325 mg & 225 mg
RLD Manufacturer	Reliant Pharmaceuticals
NDA No.	21-416
RLD Approval Date	September 4, 2003
Indication	Indicated to prolong the time to recurrence of symptomatic atrial fibrillation in patients without structural heart disease.

3.2 PK/PD Information[1]

Bioavailability	Propafenone is known to undergo extensive and saturable presystemic biotransformation which results in a dose and dosage form dependent absolute bioavailability; e.g., a 150 mg immediate release tablet had an absolute bioavailability of 3.4%, while a 300 mg immediate release tablet had an absolute bioavailability of 10.6%. Absorption from a 300 mg solution dose was rapid, with an absolute bioavailability of 21.4%. At still larger doses, above those recommended, bioavailability of propafenone from immediate release tablets increased still further. Relative bioavailability assessments have been performed between RYTHMOL SR capsules and RYTHMOL immediate release tablets. In extensive metabolizers, the bioavailability of propafenone from the SR formulation was less than that of the immediate release formulation as the more gradual release of propafenone from the prolonged-release preparations resulted in an increase in overall first pass metabolism. As a result of the increased first pass effect, higher daily doses of propafenone were required from the SR formulation relative to the immediate release formulation, to obtain similar exposure to propafenone. The relative bioavailability of propafenone from the 325 twice daily regimens of RYTHMOL SR approximates that of RYTHMOL immediate release 150 mg three times daily regimen. Mean exposure to 5-hydroxypropafenone was about 20–25% higher after SR capsule administration than after immediate-release tablet administration.
Food Effect	Food increased the exposure to propafenone 4-fold after single dose administration of 425 mg of RYTHMOL SR. However, in the multiple dose study (425 mg dose BID), the difference between the fed and fasted state was not significant.
Tmax	Maximal plasma levels of propafenone are reached between three (3) to eight (8) hours following the administration of RYTHMOL SR.
Metabolism	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 from 2–10 hours. These patients metabolize propafenone into two active metabolites: 5-hydroxypropafenone which is formed by CYP2D6 and N-depropylpropafenone (norpropafenone) which is formed by both CYP3A4 and CYP1A2. In less than 10% of patients, metabolism of propafenone is slower because the 5-hydroxy metabolite is not formed or is minimally formed. In these patients, the estimated propafenone elimination half-life ranges from 10–32 hours. Decreased ability to form the 5-hydroxy metabolite of propafenone is associated with a diminished ability to metabolize debrisoquine and a variety of other drugs such as encainide, metoprolol, and dextromethorphan whose metabolism is mediated by the CYP2D6 isozyme. In these patients, the N-depropylpropafenone metabolite occurs in quantities comparable to the levels occurring in extensive metabolizers. As a consequence of the observed differences in metabolism, administration of RYTHMOL SR to slow and extensive metabolizers

[1] Rythmol SR® labeling

	results in significant differences in plasma concentrations of propafenone, with slow metabolizers achieving concentrations about twice those of the extensive metabolizers at daily doses of 850 mg/day. At low doses the differences are greater, with slow metabolizers attaining concentrations about three to four times higher than extensive metabolizers. In extensive metabolizers, saturation of the hydroxylation pathway (CYP2D6) results in greater-than-linear increases in plasma levels following administration of RYTHMOL SR capsules. In slow metabolizers, propafenone pharmacokinetics is linear. Because the difference decreases at high doses and is mitigated by the lack of the active 5-hydroxy metabolite in the slow metabolizers, and because steady-state conditions are achieved after four to five days of dosing in all patients, the recommended dosing regimen of RYTHMOL SR is the same for all patients. The large inter-subject variability in blood levels require that the dose of the drug be titrated carefully in patients with close attention paid to clinical and ECG evidence of toxicity. The 5-hydroxypropafenone and norpropafenone metabolites have electrophysiologic properties similar to propafenone *in vitro*. In man after administration of RYTHMOL SR, the 5-hydroxypropafenone metabolite is usually present in concentrations less than 40% of propafenone. The norpropafenone metabolite is usually present in concentrations less than 10% of propafenone.
Excretion	Less than 1% of an orally administered dose is excreted unchanged in urine. 18.5% to 38% of a dose is excreted in the urine as metabolites within 48 hours. Excretion of metabolites is mainly via the feces, approximately 53% in 48 hours. Metabolites are recovered in urine and feces primarily in the form of glucuronide and sulfate conjugates.[2]
Half-life	Fast metabolizer: 2-10 hours; slow metabolizer: 10-32 hours
Inter-subject Variability	With propafenone, there is a considerable degree of inter-subject variability in pharmacokinetics which is due in large part to the first pass hepatic effect and non-linear pharmacokinetics in extensive metabolizers. A higher degree of inter-subject variability in pharmacokinetic parameters of propafenone was observed following both single and multiple dose administration of RYTHMOL SR capsules. Inter-subject variability appears to be substantially less in the poor metabolizer group than in the extensive metabolizer group, suggesting that a large portion of the variability is intrinsic to CYP2D6 polymorphism rather than to the formulation.
Stereochemistry	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 ß-antagonist than the R-enantiomer. Following administration of RYTHMOL immediate release tablets or RYTHMOL SR capsules, the S/R ratio for the area under the plasma concentration-time curve was about 1.7. The S/R ratios of propafenone obtained after administration of 225, 325 and 425 mg RYTHMOL SR is independent of dose. In addition, no difference in the average values of the S/R ratios is evident

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	between genotypes or over time.

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	425 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	425 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in appropriate biological fluid):	Propafenone and its metabolite, 5-hydroxypropafenone
Bioequivalence based on (90% CI):	Propafenone
Waiver request of in-vivo testing (appropriate strengths):	N/A
Source of most recent recommendations:	Control Document No. 06-1627 (b) (4) 11/09/2006)
Summary of OGD or DBE History	The current ANDA is the ***First Generic*** application for the drug product.

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state		
In vitro dissolution	Yes	2
Waiver requests	Yes	1
BCS Waivers		
Clinical Endpoints		
Failed Studies		
Amendments		

3.5 Pre-Study Bioanalytical Method Validation

Report location	/Module5/Module5.3.1.4.pdf
Analyte	Propafenone hydrochloride and 5-Hydroxypropafenone hydrochloride (pg 20, 21)
Internal standard (IS)	(b) (4)
Method description	Protein Precipitation Extraction with LC/MS/MS method (pg 19); Analytical Procedure (AP) Sheet included in Appendix A
Limit of quantitation (ng/mL)	0.1000/0.1000 (LLOQ) to 500.0/500.0 (ULOQ) for Propafenone/5-Hydroxypropafenone (pg 25)
Average recovery of drug (%)	92.4% for Propafenone (pg 25) 90.3% for 5-Hydroxypropafenone
Average recovery of IS (%)	91.0%
Standard curve concentrations (ng/mL)	0.1000/0.1000, 0.2000/0.2000, 0.4000/0.4000, 1.000/1.000, 4.000/4.000, 10.00/10.00, 40.00/40.00, 100.0/100.0, 420.0/420.0 and 500.0/500.0 for Propafenone/5-Hydroxypropafenone (pg 22)
QC concentrations (ng/mL)	0.3000/0.3000, 3.000/3.000, 30.00/30.00 and 400.0/400.0 for Propafenone/5-Hydroxypropafenone
QC Intraday precision range (%)	1.7 to 9.1% for Propafenone 1.5 to 8.5 for 5-Hydroxypropafenone (pg 24)
QC Intraday accuracy range (%)	95.0 to 105% for Propafenone 95.0 to 107% for 5-Hydroxypropafenone
QC Interday precision range (%)	3.7 to 6.9% for Propafenone (pg 24) 4.3 to 5.8% for 5-Hydroxypropafenone
QC Interday accuracy range (%)	98.1 to 101% for Propafenone 97.6 to 101% for 5-Hydroxypropafenone
Bench-top stability (hrs)	24 hours in human plasma @ room temperature (pg 28)
Stock stability (days/hours)	84 days @ 4°C for Propafenone, 5-Hydroxypropafenone and internal standard (Addendum to the Method Validation) 6 hours @ room temperature for drug, metabolite and the internal standard (pg 27-Method Validation)
Processed stability (hrs)	54 hours @ room temperature; 74 hours @ 4°C (pg 28, 29)
Freeze-thaw stability (freeze-thaw cycles)	6 freeze-thaw cycles (pg 27, 28)
Long-term storage stability (days)	83 days @ -20°C (Addendum to Method Validation)
Dilution integrity	2500/2500 ng/mL for Propafenone/ 5-Hydroxypropafenone diluted 10-fold (pg 26)
Selectivity	No interfering peaks noted in blank plasma samples (pg 25)

SOPs submitted	Yes
Bioanalytical method is acceptable	Acceptable

Comments on the Pre-Study Method Validation: The data from the CTD tables above were verified against the data from the pre-study validation report. The data are acceptable.

3.6 In Vivo Studies

Table 1. Summary of Bioavailability Studies

Propafenone

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hrs)	AUC_{0-t} (ng x hr/mL)	AUC_{∞} (ng x hr/mL)	$T½$ (hrs)	K_{el} (1/hr)	
Study # BA0667005	An open label, randomized, two period, two sequence, crossover, comparative evaluation of relative bioavailabilities of two formulations of propafenone HCl extended release capsules 425 mg in healthy adult male subjects under fasting conditions	Open label, randomized, two-period, two-treatment, two-sequence, balanced, single-dose crossover study design	Test: Propafenone HCl 425 mg Extended Release Capsules, p.o. [Lot No. 182097]	78 healthy adults (80 dosed in study); 78 males; 78 Asian; Age range: 18 to 39, Age mean: 25.9; Weight range: 45.0 to 75.0 kg., Weight mean: 58.5 kg.	25.043 ± 60.609	9.237	539.987 ± 1670.234	655.720 ± 1953.480	6.714	0.116	Module 5/ BA0667005/ SRBA0667005. pdf Section 11.4.1, pg. 40, pg. 42
			Reference: RYTHMOL® SR 425 mg Extended Release Tablets, p.o. [Lot No. 2BC0072]		25.505 ± 61.766	10.442	543.875 ± 1760.556	642.179 ± 2092.541	7.811	0.114	
Study # BA0667006	An open label, randomized, two period, two sequence, crossover, comparative evaluation of relative bioavailabilities of two formulations of propafenone HCl extended release capsules 425 mg in healthy adult male subjects under non-fasting conditions	Open label, randomized, two-period, two-treatment, two-sequence, balanced, single-dose crossover study design	Test: Propafenone HCl 425 mg Extended Release Capsules, p.o. [Lot No. 182097]	71 healthy adults (80 dosed in study); 71 males; 71 Asian; Age range: 18 to 38, Age mean: 24.7; Weight range: 47.0 to 77.8 kg., Weight mean: 58.5 kg.	146.630 ± 132.890	5.951	1359.452 ± 1899.157	1365.742 ± 1917.266	5.651	0.138	Module 5/ BA0667006/ SRBA0667006. pdf Section 11.4.1, pg. 42, pg. 44
			Reference: RYTHMOL® SR 425 mg Extended Release Tablets, p.o. [Lot No. 2BC0072]		151.689 ± 140.191	6.268	1382.667 ± 2010.363	1389.336 ± 2032.461	5.625	0.134	

5-Hydroxypropafenone

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. (M/F) Type Age, and Weight: (mean and range)	Mean Parameters (+/-SD)						Study Report Location
					C_{max} (ng/mL)	T_{max} (hrs)	AUC_{0-t} (ng x hr/mL)	AUC_{∞} (ng x hr/mL)	$T^{1}/_{2}$ (hrs)	K_{el} (1/hr)	
Study # BA0667005	An open label, randomized, two period, two sequence, crossover, comparative evaluation of relative bioavailabilities of two formulations of propafenone HCl extended release capsules 425 mg in healthy adult male subjects under fasting conditions	Open label, randomized, two-period, two-treatment, two-sequence, balanced, single-dose crossover study design	Test: Propafenone HCl 425 mg Extended Release Capsules, p.o. [Lot No. 182097]	78 healthy adults (80 dosed in study); 78 males; 78 Asian; Age range: 18 to 39, Age mean: 25.9; Weight range: 45.0 to 75.0 kg., Weight mean: 58.5 kg.	20.004 ± 13.319	8.038	348.634 ± 250.271	357.299 ± 256.515	9.681	0.074	Module 5/ BA0667005/ SRBA0667005. pdf Section 11.4.1, pg. 44, pg. 46
			Reference: RYTHMOL® SR 425 mg Extended Release Tablets, p.o. [Lot No. 2BC0072]		18.196 ± 13.880	8.968	335.224 ± 237.135	346.514 ± 243.391	10.269	0.074	
Study # BA0667006	An open label, randomized, two period, two sequence, crossover, comparative evaluation of relative bioavailabilities of two formulations of propafenone HCl extended release capsules 425 mg in healthy adult male subjects under non-fasting conditions	Open label, randomized, two-period, two-treatment, two-sequence, balanced, single-dose crossover study design	Test: Propafenone HCl 425 mg Extended Release Capsules, p.o. [Lot No. 182097]	71 healthy adults (80 dosed in study); 71 males; 71 Asian; Age range: 18 to 38, Age mean: 24.7; Weight range: 47.0 to 77.8 kg., Weight mean: 58.5 kg.	110.286 ± 55.522	5.620	1190.788 ± 642.165	1202.047 ± 649.459	8.103	0.088	Module 5/ BA0667006/ SRBA0667006. pdf Section 11.4.1, pg. 46, pg. 48
			Reference: RYTHMOL® SR 425 mg Extended Release Tablets, p.o. [Lot No. 2BC0072]		107.817 ± 52.099	5.993	1145.726 ± 601.171	1156.255 ± 606.242	8.064	0.088	

Table 1. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Propafenone

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals - Propafenone				
Fasting Bioequivalence Study (N=78)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/mL)	142.4	140.2	1.016	92.82 – 111.2
AUC∞ (ng.hr/mL)	148.0	148.1	0.999	90.54 – 110.2
Cmax (ng/mL)	9.088	8.671	1.048	94.48 – 116.3

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals - Propafenone				
Nonfasting Bioequivalence Study (N=71)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/mL)	730.8	735.3	0.994	92.38 – 106.9
AUC∞ (ng.hr/mL)	738.9	750.3	0.985	91.36 – 106.2
Cmax (ng/mL)	96.39	96.88	0.995	89.53 – 110.6

Table 2. Reanalysis of Study Samples

Propafenone

Study No. BA0667005 Propafenone Additional Information in Module5/BA0667005/Appendices/App16.5.pdf, Pages 15, 16, 35-37								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	1	3	0.03	0.09	1	3	0.03	0.09
Lower limit of quantitation eliminated	1	3	0.03	0.09	1	3	0.03	0.09
Data acquisition malfunction	0	1	0.00	0.03	0	1	0.00	0.03
High internal standard	0	2	0.00	0.06	0	2	0.00	0.06
Reinjected sample did not meet SOP acceptance criteria	6	7	0.18	0.20	6	7	0.18	0.20
Interference from an endogenous	1	0	0.03	0.00	1	0	0.03	0.00
Peak in pre-dose sample	3	1	0.09	0.03	3	1	0.09	0.03

5-Hydroxypropafenone

Study No. BA0667005 5-Hydroxypropafenone Additional Information in Module5/BA0667005/Appendices/App16.5.pdf, Pages 15, 16, 35-37								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Low internal standard	1	4	0.03	0.12	1	4	0.03	0.12
Data acquisition malfunction	0	1	0.00	0.03	0	1	0.00	0.03
High internal standard	0	2	0.00	0.06	0	2	0.00	0.06
Reinjected sample did not meet SOP acceptance criteria	6	7	0.18	0.20	6	7	0.18	0.20
Peak in pre-dose sample	0	1	0.00	0.03	0	1	0.00	0.03

Did use of recalculated plasma concentration data change study outcome? N/A. There was no PK repeat sample.

Comments from the Reviewer: The fasting and nonfasting studies are **acceptable.**

3.7 Formulation

Location in appendix	Section 4.2, Page 43
If a tablet, is the RLD scored?	**N/A**
If a tablet, is the test product biobatch scored	**N/A**
Is the formulation acceptable?	**Acceptable**
If not acceptable, why?	

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	DFS
Source of Method (USP, FDA or Firm)	FDA
Medium	0-2 hours: 0.08M HCl (900 mL) 2-12 hours: Phosphate buffer, pH 6.8 (1000 mL)*
Volume (mL)	See above
USP Apparatus type	II (paddle)
Rotation (rpm)	50
FDA specifications (based on the data submitted for the test product)	1 hr: (b) (4) 4 hrs: % 12 hrs: NLT (b) (4)%
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	High CV%
Is method acceptable?	**Acceptable** The firm acknowledged the FDA-recommended method and specifications in the amendment dated February 7, 2007.
If not then why?	

***NOTE:** The dissolution testing starts with 900 mL of 0.08 N HCl; at 2 hours, 100 mL of the preheated buffer concentrate was added to the original vessel.

3.9 Waiver Request(s)

Strengths for which waivers are requested	225 mg & 325 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	

3.10 Deficiency Comments

None

3.11 Recommendations

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Par Pharmaceutical on its Propafenone HCl ER Capsules, 425 mg, Lot No. 182097, comparing it to Reliant Pharmaceuticals' Rythmol SR® Capsules, 425 mg, (propafenone), Lot No. 2BC0072, are **acceptable.**

2. The dissolution testing conducted by the firm on its Propafenone HCl ER Capsules, 425 mg, 325 mg and 225 mg, is acceptable.

   The dissolution testing should be conducted in 900 mL of 0.08 M HCl for the first two (2) hours, followed by 1000 mL of pH 6.8 Phosphate Buffer for 2-12 hours, at 37°C ± 0.5°C using USP Apparatus II (paddle) @ 50 rpm (The second medium is obtained by adding a buffer concentrate to the initial (HCl) medium). The test product should meet the following specification:

   1 hr: (b) (4)
   4 hrs %
   12 hrs: NLT (b) (4) %

3. The waiver requests for the lower strengths of the test product, Par Pharmaceutical's Propafenone HCl ER Capsules, 220 mg and 325 mg, are granted.

The application is **complete.**

3.12 Comments for Other OGD Disciplines

Discipline	Comment
	None

4. APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study

4.1.1.1 Study Design

Table 3 Study Information

Study Number	BA0667005
Study Title	An Open Label, Randomized, Two Period, Two Sequence, Crossover, Comparative Evaluation of Relative Bioavailabilities of Two Formulations of Propafenone HCl Extended Release Capsules 425 mg in Healthy Adult Male Subjects Under Fasting Conditions
Clinical Site (Name & Address)	BA Research India Ltd., Badakdev, Ahmedabad, India
Principal Investigator	Roma Choudhury
Dosing Dates	Period I: May 23, 2006 (Group I) and May 27, 2006 (Group II); Period II: June 1, 2006 (Group I) and June 5, 2006 (Group II)
Analytical Site (Name & Address)	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	June 13, 2006 – July 7, 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	45 days

Table 4. Product information

Product	**Test**	**Reference**
Treatment ID	A	B
Product Name	Propafenone	Rythmol SR®
Manufacturer	Par Pharmaceutical	Reliant Pharmaceutical
Batch/Lot No.	182097	2BC0072
Manufacture Date	04/2006	
Expiration Date		08/2006
Strength	425 mg	425 mg
Dosage Form	Capsules	Capsules
Bio-Batch Size	(b) (4)	
Production Batch Size	Not provided	
Potency (Assay)	98.5%	100.7%

Content Uniformity (mean, %CV)	98.9%(RSD=1.9%)	
Dose Administered	1x425 mg	1x425 mg
Route of Administration	Oral	Oral

Table 5. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	80 participated (dosed); 78 completed (NOTE: 40 plus 4 alternates were enrolled for Group I; 40 plus 4 alternates were enrolled for Group II. Alternate Subject #81 replaced Subject #32 in Group I prior to Period I; three remaining alternates were checked out after Period I dosing of 40 subjects. Alternate Subjects #82, 83 and 84 replaced Subjects #79, 63 and 69, respectively, in Group II, prior to Period I; remaining alternate subject was checked out after Period I dosing of 40 subjects.)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	AB: 2, 3, 5, 8, 10, 11, 14, 15, 18, 20, 21, 24, 26, 27, 30, 32, 33, 35, 38, 39 (from Group I); 41, 44, 46, 48, 50, 52, 53, 56, 58, 60, 61, 63, 66, 67, 70, 72, 73, 75, 77, 80 (NOTE: Randomization was done on 80 subjects dosed, not on 88 subjects enrolled) BA: remaining subjects
Blood Sampling Times	Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 24, 36, 48 and 60 hours postdose
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	Blood samples were collected in K_3EDTA collection tubes, centrifuged at high speed in a refrigerated centrifuge for 15 minutes, and harvested for plasma which was stored at -20°C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	At least 10 hours predose until 4 hours postdose
Length of Confinement	At least 10 hours predose until 24 hours postdose
Safety Monitoring	Sitting vital signs were measured at predose and at approximately 2, 4, 6, 8 and 12 hours postdose for each study period. ECG recording was done at 2 and 6 hours postdose for each study period.

Comments on Study Design:

The study design is acceptable.

4.1.1.2 Clinical Results

Table 6. Demographics Profile of Subjects Completing the Bioequivalence Study

Study No. BA0667005		
	Treatment Groups	
	Test Product N = 78	Reference Product N = 78
Age (years)		
Mean ± SD	25.9± 5.5	25.9± 5.5
Range	18-39	18-39
Groups		
< 18	-	-
18 - 40	78 (100%)	78 (100%)
40 - 64	-	-
65 - 75	-	-
> 75	-	-
Sex		
Female	-	-
Male	78 (100%)	78 (100%)
Race		
Asian	78(100%)	78 (100%)
Black	-	-
Caucasian	-	-
Hispanic	-	-
Other	-	-
Other Factors	-	-

Table 7. Dropout Information, Fasting Bioequivalence Study

Subject No.	Reason	Period	Replaced?
32	Low pulse rate	Prior to Period I	Yes, with Subject #81
79	Vomiting	Prior to Period I	Yes, with Subject #82
63	Low pulse rate	Prior to Period I	Yes, with Subject #83
69	Low pulse rate	Period to Period I	Yes, with Subject #84
59	High heart rate and pulse rate; fever	Period II	No
83	Fever (48 minutes postdose); high pulse rate	Period I	No

Table 8. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No. BA0667005		Fed Bioequivalence Study Study No.		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body As A Whole						
Weakness	-	1(1.28%)	-	-	-	-
Fever	2(2.56%)	1(1.28%)	-	-	-	-
Heartburn due to acidity	1(1.28%)	-	-	-	-	-
Dry skin	-	1(1.28%)	-	-	-	-
Respiratory Syste			-	-	-	-
Dry Cough	-	1(1.28%)	-	-		
Total	3(3.85%)	4(5.13%)	-	-	-	-

Table 9. Protocol Deviations, Fasting Bioequivalence Study

There was no significant protocol deviation that might have affected the integrity of the study results.

Comments on Dropouts/Adverse Events/Protocol Deviations:

There was no significant sampling time deviation reported.

4.1.1.3 Bioanalytical Results

Table 10. Assay Validation – Within the Fasting Bioequivalence Study

Propafenone										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	0.400	1.00	4.00	10.0	40.0	100.0	420.0	500.0
Inter day Precision (%CV)	2.8	5.0	3.3	3.2	2.8	2.5	2.8	2.3	4.1	4.9
Inter day Accuracy (%Actual)	97.4	103	104	96.6	102	100	103	101	95.6	96.7
Linearity	0.9933 – 0.9996									
Linearity Range (ng/mL)	0.100 – 500.0									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	400.0 (n=80)	30.00 (n=80)	3.00 (n=79)	0.300 (n=79)
Inter day Precision (%CV)	5.3	6.1	7.2	13.6
Inter day Accuracy (%Actual)	93.7	103	102	104

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Comments on Chromatograms: Acceptable.

Table 11. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
SOP L200.113	03/06/06	Sample Analysis (Chromatographic)
SOP L1100.100	01/17/06	Sample Reanalysis and Reporting Criteria

Table 12. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	There was no PK repeat assay.

Summary/Conclusions, Study Assays: Acceptable.

4.1.1.4 Pharmacokinetic Results

Table 13. Arithmetic Mean Pharmacokinetic Parameters of Propafenone

Propafenone Dose=1x425 mg									
Fasting Bioequivalence Study No. BA0667005 (N=78)									
	Test				Reference				
Parameter	Mean	Coeff of Variation	Minimum	Maximum	Mean	Coeff of Variation	Minimum	Maximum	Mean T/R*
AUCT (ng.hr/mL)	528.09	311.36	25.34	10832.54	539.43	325.32	20.71	12087.29	1.15
AUCI (ng.hr/mL)	574.64	312.12	28.59	12008.36	621.36	332.48	22.97	13692.18	1.15
CPEAK (ng/mL)	25.04	242.02	1.84	345.40	25.50	242.17	0.90	321.50	1.24
TPEAK (hrs)	9.24	63.26	4.50	24.00	10.44	62.76	4.50	36.00	1.04
THALF (hrs)	7.36	67.26	3.16	36.40	7.96	89.34	2.77	58.88	1.09
KEL (hrs^{-1})	0.12	35.16	0.02	0.22	0.11	37.97	0.01	0.25	1.19

*__NOTE:__ This column represents means of individual T/R ratios, not ratios of the T/R means.

Table 14. Geometric Means and 90% Confidence Intervals Calculated by the Firm

Propafenone

Propafenone HCl 1 x 425 mg Extended Release Capsule Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t}	142.963	140.430	102	(93.0; 111)
AUC_{∞}	151.004	147.822	102	(91.8; 114)
C_{max}	9.088	8.671	105	(94.5; 116)

5-Hydroxypropafenone

Propafenone HCl 1 x 425 mg Extended Release Capsule Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t}	268.317	253.441	106	(97.8; 115)
AUC_{∞}	275.722	261.956	105	(97.2; 114)
C_{max}	16.173	13.648	119	(108; 130)

Table 15. Geometric Means and 90% Confidence Intervals Calculated by the Reviewer - Propafenone

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (N=78)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/mL)	142.4	140.2	1.016	92.82 – 111.2
AUC∞ (ng.hr/mL)	148.0	148.1	0.999	90.54 – 110.2
Cmax (ng/mL)	9.088	8.671	1.048	94.48 – 116.3

Table 16. Additional Study Information - Propafenone

Root mean square error, AUC0-t	0.339274	
Root mean square error, AUC∞	0.347593	
Root mean square error, Cmax	0.389547	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	0.96 (0.72-1.00)	0.95 (0.30-1.00)
Kel and AUC∞ determined for how many subjects?	74	74
Do you agree or disagree with firm's decision?	No; however, the study outcome was the same by either determination.	No; however, the study outcome was the same by either determination.
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1 (<5% of Cmax)	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	Yes (2 groups)	Yes (2 groups)

Comments on Pharmacokinetic and Statistical Analysis:

1. Subject #12 had the AUCt/AUCinfinity ratio of 0.30173 under Reference treatment. Analysis without Subject #12 did not change the study outcome, as shown below:

Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study (N=78)				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng hr/mL)	145.8	143.3	1.017	92.81 – 111.5
AUC∞ (ng.hr/mL)	151.4	149.2	1.015	92.26 – 111.7
Cmax (ng/mL)	9.286	8.919	1.041	93.77 – 115.6

2. The group*treatment interaction term was not statistically significant and dropped from the final statistical analysis.

3. The study results met the confidence interval acceptance criteria for the parent drug, propafenone. Although the study results of the metabolite, 5-Hydroxypropafenone, as reported by the firm, did not meet the confidence interval acceptance criteria with respect to log-transformed Cmax, the 5-Hydroxypropafenone Cmax point estimate was less than 20%. The Root MSE values for lnAUCt, lnAUCinfinity and lnCmax of the metabolite were 0.295457, 0.297154 and 0.338068, respectively. The intra-subject variability of the metabolite was similar to that of the parent drug.

Currently, the DBE does not apply the confidence interval criteria to the metabolite results.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:

The fasting study is **acceptable.**

Table 17. Propafenone Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (ng/mL)

Test Treatment

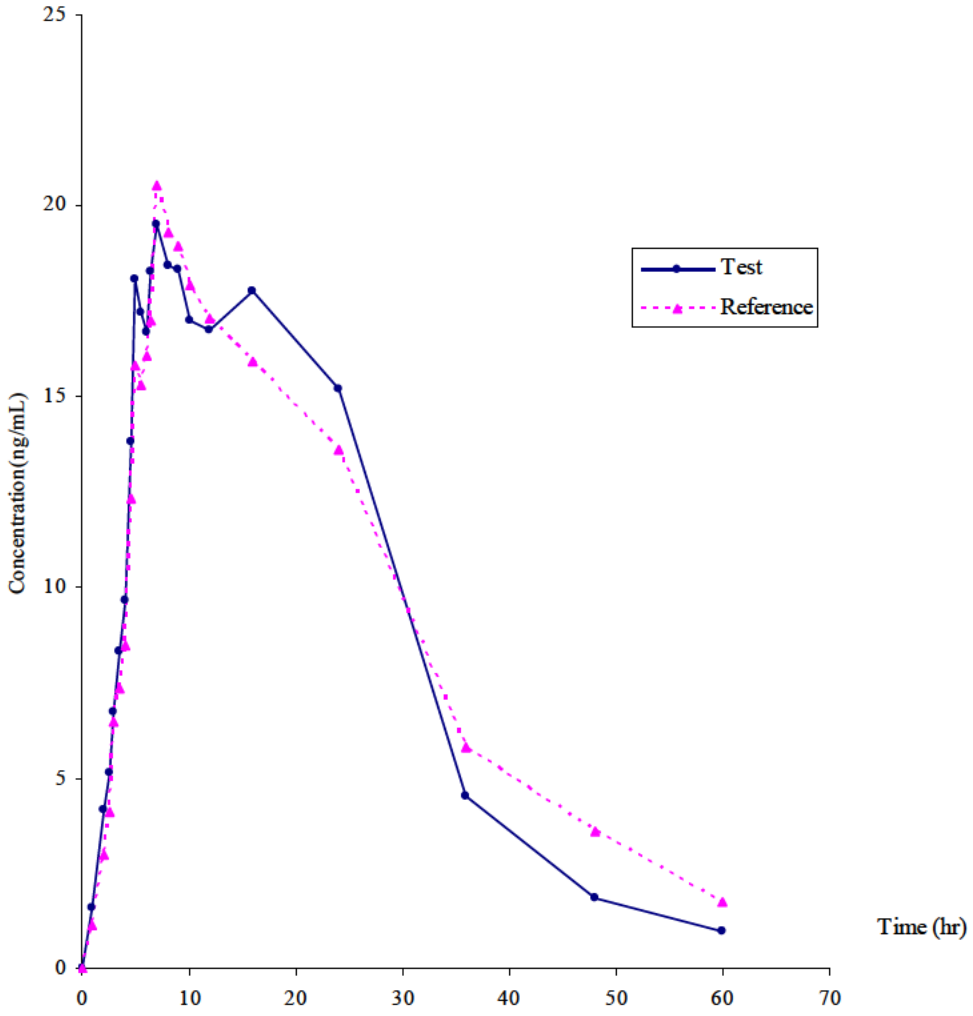
Time	Mean	N	Coeff of Variation	Minimum	Maximum
Hour0	0.006	78	883.176	0.000	0.485
Hour1	1.573	78	212.051	0.000	25.800
Hour2	4.161	78	265.515	0.140	77.080
Hour2.50	5.124	78	273.471	0.235	102.300
Hour3	6.730	78	269.327	0.326	132.200
Hour3.50	8.319	78	289.204	0.382	183.500
Hour4	9.649	78	278.393	0.399	186.300
Hour4.50	13.811	78	232.334	0.705	206.300
Hour5	18.095	78	240.114	0.841	268.600
Hour5.50	17.194	78	239.596	0.813	264.700
Hour6	16.675	78	238.770	0.426	240.100
Hour6.50	18.286	78	237.219	1.039	259.500
Hour7	19.512	78	246.359	0.660	256.100
Hour8	18.446	78	257.675	0.862	272.300
Hour9	18.334	78	258.082	0.777	252.400
Hour10	17.010	78	260.349	0.747	241.900
Hour12	16.718	78	289.340	0.679	296.900
Hour16	17.737	78	309.753	0.600	345.400
Hour24	15.195	78	317.398	0.237	311.500
Hour36	4.522	78	485.061	0.000	176.200
Hour48	1.851	78	515.396	0.000	79.340
Hour60	0.979	78	674.166	0.000	57.490

Reference Treatment

Time	Mean	N	Coeff of Variation	Minimum	Maximum
Hour0	0.000	78	.	0.000	0.000
Hour1	1.109	78	163.052	0.000	10.190
Hour2	3.003	78	220.214	0.211	42.410
Hour2.50	4.120	78	231.410	0.277	49.920
Hour3	6.467	78	294.729	0.241	141.100
Hour3.50	7.325	78	262.479	0.201	107.000
Hour4	8.474	78	267.874	0.400	126.000
Hour4.50	12.335	78	246.632	0.455	167.000
Hour5	15.799	78	239.990	0.716	225.100
Hour5.50	15.313	78	233.421	0.675	205.700
Hour6	16.081	78	238.622	0.580	222.800
Hour6.50	17.012	78	233.520	0.711	205.700
Hour7	20.528	78	262.701	0.757	301.300
Hour8	19.291	78	261.990	0.764	265.400
Hour9	18.965	78	266.003	0.900	253.700
Hour10	17.935	78	270.821	0.747	240.300
Hour12	17.064	78	274.459	0.790	256.000
Hour16	15.904	78	292.097	0.828	295.500
Hour24	13.608	78	333.511	0.264	321.500
Hour36	5.805	78	468.364	0.000	215.200
Hour48	3.582	78	562.651	0.000	158.100
Hour60	1.767	78	586.104	0.000	67.030

Figure 1

Propafenone Mean Plasma Concentrations
Single Dose Fasting Study



4.1.2 Single-dose Fed Bioequivalence Study

4.1.2.1 Study Design

Table 18. Study Information

Study Number	BA0667006
Study Title	An Open Label, Randomized, Two Period, Two Sequence, Crossover, Comparative Evaluation of Relative Bioavailabilities of Two Formulations of Propafenone HCl Extended Release Capsules 425 mg in Healthy Adult Male Subjects Under Non-Fasting Conditions
Clinical Site (Name & Address)	BA Research India Ltd., Badakdev, Ahmedabad, India
Principal Investigator	Roma Choudhury
Dosing Dates	Period I: August 1, 2006 (Group I) and August 3, 2006 (Group II); Period II: August 8, 2006 (Group I) and August 10, 2006 (Group II)
Analytical Site (Name & Address)	(b) (4)
Analytical Director	(b) (6)
Analysis Dates	September 14, 2006 – September 26, 2006
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	57 days

Table 19. Product Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Propafenone	Rythmol SR®
Manufacturer	Par Pharmaceutical	Reliant Pharmaceutical
Batch/Lot No.	182097	2BC0072
Manufacture Date	04/2006	
Expiration Date		08/2006
Strength	425 mg	425 mg
Dosage Form	Capsules	Capsules
Bio-Batch Size	(b) (4)	
Production Batch Size	Not provided	
Potency (Assay)	98.5%	100.7%
Content Uniformity (mean, %CV)	98.9%(RSD=1.9%)	
Dose Administered	1x425 mg	1x425 mg

Route of Administration	Oral	Oral

Table 20. Study Design, Single-Dose Fed Bioequivalence Study

No. of Subjects	80 participated (dosed); 71 completed (NOTE: 40 plus 6 alternates were enrolled for Group I; 40 plus 6 alternates were enrolled for Group II. Alternate Subject #81 replaced Subject #28 in Group I prior to Period I; five remaining alternates were checked out after Period I dosing of 40 subjects. Alternate Subject #82 replaced Subject #63 in Group II, prior to Period I; remaining five alternate subjects were checked out after Period I dosing of 40 subjects.)
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	AB: 2, 4, 5, 7, 9, 11, 14, 15, 17, 20, 22, 24, 25, 28, 29, 32, 33, 35, 37, 39 (from Group I); 41, 43, 46, 48, 50, 52, 54, 56, 58, 59, 61, 64, 66, 68, 69, 71, 74, 76, 78, 80 (NOTE: Randomization was done on 80 subjects dosed, not on 92 subjects enrolled) BA: remaining subjects
Blood Sampling Times	Predose, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48 and 60 hours postdose
Blood Volume Collected/Sample	5 mL
Blood Sample Processing/Storage	Blood samples were collected in K_3EDTA collection tubes, centrifuged at high speed in a refrigerated centrifuge for 15 minutes, and harvested for plasma which was stored at -20°C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting Before Meal	At least 10 hours predose until 4 hours postdose
Length of Confinement	At least 10 hours predose until 24 hours postdose
Safety Monitoring	Sitting vital signs were measured at predose and at approximately 2, 4, 6, 8 and 12 hours postdose for each study period. ECG recording was done at 2 and 6 hours postdose for each study period.
Standard FDA Meal Used?	No
If No, then meal composition is listed in the table below	The breakfast consisted of a glass of milk, chicken cutlet, tomato slices, 2 slices of buttered bread. See meal composition below.

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**

Fat	59	597
Carbohydrate	24	246
Protein	17	170
Total		1013

Comments on Study Design:

The study design is acceptable.

4.1.2.2 Clinical Results

Table 21. Demographics of Subjects Completing the Bioequivalence Study

Study No. BA0667006		
	Treatment Groups	
	Test Product N = 71	Reference Product N = 71
Age (years)		
Mean ± SD	24.7± 4.9	24.7± 4.9
Range	18-38	18-38
Groups		
< 18	-	-
18 - 40	71 (100%)	71 (100%)
40 - 64	-	-
65 - 75	-	-
> 75	-	-
Sex		
Female	-	-
Male	71 (100%)	71 (100%)
Race		
Asian	71 (100%)	71 (100%)
Black	-	-
Caucasian	-	-
Hispanic	-	-
Other	-	-
Other Factors	-	-

Table 22. Dropout Information, Fed Bioequivalence Study

Subject No.	Reason	Period	Replaced?
12	Personal reasons	II	No
17	Accidental injury at right great toe	II	No
26	Adverse events (vomiting, nausea and abdominal pain at around 3 hours 26 minutes postdose	I	No
27	Fever	I	No
29	Vomiting at 4 hours 5 minutes postdose	I	No
32	Vomiting at 6 hours 29 minutes postdose	I	No
54	Cough	II	No
56	Fever	II	No
68	Complaint of a stye at the lower lid of the right eye	II	No

Table 23. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event	Reported Incidence by Treatment Groups					
	Fasted Bioequivalence Study Study No.		Fed Bioequivalence Study Study No. BA0667006		Other Bioequivalence Study Study No.	
	Test	Reference	Test	Reference	Test	Reference
Body As A Whole						
Accidental injury right toe of right l			1(1.41%)	-		
Fever with headac			-	1(1.41%)		
Viral Fever	-	-	1(1.41%)	1(1.41%)		
Gastrointestina System						
Vomiting with gastritis	-	-	-	1(1.41%)		
Vomiting	-	-	1(1.41%)	1(1.41%)		
Abdominal pain (Gastritis)	-	-	1(1.41%)	-		
Special Senses						
Stye right lower l	-	-	1(1.41%)	-		
Upper respirator tract infection						
URTI with sputu			1(1.41%)	-		
Total	-	-	6(8.45%)	4(5.63%)	-	-

NOTE: All subjects who vomited were discontinued (Subjects #26, 29 and 32).

Table 24. Protocol Deviations, Fed Bioequivalence Study

There was no significant protocol deviation that might have affected the integrity of the study results.

Comments on Adverse Events/Protocol Deviations: There was no significant blood sampling time deviation.

4.1.2.3 Bioanalytical Results

Table 25. Assay Validation – Within the Fed Bioequivalence Study

Propafenone										
Parameter	**Standard Curve Samples**									
Concentration (ng/mL)	0.100	0.200	0.400	1.00	4.00	10.0	40.0	100.0	420.0	500.0
Inter day Precision (%CV)	3.6	6.4	4.6	3.4	2.9	2.7	2.5	2.7	3.3	3.5
Inter day Accuracy (%Actual)	100	100	101	94.8	97.4	98.0	104	104	101	99.1
Linearity	0.9942 – 0.9993									
Linearity Range (ng/mL)	0.100 – 500.0									
Sensitivity/LOQ (ng/mL)	0.100									

Parameter	**Quality Control Samples**				
Concentration (ng/mL)	400.0 (n=74)	30.00 (n=74)	3.00 (n=74)	0.300 (n=73)	400.0 (dil.) (n=3)
Inter day Precision (%CV)	4.6	6.2	7.2	7.8	1.7
Inter day Accuracy (%Actual)	100	103	96.4	95.6	94.7

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially

Table 26. SOP's Dealing with Bioanalytical Repeats of Study Samples

See under the Fasting Study.

Table 27. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of plasma concentrations change the study outcome?	N/A
Does the reviewer agree with the outcome of the repeat assays?	There was no PK repeat sample.

Summary/Conclusions, Study Assays: The during-study validation is **acceptable.**

4.1.2.4 Pharmacokinetic Results

Table 28. Arithmetic Mean Pharmacokinetic Parameters

Propafenone HCl ER Capsules Dose=1x425 mg									
Non-Fasting Bioequivalence Study No. BA0667006									
	Test				Reference				
Parameter	Mean	Coeff of Variation	Minimum	Maximum	Mean	Coeff of Variation	Minimum	Maximum	Mean T/R*
AUCT (ng.hr/mL)	1359.47	139.70	99.89	10866.68	1381.83	145.43	90.82	11789.47	1.09
AUCI (ng.hr/mL)	1375.48	140.26	104.24	11083.48	1327.93	153.22	92.34	11987.05	1.07
CPEAK (ng/mL)	146.63	90.63	13.66	527.60	151.69	92.42	7.79	588.40	1.17
TPEAK (hrs)	5.95	29.73	2.00	9.00	6.27	35.54	2.00	16.00	1.04
THALF (hrs)	5.45	35.81	3.07	16.47	5.52	25.76	2.72	9.67	1.01
KEL (hrs^{-1})	0.14	25.91	0.04	0.23	0.13	25.70	0.07	0.25	1.06

*NOTE: This column represents means of individual T/R ratios, not ratios of the T/R means.

Table 29. Geometric Means and 90% Confidence Intervals Calculated by the Firm

Propafenone

Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}	730.752	735.528	99.4	(92.4; 107)
AUC_{∞}	734.334	739.590	99.3	(92.3; 107)
C_{max}	96.391	96.877	99.5	(89.5; 111)

5-Hydroxypropafenone

Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}	1026.68	993.56	103	(98.7; 108)
AUC_{∞}	1036.06	1002.68	103	(98.7; 108)
C_{max}	97.97	95.26	103	(96.4; 110)

Table 30. Geometric Means and 90% Confidence Intervals of Propafenone Calculated by the Reviewer

Least Squares Geometrics Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study BA0667006 (N=71)				
Parameter	Test	Reference	Ratio	90% C.I.
AUC0-t (ng hr/mL)	730.8	735.3	0.994	92.38 – 106.9
AUC∞ (ng.hr/mL)	738.9	750.3	0.985	91.36 – 106.2

Cmax (ng/mL)	96.39	96.88	0.995	89.53 – 110.6

Table 31. Additional Study Information - Propafenone

Root mean square error, AUC0-t	0.260559	
Root mean square error, AUC∞	0.260317	
Root mean square error, Cmax	0.376636	
	Test	**Reference**
Ratio of AUC0-t/AUC∞ : Mean (Range)	1.00 (0.96-1.00)	0.99 (0.94-1.00)
Kel and AUC∞ determined for how many subjects?	70	67
Do you agree or disagree with firm's decision?	Yes; however, the study outcome was the same by either determination.	Yes; however, the study outcome was the same by either determination.
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	1 (<5% of Cmax)	1 (<5% of Cmax)
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	Yes (2 groups)	Yes (2 groups)

Comments on Pharmacokinetic and Statistical Analysis:

1. The group*treatment interaction term was not statistically significant and dropped from the final statistical analysis.

2. The study results met the confidence interval acceptance criteria.

Summary/Conclusions, Single-Dose Fed Bioequivalence Study: The nonfasting study is **acceptable.**

Table 32. Propafenone Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (ng/mL)

Test Treatment

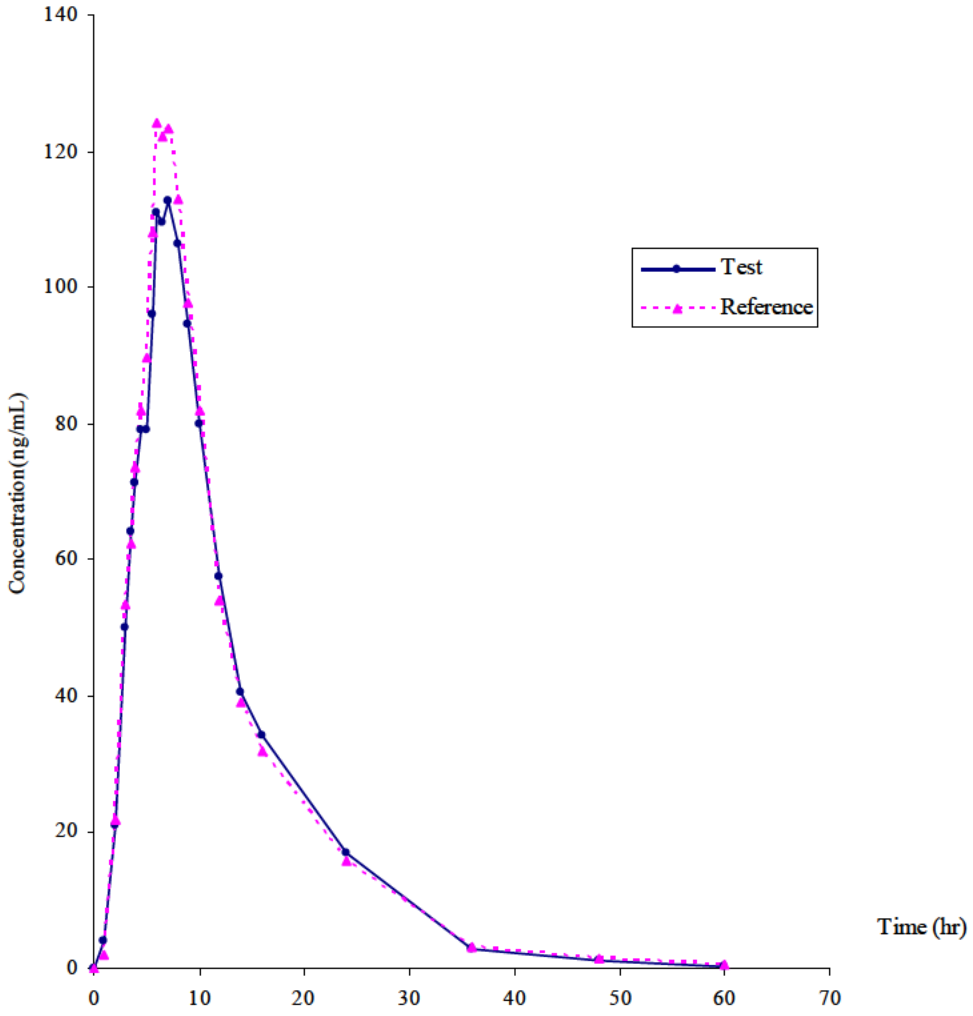
Time	Mean	N	Coeff of Variation	Minimum	Maximum
Hour0	0.002	71	842.615	0.000	0.139
Hour1	4.050	71	250.217	0.000	55.100
Hour2	20.937	71	189.648	0.000	227.700
Hour3	50.152	71	146.120	0.387	334.400
Hour3.50	63.971	71	138.223	0.994	425.600
Hour4	71.431	71	121.626	1.480	401.600
Hour4.50	78.934	71	129.165	2.078	492.200
Hour5	78.998	71	124.869	3.187	489.100
Hour5.50	96.046	71	104.980	8.454	480.400
Hour6	110.998	71	99.771	8.930	519.400
Hour6.50	109.451	71	102.182	9.013	520.400
Hour7	112.795	71	102.362	8.318	527.600
Hour8	106.449	71	112.305	6.810	523.900
Hour9	94.472	71	122.124	5.884	504.900
Hour10	80.021	71	132.360	4.585	486.000
Hour12	57.510	71	158.857	3.267	467.200
Hour14	40.677	71	180.587	1.885	394.400
Hour16	34.083	71	199.679	1.316	357.300
Hour24	17.093	71	222.946	0.350	209.400
Hour36	2.866	71	327.452	0.000	67.690
Hour48	1.118	71	402.014	0.000	35.620
Hour60	0.374	71	499.935	0.000	15.330

Reference Treatment

Time	Mean	N	Coeff of Variation	Minimum	Maximum
Hour0	0.005	71	842.615	0.000	0.320
Hour1	1.937	71	230.127	0.000	30.810
Hour2	21.886	71	186.327	0.114	220.400
Hour3	53.417	71	176.004	0.437	450.400
Hour3.50	62.499	71	158.599	0.775	457.900
Hour4	73.514	71	145.920	1.107	457.800
Hour4.50	81.993	71	132.753	1.682	458.300
Hour5	89.683	71	130.854	1.966	502.900
Hour5.50	108.149	71	112.690	2.339	499.200
Hour6	124.263	71	102.635	4.417	538.700
Hour6.50	122.086	71	101.732	7.032	531.400
Hour7	123.407	71	102.273	7.789	567.400
Hour8	112.834	71	108.840	5.032	588.400
Hour9	97.784	71	115.708	4.927	509.300
Hour10	82.056	71	129.790	3.905	538.900
Hour12	53.932	71	151.567	3.021	463.100
Hour14	39.067	71	173.975	1.947	412.000
Hour16	31.892	71	194.299	1.436	374.800
Hour24	15.800	71	262.181	0.464	268.600
Hour36	3.300	71	400.630	0.000	92.510
Hour48	1.329	71	441.476	0.000	41.540
Hour60	0.453	71	472.789	0.000	15.430

Figure 2

Propafenone Mean Plasma Concentrations
Single Dose Nonfasting Study



4.2 Formulation Data

Unit Composition for Propafenone Hydrochloride Extended Release Capsules, 225 mg		
Component	mg/capsule	%
Propafenone Hydrochloride Granules (b) (4) Propafenone hydrochloride Ethylcellulose (b) (4) Povidone (b) (4) (b) (4) Lactose Anhydrous (b) (4) Magnesium Stearate	(b) (4)	(b) (4)
Total		**100.00%**
Empty Hard Gelatin Capsules: Size 0		
D&C Red #28 FD&C Blue #1 FD&C Yellow #5 Titanium Dioxide Gelatin	(b) (4)	(b) (4)
	[a]	100.00%
Ink Constituents:		
Shellace Glaze Ethanol Iron Oxide Black N-Butyl Alcohol Propylene Glycol FD&C Blue #2 Aluminum Lake FD&C Red #40 Aluminum Lake FD&C Blue #1 Aluminum Lake D&C Yellow #10 Aluminum Lake (b) (4)	[b]	
Total Filled Capsule Weight	380.81 mg	
[a] Based on average expected empty capsule weight with range of (b) (4) [b] Refer to the manufacturer's COA and related documents for quantitative formulation. (b) (4)		

Unit Composition for Propafenone Hydrochloride Extended Release Capsules, 425 mg		
Component	mg/capsule	%
Propafenone Hydrochloride Granules (b) (4):	(b) (4)	(b) (4)
Propafenone hydrochloride Ethylcellulose (b) (4) Povidone (b) (4) (b) (4) Lactose Anhydrous (b) (4) Magnesium Stearate		
Total		**100.00%**
Empty Hard Gelatin Capsules: Size 00		
FD&C Blue #1 FD&C Red #40 FD&C Yellow #6 Titanium Dioxide Gelatin	(b) (4)	(b) (4)
	[a]	100.00%
Ink Constituents:		
Shellace Glaze Ethanol Iron Oxide Black N-Butyl Alcohol Propylene Glycol FD&C Blue #2 Aluminum Lake FD&C Red #40 Aluminum Lake FD&C Blue #1 Aluminum Lake D&C Yellow #10 Aluminum Lake (b) (4)	[b]	
Total Filled Capsule Weight	657.975 mg	
[a] Based on average expected empty capsule weight with range of (b) (4). [b] Refer to the manufacturer's COA and related documents for quantitative formulation. (b) (4).		

Unit Composition for Propafenone Hydrochloride Extended Release Capsules, 325 mg		
Component	**mg/capsule**	**%**
Propafenone Hydrochloride Granules (b) (4)	(b) (4)	(b) (4)
Propafenone hydrochloride		
Ethylcellulose (b) (4)		
Povidone (b) (4)		
(b) (4)		
Lactose Anhydrous (b) (4)		
Magnesium Stearate		
Total		**100.00%**
Empty Hard Gelatin Capsules: Size 0		
(b) (4)	(b) (4)	(b) (4)
FD&C Blue #1		
FD&C Red #40		
Titanium Dioxide		
Gelatin		
		100.00%
Ink Constituents:		
Shellac Glaze	[b]	
Ethanol		
Iron Oxide Black		
N-Butyl Alcohol		
Propylene Glycol		
FD&C Blue #2 Aluminum Lake		
FD&C Red #40 Aluminum Lake		
FD&C Blue #1 Aluminum Lake		
D&C Yellow #10 Aluminum Lake		
(b) (4)		
Total Filled Capsule Weight	510.8 mg	100.0%
[a] Based on average expected empty capsule weight with range of (b) (4)		
[b] Refer to the manufacturer's COA and related documents for quantitative formulation. (b) (4)		

- Is there an overage of the active pharmaceutical ingredient (API)? No
- If the answer is yes, has the appropriate chemistry division been notified? N/A
- If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted? N/A

Comments on the drug product formulation: The inactive ingredients are within the approved ranges of the IIG (See next page). The formulations are proportionally similar. The formulations are acceptable.

From the review of 78540.chk.pdf (in DFS), following is the list of the IIG approved amounts of the inactive ingredients contained in the test formulations:

INACTIVE INGREDIENTS	ROUTE; DOSAGE FORM	CAS NUMBER	NDA COUNT	LAST NDA	APPROVAL DATE	MAXIMUM POTENCY/UNIT
ETHYLCELLULOSE						(b) (4)
POVIDONE (b) (4)						
LACTOSE, ANHYDROUS						
MAGNESIUM STEARATE						

4.3 Dissolution Data

Dissolution Review Path	DFS

Table 33. Dissolution Data

FDA-Recommended Dissolution Method		
Medium	0-2 hours	0.08N HCl, 900 mL
	2-12 hours	Phosphate buffer, pH 6.8
	The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours	
Temperature (°C)	37°C ± 0.5°C	
Apparatus	II (Paddle)	
Rotational Speed (rpm)	50 rpm	
Sampling Times (min)	1, 2, 4 and every 2 hours thereafter	
Specifications	Q = (b) (4)% at 1 hr	
	Q = % at 4 hrs	
	Q = (b) (4)% (Q) in 12 hours	
Dosage Units	12	

Based on the data submitted, the DBE recommended the following specifications:

1 hr: (b) (4)
4 hrs: %
12 hrs: NLT (b) (4)%

The firm acknowledged the above FDA-recommended dissolution method and specifications in the amendment dated February 7, 2007.

A. 425 mg Propafenone Hydrochloride Extended-Release Tablets[1]

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV] 1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	Study Report Location
Comparative Study Report # CS06.010.0	Test product Propafenone HCl ER Capsules Lot No. 595551	425 mg Capsules	Conditions of Dissolution Testing: Apparatus: II (Paddle) Speed of Rotation: 50 rpm Medium: 0-2 hrs: 900 mL 0.08N HCl 2-12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours Temperature: 37 °C+ 0.5 °C	12	18 %RSD = 5.2	28 % RSD = 6.1	49 % RSD = 8.1	63 %RSD = 9.6	73 %RSD = 8.7	83 % RSD = 6.8	90 %RSD = 4.8	95 (b) (4) %RSD = 3.5	HP Bio
	Rythmol® (propafenone HCl) ER Capsules 2BC0072			12	12 %RSD = 3.9	22 %RSD = 4.7	43 %RSD = 6.1	57 %RSD = 8.0	69 %RSD = 7.5	78 %RSD = 6.7	85 %RSD = 5.9	90 (b) (4) %RSD = 5.0	

[1] The in vitro dissolution summary table contains the data submitted by the firm. The dissolution reviewer put the data into the table.

B. 325 mg Propafenone Hydrochloride Extended-Release Tablets[1]

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV] 1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	Study Report Location
Comparative Study Report # CS06.014.0	Test product Propafenone HCl ER Capsules Lot No. 604728	325 mg Capsules	Conditions of Dissolution Testing: Apparatus: II (Paddle) Speed of Rotation: 50 rpm Medium: 0-2 hrs: 900 mL 0.08N HCl 2-12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours Temperature: 37 °C± 0.5 °C	12	18 %RSD = 9.6	30 %RSD = 10.4	53 %RSD = 11.0	68 %RSD = 12.1	79 %RSD = 11.2	87 %RSD = 10.1	91 %RSD = 9.3	93 (b) (4) %RSD = 8.4	HP Bio
	Rythmol® (propafenone HCl) ER Capsules 2BE0118			12	14 %RSD = 10.8	25 %RSD = 7.4	49 %RSD = 5.7	65 %RSD = 8.6	78 %RSD = 8.5	87 %RSD = 7.2	93 %RSD = 5.0	97 (b) (4) %RSD = 4.1	

[1] The in vitro dissolution summary table contains the data submitted by the firm. The dissolution reviewer put the data into the table.

C. 225 mg Propafenone Hydrochloride Extended-Release Tablets[1]

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV] 1 hr	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	12 hrs	14 hrs	Study Report Location
Comparative Study Report # CS06.013.0	Test product Propafenone HCl ER Capsules Lot No. 598399	225 mg Capsules	Conditions of Dissolution Testing: Apparatus: II (Paddle) Speed of Rotation: 50 rpm Medium: 0-2 hrs: 900 mL 0.08N HCl 2-12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours Temperature: 37 °C± 0.5 °C	12	19 %RSD = 5.4	30 %RSD = 5.8	54 %RSD = 8.9	69 %RSD = 10.3	80 %RSD = 8.5	88 %RSD = 6.1	93 %RSD = 4.1	95 (b) (4) %RSD = 3.2	HP Bio
	Rythmol® (propafenone HCl) ER Capsules Lot No. 2BE0065			12	15 %RSD = 6.1	26 %RSD = 8.8	48 %RSD = 7.3	63 %RSD = 5.8	78 %RSD = 5.5	88 %RSD = 5.3	94 %RSD = 4.9	98 (b) (4) %RSD = 4.5	

[1] The in vitro dissolution summary table contains the data submitted by the firm. The dissolution reviewer put the data into the table.

SOURCE OF FDA METHOD: [OCPB –Clinical Pharmacology & Biopharmaceutics Review, NDA # 21-416 SE5 029, Submission date: January 31, 2003, Rythmol® (propafenone hydrochloride) Extended Release Tablets by Abbott Laboratories (in DFS)]

A. Dissolution Profile in pH 1.2 SGF without enzyme, pH 1.2 buffer

1. 425 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 425 mg, Par Pharmaceutical, Inc., Batch# 595551

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	16	27	41	52	60	68	73	78
% RSD	4.5	6.5	7.9	7.8	6.8	6.4	5.9	5.3
High	(b) (4)							
Low								

Reference: (b) (6) R06-113, page 1

Rythmol SR 425 mg, Reliant, Lot # 2BC0072

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	14	24	42	56	67	75	83	90
% RSD	5.6	7.6	6.9	5.8	5.9	3.7	3.4	4.1
High	(b) (4)							
Low								

Reference: (b) (6) R06-093, page 174

2. 325 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 325 mg, Par Pharmaceutical, Inc., Batch# 604728

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	13	22	34	44	51	58	64	69
% RSD	6.6	5.1	6.1	8.1	8.4	8.6	8.4	7.6
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 106

Rythmol SR 325 mg, Reliant, Lot # 2BE0118

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	11	20	36	47	57	65	72	78
% RSD	21.9	24.0	23.7	20.4	17.3	15.2	12.7	10.6
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 112

3. 225 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 225 mg, Par Pharmaceutical, Inc., Batch# 598399

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	16	26	39	50	59	67	73	79
% RSD	17.4	16.1	10.9	11.5	11.3	11.0	10.0	9.4
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 98, 100

Rythmol SR 225 mg, Reliant, Lot # 2BE0065

Capsule #	% Released							
	1 hour	2 hours	4 hours	6 hours	8 hours	10 hours	12 hours	14 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	10	19	35	48	60	71	80	87
% RSD	10.0	11.5	13.5	13.6	11.9	9.9	8.1	6.6
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 103

B. Dissolution Profile in Acetate Buffer, pH 4.5

1. 425 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 425 mg, Par Pharmaceutical, Inc., Batch# 595551

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	36	60	77	88	95	98	99	99
% RSD	7.5	9.0	7.9	5.4	3.7	3.0	3.1	3.1
High								(b) (4)
Low								

Reference: (b) (6) R06-084, page 180

Rythmol SR 425 mg, Reliant, Lot # 2BC0072

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	33	57	73	84	91	96	99	100
% RSD	18.6	17.0	13.2	9.3	5.6	3.0	2.1	2.1
High								(b) (4)
Low								

Reference: (b) (6) R06-086, page 182

2. 325 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 325 mg, Par Pharmaceutical, Inc., Batch# 604728

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	36	59	74	84	91	95	97	98
% RSD	6.5	6.9	6.9	5.4	4.0	3.0	3.1	3.4
High								(b) (4)
Low								

Reference: (b) (6) R06-125, page 121

Rythmol SR 325 mg, Reliant, Lot # 2BE0118

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	35	58	74	86	92	97	99	99
% RSD	3.8	6.2	6.3	4.9	3.7	3.1	2.7	2.7
High								(b) (4)
Low								

Reference: (b) (6) R06-131, page 111

3. 225 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 225 mg, Par Pharmaceutical, Inc., Batch# 598399

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	37	57	72	84	91	95	98	99
% RSD	8.2	8.7	8.4	7.4	5.7	4.2	3.9	3.0
High								(b) (4)
Low								

Reference: (b) (6) R06-115 page 144

Rythmol SR 225 mg, Reliant, Lot # 2BE0065

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	38	60	76	83	97	101	102	103
% RSD	6.7	6.0	5.2	10.2	3.9	3.7	3.7	3.9
High								(b) (4)
Low								

Reference: (b) (6) R06-131, page 97; Kalpana Singh R06-123, page 105

C. Dissolution Profile in Phosphate Buffer, pH 6.8

1. 425 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 425 mg, Par Pharmaceutical, Inc., Batch# 595551

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	38	63	79	90	96	98	98	98
% RSD	6.5	6.1	4.6	3.6	3.4	3.4	3.6	3.3
High								(b) (4)
Low								

Reference: (b) (6) R06-101, page 96

Rythmol SR 425 mg, Reliant, Lot # 2BC0072

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	39	64	80	90	97	99	99	99
% RSD	6.4	4.5	4.0	2.9	2.0	2.0	1.7	1.8
High								(b) (4)
Low								

Reference: (b) (6) R06-115, page 36

2. 325 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 325 mg, Par Pharmaceutical, Inc., Batch# 604728

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	40	63	81	91	96	97	98	97
% RSD	8.0	5.1	3.8	2.5	2.3	2.6	2.5	2.7
High								(b) (4)
Low								

Reference: (b) (6) R06-135, page 21, 26

Rythmol SR 325 mg, Reliant, Lot # 2BE0118

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	40	65	81	92	98	100	100	100
% RSD	4.3	3.8	3.7	3.3	2.8	2.5	2.4	2.2
High								(b) (4)
Low								

Reference: (b) (6) R06-115, page 157

3. 225 mg Propafenone Hydrochloride Extended-Release Tablets

Propafenone HCl ER Capsules 225 mg, Par Pharmaceutical, Inc., Batch# 598399

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	40	66	84	95	99	100	100	100
% RSD	7.0	4.8	2.3	0.9	1.2	1.4	1.4	1.4
High								(b) (4)
Low								

Reference: (b) (6) R06-135, page 18

Rythmol SR 225 mg, Reliant, Lot # 2BE0065

Capsule #	% Released							
	30 min.	1 hour	1½ hours	2 hours	2½ hours	3 hours	3½ hours	4 hours
1								(b) (4)
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Average	39	53	79	91	96	98	99	99
% RSD	9.0	26.9	3.8	3.3	3.4	3.2	4.3	3.3
High								(b) (4)
Low								

Reference: (b) (6) R06-135, page 14

[1]These tables were provided by the firm

Comments from the Dissolution Review:

The dissolution testing using the FDA method is acceptable. Based on the data submitted, the DBE recommended the following specifications:

1 hr: (b) (4)
4 hrs: %
12 hrs: NLT (b) (4) %

The firm acknowledged the above FDA-recommended dissolution method and specifications in the amendment dated February 7, 2007. The dissolution testing is **complete.**

Following this page, 33 pages withheld in full - (b)(4) SAS data

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540

APPLICANT: Par Pharmaceutical

DRUG PRODUCT: Propafenone Hydrochloride ER Capsules, 425 mg, 325 mg & 225 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that you have conducted dissolution testing using the following FDA-recommended dissolution method and specifications:

The dissolution testing should be conducted in 900 mL of 0.08 M HCl for the first two (2) hours, followed by 1000 mL of pH 6.8 Phosphate Buffer for 2-12 hours, at 37°C ± 0.5°C using USP Apparatus II (paddle) @ 50 rpm (The second medium is obtained by adding a buffer concentrate to the initial (HCl) medium). The test product should meet the following specification:

1 hr: (b) (4)
4 hrs: %
12 hrs: NLT (b) (4) %

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA: 78-540

1.	**Fasting Study**	Strength:	425 mg
	(STF)	Outcome:	**AC**
	Submission Date(s)	**October 10, 2006**	
	Clinical Site:	BA Research India Ltd., India	
	Analytical Site:	(b) (4)	
2.	**Fed Study**	Strength:	425 mg
	(STP)	Outcome:	**AC**
	Submission Date(s)	**October 10, 2006**	
	Clinical Site:	BA Research India Ltd., India	
	Analytical Site:	(b) (4)	
3.	**Dissolution Waiver**	Strength(s):	325 mg
	(DIW)	Outcome:	**AC**
	Submission Date(s)	**October 10, 2006**	
4.	**Dissolution Waiver**	Strength(s):	225 mg
	(DIW)	Outcome:	**AC**
	Submission Date(s)	**October 10, 2006**	

BIOEQUIVALENCE OUTCOME DECISIONS:	AC – Acceptable IC – Incomplete UN – Unacceptable WC – Without Credit

---

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

/s/

Hoainhon T. Nguyen
6/15/2007 09:52:59 AM
BIOPHARMACEUTICS

Moheb H. Makary
6/15/2007 09:57:40 AM
BIOPHARMACEUTICS

Barbara Davit
6/15/2007 04:02:03 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-540

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2
Copy 3 (field)*

October 10, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg
ANDA – Original Submission

Dear Staff:

Pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act, Par Pharmaceutical, Inc. herewith submits an abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg. Archive and review copies, as required, are provided for this submission along with the required field copy certification (Module 1.3.2.). This submission consists of 7 volumes.

The official name of the drug relied upon as the basis for this application is Propafenone Hydrochloride, USP. The proprietary name of the reference-listed drug is RYTHMOL® SR. A copy of the appropriate pages from the Electronic Orange Book is included in Module 1.12.11, confirming that the proposed drug is the same as the listed drug.

In accordance with the Common Technical Document (CTD) format, the U.S. regional information is provided in Module 1 including all required certifications. This includes the required certifications (e.g. debarment, patent, environmental, etc.). The approved insert labeling for the listed drug and Par's proposed draft labeling (Module 1.14) are provided in electronic format on the enclosed CD Rom . These electronic media have been scanned for viruses and are virus-free. The approximate size of the electronic submission is 1.4 Gb.

Module 2 contains the CTD summaries, with the related detailed information provided in the Quality section (Module 3) of this ANDA.

Executed batch records are provided in Module 3.2.R, Regional Information. The blank master batch records for the intended commercial production are located in Module 3.2.P.3.3. Comparative dissolution data for all these batches with f_2 calculations are included in Module 5.3.1.3.

Nonclinical studies were not required to support this submission, therefore Module 4 is omitted from this application. Module 5 (Clinical Study Reports) contains two bioequivalence studies which are provided in electronic format on the enclosed CD Roms. These electronic media have been scanned for viruses and are virus-free. The approximate size of the electronic submission is 1.4 Gb.

The following studies were conducted to support this application:

1. A randomized, single-dose, 2-way crossover, bioequivalence study comparing Par Pharmaceutical, Inc. Propafenone Hydrochloride Extended Release Capsules and RYTHMOL® SR, Reliant Pharmaceuticals, Inc., administered as a single 425 mg capsule in healthy adult subjects under fasting conditions.

2. A randomized, single-dose, 2-way crossover bioequivalence study comparing Par Pharmaceutical, Inc. Propafenone Hydrochloride Extended Release Capsules and RYTHMOL® SR, Reliant Pharmaceuticals, Inc., administered as a single 425 mg capsule in healthy adult subjects fed conditions.

The required *in vitro* data is provided on the CD Rom for Module 5. The financial disclosure certification is included in Module 1.3.4 and electronically in Module 5.

Analytical methods validation information is included in Module 3.2.R.3.P. Additionally, three (3) separately bound copies of this Methods Validation Package are provided with this submission. Par commits to resolving any issues identified in the methods validation process after approval if requested.

The electronic submission portion of this application (Module 1 and Module 5) is approximately 1.4 Gb in size with 290 files and 22 folders. There are 3 CDs included with this submission. The CDs are named/burned as follows:

Propafenone_CD1 – contains all of Module 1 in its original folder. Copy this folder to the FDA network intact - as is. The CD also includes folders/files that are a part of Module 5. Please create a folder called Module 5 and copy all files from CD1 that are not a part of the Module 1 folder into that Module 5 folder.

Propafenone_CD2 – contains all Module 5 folders and files. Under the Module 5 folder that you created from CD1, create a subfolder called \BA0667005 and copy all the files from this CD to that folder.

Propafenone_CD3 – contains one folder which is the\CRFs folder for the BA0667005 subfolder that you created from CD 2 under Module 5. Copy the folder \CRFs from this CD into the \BA0667005 subfolder.

The electronic structure for these modules follows:

Module1 contains:	Module5 contains:	
coverltr.pdf	summtables.pdf	\BA0667005
356h.pdf	dissolution.pdf	\appendices
3454.pdf	dissolution225.pdf	\CRFs
CTDtoc.pdf	Module5.1.pdf	\SAS
\labeling	Module5.2.pdf	SRBA0667005.pdf
\proposed	Module5.3.pdf	(Study Report)
\draft	Module5.4.pdf	\BA0667006
\listed	Module5.3.1.1.pdf	\appendices
\sbs	Module5.3.1.2.pdf	\CRFs
\spl	Module5.3.1.3.pdf	\SAS
compare.pdf	Module5.3.1.4.pdf	SRBA0667006.pdf
labeltoc.pdf	Module5.3.1.pdf	(Study Report)
	Module5.3.2.pdf	
	Module5.3.3.pdf	
	Module5.3.4.pdf	
	Module5.3.5.pdf	
	Module5.3.6.pdf	
	Module5.3.7.pdf	

Once you have copied all the files over correctly, you will be able to navigate the submission by opening the file in Module1 named CTDtoc.pdf and using the bookmarks to get to each of the modules.

We appreciate the Agency's time and efforts in reviewing this ANDA. Please do not hesitate to contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Janis A. Picurro
Director, Regulatory Affairs

Enclosures

* Mr Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

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Copy 1
Copy 2
Copy 3 (Field)*

November 6, 2006

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Amendment to Pending Application
Addition of the 325 mg Strength

RE: Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg

Dear Staff:

Reference is made to our pending abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg. We herewith submit, in duplicate, an amendment to our pending application to provide for the addition of the 325 mg strength of Propafenone Hydrochloride Extended Release Capsules.

The proprietary name of the drug product is Rythmol®. A copy of the appropriate pages from the Electronic Orange Book is enclosed in Module 1.12.11 to show that the proposed drug is the same as the listed drug.

The U.S. regional information is provided in Module 1. The content of our labeling, updated to incorporate the 325 mg strength, is provided in electronic format (PDF, SPL and Word Files) on the enclosed CD Rom.

Module 2 contains the CTD summaries with the related detailed information provided in the Quality section of this amendment.

Executed batch records are provided in the Regional Section of Module 3. Comparative Dissolution data for the 325 mg as well as the 225 mg strength conducted to reflect additional medias are included on the enclosed CD Rom together with the summary tables. These electronic media have been scanned for viruses and are virus free. The approximate size of the electronic portion of this submission is 2.6 MB.

Par Pharmaceutical hereby requests a waiver of the *in-vivo* bioequivalence study requirements for Propafenone Hydrochloride Extended Release Capsules, 325 mg on the basis of proportionally similar quantitative formulation, *in-vitro* dissolution data and the *in-vivo* bioavailability studies performed under fasting and fed conditions comparing Par's Propafenone Hydrochloride Extended Release Capsules, 425 mg with the reference listed product, Rythmol® 425 mg.

The analytical methods validation protocols submitted in the original ANDA dated 10/10/06 remain unchanged. Please refer to the original submission for the Methods Validation Reports.

Please note that the Specifications page, 3.2.5.1 for the 225 mg and 425 mg strengths has been corrected to reflect both [redacted] (b) (4) will be performed for the finished product release. In addition, the Stability summary page, 3.2.P.8.1 has also been corrected to reflect [redacted] (b) (4) will be performed for the finished product stability for the 225 mg and 425 mg strengths. The referenced corrected pages for the 225 mg and 425 mg strengths are included in this amendment.

We certify that the field copy is a true copy of the technical sections contained in the archival and review copies of this amendment for the addition of the 325 mg strength submitted to the Office of Generic Drugs.

This concludes our amendment to the original ANDA submitted on October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg.

If you have any questions or require additional information, please do not hesitate to contact me at (845) 639-5128, by fax (845) 639-5201 or by e-mail *jszozda@parpharm.com.*

Sincerely yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs

Enclosures

* Mr Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

ORIGINAL

XP

Copy 1
Copy 2

78-540

November 9, 2006

Martin Shimer, Branch Chief, Regulatory Support Branch
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

PATENT AMENDMENT

RE: Propafenone Hydrochloride Extended Release Capsules, 325 mg
Notice of Paragraph IV Certification (CTD Module 1.3.5)

Dear Mr. Shimer:

Reference is made to our amendment of November 6, 2006 to our abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg. The amendment provided for the addition of the 325 mg dosage strength.

With respect to the 325 mg strength, Par declares the following:

- In accordance with 21 CFR 314.95(d) "*Amendment to an abbreviated application,*" Par Pharmaceutical, Inc. certifies that notice was provided by U.S. registered mail, return receipt requested, to each person identified under CFR 314.95(a) on November 7, 2006, and the notice met the available content requirements under 314.95(c)
- A copy of the Patent Certification Notice letter for U.S. Patent 5,681,588, referencing the 325 mg strength, is provided with this amendment.

This concludes our Patent Amendment regarding the Notice of Paragraph IV Certification for Propafenone Hydrochloride Extended Release Capsules, 325 mg. If additional information is required, please do not hesitate to contact me directly at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL

Julie Szozda
Senior Associate, Regulatory Affairs

Enclosure

RECEIVED
NOV 13 2006
OGD / CDER

M E M O R A N D U M

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

DATE : December 19, 2006

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

SUBJECT: Examination of the bioequivalence study submitted with an ANDA 78-540 for Propafenone Hydrochloride Extended-Release Capsules, 225 mg, 325 mg and 425 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to 21 USC 355(j)(5)(B)(iv).

Par Pharmaceuticals Inc. has submitted ANDA 78-540 for Propafenone Hydrochloride Extended-Release Capsules, 225 mg, 325mg and 425 mg. The ANDA contains a certification pursuant to 21 USC 355(j) (5) (B) (IV) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Par Pharmaceuticals Inc. on October 10 and November 6, 2006 for its Propafenone Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms to an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

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

/s/

Martin Shimer
12/19/2006 02:44:04 PM
CSO

BIOEQUIVALENCE CHECKLIST for First Generic ANDA
FOR APPLICATION COMPLETENESS

ANDA# 78-540 **FIRM NAME** **Par Pharmaceutical**

DRUG NAME Propafenone HCl Extended Release

DOSAGE FORM **425 mg, 325 mg and 225 mg Calpsules**
SUBJ: Request for examination of: Bioequivalence Study

Requested by: _____ Date: _____
Chief, Regulatory Support Team, (HFD-615)

	Summary of Findings by Division of Bioequivalence
☒	**Study meets statutory requirements**
☐	**Study does NOT meet statutory requirements**
	Reason:
☒	**Waiver meets statutory requirements**
☐	**Waiver does NOT meet statutory requirements**
	Reason:

RECOMMENDATION: ☒ **COMPLETE** ☐ **INCOMPLETE**

Reviewed by:

_____ Date: _____
Sarah Robertson
Reviewer

_____ Date: _____
Chandra Chaurasia
Team Leader

Item Verified:	YES	NO	Required Amount	Amount Sent	Comments
Protocol	☒	☐	2	2	1 Fasting and 1 Non-fasting study on 425 mg strength
Assay Methodology	☒	☐	1	1	
Procedure SOP	☒	☐	1	1	
Methods Validation	☒	☐	1	1	
Study Results Ln/Lin	☒	☐	2	2	
Adverse Events	☒	☐	2	2	
IRB Approval	☒	☐	2	2	
Dissolution Data	☒	☐			
Pre-screening of Patients	☒	☐	2	2	
Chromatograms	☒	☐	2	2	
Consent Forms	☒	☐	2	2	
Composition	☒	☐	1	1	
Summary of Study	☒	☐	2	2	
Individual Data & Graphs, Linear & Ln	☒	☐	2	2	
PK/PD Data Disk Submitted)	☒	☐	2	2	
Randomization Schedule	☒	☐	2	2	
Protocol Deviations	☒	☐	2	2	
Clinical Site	☒	☐	2	2	
Analytical Site	☒	☐	2	2	
Study Investigators	☒	☐	2	2	

Medical Records	☒	☐	2	2	
Clinical Raw Data	☐	☒			N/A
Test Article Inventory	☒	☐			
BIO Batch Size	☒	☐			
Assay of Active Content Drug	☒	☐			
Content Uniformity	☒	☐			
Date of Manufacture	☒	☐			
Exp. Date of RLD	☒	☐			
BioStudy Lot Numbers	☒	☐			
Statistics	☒	☐			
Summary results provided by the firm indicate studies pass BE criteria	☒	☐			Parent drug (propafenone) passes all criteria in both fed and fasted; OH-metabolite fails Cmax in fasted.
Waiver requests for other strengths / supporting data	☒	☐			Waiver request for 325 mg and 225 mg strengths

Additional Comments regarding the ANDA:

As noted in the table above, the parent drug (propafenone) passes all of the BE criteria for both the fed and fasted studies. The metabolite (5-OH Propafenone), however, does not meet the BE criteria for Cmax for the fasted study. Since DBE considers metabolite data to be supportive, DBE will compare test and reference plasma metabolite concentrations at the time of review.

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

/s/

Barbara Davit

12/28/2006 01:54:22 PM

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2
Copy 3 (field)*

January 4, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
7500 Standish Place, Room 150
Rockville, Maryland 20855

New Correspondence

RE: ANDA – 78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Staff:

Reference is made to our pending abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg dated October 10, 2006 and the subsequent amendment dated November 06, 2006 which provided for the addition of the 325 mg strength. Reference is also made to the December 20, 2006 telephone call from Peter Chen, Project Manager, at FDA requesting the QBR for Module 2 be provided electronically in MS Word and PDF format.

In accordance with the Agency's December 20, 2006 request, we herewith submit the QBR for Module 2 that was previously submitted in paper with the October 10, 2006 original application and with the November 6, 2006 amendment, electronically in MS Word and PDF format on the enclosed CD Rom.

Please do not hesitate to contact us if we may offer any assistance in your review of this application.

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs

Enclosures

* Mr Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
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www.parpharm.com

Copy 1
Copy 2

January 10, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

Labeling Amendment – Replacement of SPL Labeling

RE: ANDA #78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Staff:

Reference is made to our abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg and the subsequent November 6, 2006 amendment which provided for the addition of the 325 mg strength. Reference is also made to a telephone call from the SPL Team regarding Tier 1 validation issues in ELIPS of our SPL labeling.

In accordance with the Agency's request, the SPL labeling file previously submitted on October 10, 2006 and November 6, 2006 is being replaced with the current SPL file on the enclosed CD ROM.

This concludes our labeling amendment to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs

Enc.

ANDA CHECKLIST FOR CTD or eCTD FORMAT
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION FOR FILING

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to: http://www fda.gov/cder/regulatory/ersr/ectd.htm
***For a Comprehensive Table of Contents Headings and Hierarchy please go to:**
http://www fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
**** For more** CTD and eCTD informational links **see the final page of the ANDA Checklist**
***** A model Quality Overall Summary for an immediate release tablet and an extended release capsule can be found on the OGD webpage** http://www.fda.gov/cder/ogd/ *****

ANDA #: 78-540 **FIRM NAME**: PAR PHARMACEUTICAL, INC.

PIV: YES **Electronic or Paper Submission:** CTD FORMAT PAPER

RELATED APPLICATION(S): NA

First Generic Product Received? YES PER

PETER CHEN 12/19/06

Bio Assignments:		
☒ **BPH**	☐ **BCE**	☐ **Micro Review (No)**
☐ **BST**	☒ **BDI**	

DRUG NAME: PROPAFENONE HYDROCHLORIDE

DOSAGE FORM: EXTENDED-RELEASE CAPSULES, 225 MG AND 425 MG

Random Queue: 8

Chem Team Leader: Venkataram, Ubrani PM: Cheryl Wiseman Labeling Reviewer: Adolph Vezza

Letter Date: OCTOBER 10, 2006 **Received Date**: OCTOBER 11, 2006

Comments: EC- 2 YES **On Cards:** YES

Therapeutic Code: 1010400 ANTI- ARRHYTHMICS

Archival copy: CTD FORMAT PAPER **Sections** I

Review copy: YES E-Media Disposition: YES SENT TO EDR

Not applicable to electronic sections

PART 3 Combination Product Category N Not a Part3 Combo Product

(Must be completed for ALL Original Applications) Refer to the Part 3 Combination Algorithm

Reviewing CSO/CST Peter Chen	**Recommendation:**
Date 1/9/2007	☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date: _____	**Date:** _____

ADDITIONAL COMMENTS REGARDING THE ANDA: Prefiling review started on 12/19/2006

Janis Picurro of Par Pharmaceuticals was contacted on 12/20/2006 to provide a PDF and Word file for the Module 2 QBR. Janis was also informed that the acceptance for filing cannot be completed until DBE provides a recommendation since the fasted biostudy for the metabolite 5-hydroxypropafenone Cmax falls outside the acceptable range. (PC 12/20/2006)

This is a DBE review issue. See DBE memo to file in DFS signed off by Barbara Davit on 12/28/2006. (PC 1/9/2007)

MODULE 1
ADMINISTRATIVE

		ACCEPTABLE
1.1	**1.1.2** **Signed and Completed Application Form (356h) (original signature)** (Check Rx/OTC Status) RX YES	☒
1.2	**Cover Letter** Dated: OCTOBER 10, 2006	☒
*	**Table of Contents (paper submission only)** YES	☒
1.3.2	**Field Copy Certification (original signature)** YES **(N/A for E-Submissions)**	☒
1.3.3	**Debarment Certification-GDEA (Generic Drug Enforcement Act)/Other:** 1. Debarment Certification (original signature) YES 2. List of Convictions statement (original signature) none used	☒
1.3.4	**Financial Certifications** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) or Disclosure Statement (Form FDA 3455) YES	☒
1.3.5	**1.3.5.1** **Patent Information** Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2** **Patent Certification** 1. Patent number(s) 5681588 2. Paragraph: (Check all certifications that apply) MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ No Relevant Patents ☐ 3. Expiration of Patent(s): 10-28-2014 a. Pediatric exclusivity submitted? b. Expiration of Pediatric Exclusivity? 4. Exclusivity Statement: YES	☒

1.4.1	**References** Letters of Authorization 1. DMF letters of authorization a. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient submitted DMF (b) (4) b. Type III DMF authorization letter(s) for container closure submitted 2. US Agent Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])	☒
1.12.11	**Basis for Submission** NDA# : 21-416 Ref Listed Drug: RYTHMOL SR Firm: RELIANT PHARMACEUTICALS ANDA suitability petition required? NA If Yes, then is change subject to PREA (change in dosage form, route or active ingredient) see section 1.9.1	☒

MODULE 1 (Continued)
ADMINISTRATIVE

ACCEPTABLE

1.12.12	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use Same as RLD 2. Active ingredients Same as RLD 3. Inactive ingredients Different from RLD 4. Route of administration Same as RLD 5. Dosage Form Same as RLD 6. Strength 225 mg and 425 mg (325 mg added as a NS amendment on 11/6/06)	☒
1.12.14	**Environmental Impact Analysis Statement** YES	☒
1.12.15	**Request for Waiver** Request for Waiver of In-Vivo BA/BE Study(ies): Paper, YES ON 225 MG	☒
1.14.1	**Draft Labeling (Mult Copies N/A for E-Submissions)** **1.14.1.1** draft (each strength and container) submitted **1.14.1.2** 1 side by side labeling comparison of containers and carton with all differences annotated and explained submitted **1.14.1.3** 1 package insert (content of labeling) submitted electronically submitted ***Was a proprietary name request submitted? no (If yes, send email to Labeling Reviewer indicating such.)	☒
1.14.3	**Listed Drug Labeling** **1.14.3.1** 1 side by side labeling (package and patient insert) comparison with all differences annotated and explained submitted **1.14.3.3** 1 RLD label and 1 RLD container label submitted	☒

MODULE 2
SUMMARIES

ACCEPTABLE

2.3	**Quality Overall Summary** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** A model Quality Overall Summary for an immediate release table and an extended release capsule can be found on the OGD webpage http://www.fda.gov/cder/ogd/ **Question based Review (QbR) ___X__ YES _____ NO** **Par asked to submit PDF and Word files of QBR** **2.3.S submitted** **Drug Substance (Active Pharmaceutical Ingredient)** **2.3.S.1** **General Information** **2.3.S.2** **Manufacture** **2.3.S.3** **Characterization** **2.3.S.4** **Control of Drug Substance** **2.3.S.5** **Reference Standards or Materials** **2.3.S.6** **Container Closure System** **2.3.S.7** **Stability** **2.3.P submitted** **Drug Product** **2.3.P.1** **Description and Composition of the Drug Product** **2.3.P.2** **Pharmaceutical Development** **2.3.P.2.1** **Components of the Drug Product** **2.3.P.2.1.1** **Drug Substance** **2.3.P.2.1.2** **Excipients** **2.3.P.2.2** **Drug Product** **2.3.P.2.3** **Manufacturing Process Development** **2.3.P.2.4** **Container Closure System** **2.3.P.3** **Manufacture** **2.3.P.4** **Control of Excipients** **2.3.P.5** **Control of Drug Product** **2.3.P.6** **Reference Standards or Materials** **2.3.P.7** **Container Closure System** **2.3.P.8** **Stability**	☒

2.7	**Clinical Summary (Bioequivalence)** **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word** **2.7.1** **Summary of Biopharmaceutic Studies and Associated Analytical Methods** **2.7.1.1** **Background and Overview submitted** **2.7.1.2** **Summary of Results of Individual Studies submitted** **Fasted biostudy of metabolite 5-hydroxypropafenone Cmax falls outside the range (108 – 130) . This is a DBE review issue. See DBE memo to file in DFS signed off by Barbara Davit on 12/28/2006.** **2.7.1.3** **Comparison and Analyses of Results Across Studies submitted** 1. Summary Bioequivalence tables: Table 1. Summary of Comparative Bioavailability (BA) Studies Table 2. Statistical Summary of the Comparative BA Data Table 4. Summary of In Vitro Dissolution Studies **2.7.1.4** **Appendix**	☒

MODULE 3

3.2.S DRUG SUBSTANCE

ACCEPTABLE

3.2.S.1	**General Information** **3.2.S.1.1** **Nomenclature submitted** **3.2.S.1.2** **Structure submitted** **3.2.S.1.3** **General Properties submitted**	☒
3.2.S.2	**Manufacturer** **3.2.S.2.1** **Manufacturer(s) (This section includes contract manufacturers and testing labs)** **Drug Substance (Active Pharmaceutical Ingredient)** 1. Addresses of bulk manufacturers submitted (b) (4) 2. Manufacturing Responsibilities submitted 3. Type II DMF number for API DMF (b) (4) 4. CFN or FEI numbers submitted	☒
3.2.S.3	**Characterization** **Reference to DMF**	☒

<table>
<tr>
<td>3.2.S.4</td>
<td>
Control of Drug Substance (Active Pharmaceutical Ingredient)
3.2.S.4.1
Specification
Testing specifications and data from drug substance manufacturer(s) submitted
3.2.S.4.2
Analytical Procedures submitted
3.2.S.4.3
Validation of Analytical Procedures submitted in Section 3.2.R.3.P
1. Spectra and chromatograms for reference standards and test samples
2. Samples-Statement of Availability and Identification of: submitted
a. Drug Substance
b. Same lot number(s) yes
3.2.S.4.4
Batch Analysis
1. COA(s) specifications and test results from drug substance mfgr(s) submitted
2. Applicant certificate of analysis submitted
<table>
<tr><td colspan="2">Table 3.2.S.4.1-1 Drug Substance Lot Information</td></tr>
<tr><td>Drug Substance:</td><td>Propafenone Hydrochloride, USP</td></tr>
<tr><td>Monograph Number:</td><td>RM-RA100152-004</td></tr>
<tr><td>Par Product Code:</td><td>RA100167</td></tr>
<tr><td>Par Lot Number (BCPS#):</td><td>502949</td></tr>
<tr><td>Drug Substance Manufacturer:</td><td>(b) (4)</td></tr>
<tr><td>Manufacturer's Lot Number:</td><td>0000062130</td></tr>
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<table>
<tr><td>Drug Substance:</td><td>Propafenone Hydrochloride, USP</td></tr>
<tr><td>Monograph Number:</td><td>RM--RA100152-004</td></tr>
<tr><td>Par Product Code:</td><td>RA100167</td></tr>
<tr><td>Par Lot Number (BCPS#):</td><td>504159</td></tr>
<tr><td>Drug Substance Manufacturer:</td><td>(b) (4)</td></tr>
<tr><td>Manufacturer's Lot Number:</td><td>0000071418</td></tr>
</table>
3.2.S.4.5
Justification of Specification Reference to DMF
</td>
<td>☒</td>
</tr>
<tr>
<td>3.2.S.5</td>
<td>Reference Standards or Materials submitted</td>
<td>☒</td>
</tr>
<tr>
<td>3.2.S.6</td>
<td>Container Closure Systems Reference to DMF</td>
<td>☒</td>
</tr>
<tr>
<td>3.2.S.7</td>
<td>Stability Reference to DMF</td>
<td>☒</td>
</tr>
</table>

MODULE 3

3.2.P DRUG PRODUCT ACCEPTABLE

3.2.P.1	**Description and Composition of the Drug Product** 1) Unit composition submitted and inactives are proportional between strengths 2) Inactive ingredients are appropriate per IIG All inactives are appropriate per regulation and IIG	☒
3.2.P.2	**Pharmaceutical Development** Pharmaceutical Development Report submitted	☒
3.2.P.3	**Manufacture** **3.2.P.3.1** **Manufacture(s)** (Finished Dosage Manufacturer and Outside Contract Testing Laboratories) 1. Name and Full Address(es)of the Facility(ies) submitted 2. CGMP Certification: YES submitted 3. Function or Responsibility submitted 4. CFN or FEI numbers **3.2.P.3.2** **Batch Formula** Batch Formulation submitted **3.2.P.3.3** **Description of Manufacturing Process and Process Controls** 1. Description of the Manufacturing Process submitted 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified submitted 225 mg commercial batch size (b) (4) units 425 mg commercial batch size units 3. If sterile product: Aseptic fill / Terminal sterilization n.a. 4. Reprocessing Statement submitted **3.2.P.3.4** **Controls of Critical Steps and Intermediates submitted** **3.2.P.3.5** **Process Validation and/or Evaluation n.a.** 1. Microbiological sterilization validation 2. Filter validation (if aseptic fill)	☒

3.2.P.4	**Controls of Excipients (Inactive Ingredients)** Source of inactive ingredients identified submitted **3.2.P.4.1** **Specifications** 1. Testing specifications (including identification and characterization) submitted 2. Suppliers' COA (specifications and test results) submitted **3.2.P.4.2** **Analytical Procedures submitted** **3.2.P.4.3** **Validation of Analytical Procedures** **Par states per USP/NF** **3.2.P.4.4** **Justification of Sepcifications** Applicant COA submitted	☒

MODULE 3

3.2.P DRUG PRODUCT

ACCEPTABLE

3.2.P.5	**Controls of Drug Product** **3.2.P.5.1** **Specification(s)** submitted **3.2.P.5.2** **Analytical Procedures** submitted **3.2.P.5.3** **Validation of Analytical Procedures reference to section 3.2.R.3.P** Samples - Statement of Availability and Identification of: 1. Finished Dosage Form submitted 2. Same lot numbers 225 mg lot #182353 425 mg lot #182097 **3.2.P.5.4** **Batch Analysis** Certificate of Analysis for Finished Dosage Form submitted **3.2.P.5.5** **Characterization of Impurities submitted** **3.2.P.5.6** **Justification of Specifications submitted**	☒
3.2.P.7	**Container Closure System** 1. Summary of Container/Closure System (if new resin, provide data) submitted 2. Components Specification and Test Data submitted 3. Packaging Configuration and Sizes submitted 4. Container/Closure Testing submitted 5. Source of supply and suppliers address submitted	☒
3.2.P.8	**3.2.P.8.1** **Stability (Finished Dosage Form)** 1. Stability Protocol submitted submitted 2. Expiration Dating Period 24 months for market containers and (b)(4) months for bulk container **3.2.P.8.2** **Post-approval Stability and Conclusion** Post Approval Stability Protocol and Commitments submitted **3.2.P.8.3** **Stability Data** 1. 3 month accelerated stability data submitted 2. Batch numbers on stability records the same as the test batch **yes**	☒

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Substance)	**3.2.R.1.S** **Executed Batch Records for drug substance (if available)** **3.2.R.2.S** **Comparability Protocols** **3.2.R.3.S** **Methods Validation Package** YES Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☐

MODULE 3

3.2.R Regional Information

ACCEPTABLE

3.2.R (Drug Product)	**3.2.R.1.P.1** **Executed Batch Records** Copy of Executed Batch Record submitted with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation submitted Table 3.2.R.1.P.1-2 Batch Reconciliation for Propafenone Hydrochloride Extended Release Capsules, 225 mg (b) (4) [redacted]	☒

3.2.R (Drug Product)	Table 3.2.R.1.P.1-3 Batch Reconciliation for Propafenone Hydrochloride Extended Release Capsules, 425 mg (b) (4) [redacted] **3.2.R.1.P.2** **Information on Components** reference to different sections **3.2.R.2.P** **Comparability Protocols** none submitted **3.2.R.3.P** **Methods Validation Package** submitted Methods Validation Package (3 copies) (Mult Copies N/A for E-Submissions) (Required for Non-USP drugs)	☒

MODULE 5
CLINICAL STUDY REPORTS

ACCEPTABLE

5.2	**Tabular Listing of Clinical Studies**	☐
5.3.1 (complete study data)	**Bioavailability/Bioequivalence** **1. Formulation data same?** a. Comparison of all Strengths (check proportionality of multiple strengths) proportional b. Parenterals, Ophthalmics, Otics and Topicals per 21 CFR 314.94 (a)(9)(iii)-(v) **2. Lot Numbers of Products used in BE Study(ies):** **3. Study Type:** (Continue with the appropriate study type box below)	☒

5.3.1.2

Comparative BA/BE Study Reports

1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC)

Fasted biostudy of metabolite 5-hydroxypropafenone Cmax falls outside the range (108 – 130) . This is a DBE review issue. See DBE memo to file in DFS signed off by Barbara Davit on 12/28/2006.

Table 2. Statistical Summary of the Comparative Bioavailability Data Propafenone

Propafenone HCl 1 x 425 mg Extended Release Capsule Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t}	142.963	140.430	102	(93.0; 111)
AUC_{∞}	151.004	147.822	102	(91.8; 114)
C_{max}	9.088	8.671	105	(94.5; 116)
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}	730.752	735.528	99.4	(92.4; 107)
AUC_{∞}	734.334	739.590	99.3	(92.3; 107)
C_{max}	96.391	96.877	99.5	(89.5; 111)

Table 2. Statistical Summary of the Comparative Bioavailability Data 5-Hydroxypropafenone

Propafenone HCl 1 x 425 mg Extended Release Capsule Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasted Bioequivalence Study				
Parameter	Test	Reference	Ratio	90% C.I.
AUC_{0-t}	268.317	253.441	106	(97.8; 115)
AUC_{∞}	275.722	261.956	105	(97.2; 114)
C_{max}	16.173	13.648	119	(108; 130)
Fed Bioequivalence Study				
Parameter	Test	Reference	100*Ratio	90% C.I.
AUC_{0-t}	1026.68	993.56	103	(98.7; 108)
AUC_{∞}	1036.06	1002.68	103	(98.7; 108)
C_{max}	97.97	95.26	103	(96.4; 110)

2. Summary Bioequivalence tables: submitted

Table 6. Demographic Profile of Subjects Completing the Comparative BA Study

Table 7. Incidence of Adverse Events in Individual Studies

Table 8. Reanalysis of Study Samples

5.3.1.3

In Vitro-In-Vivo Correlation Study Reports

1. Summary Bioequivalence tables:
   Table 4. Summary of In Vitro Dissolution Studies submitted
   Table 5. Formulation Data submitted

5.3.1.4

Reports of Bioanalytical and Analytical Methods for Human Studies

1. Summary Bioequivalence table:
   Table 3. Bioanalytical Method Validation submitted

5.3.7

Case Report Forms and Individual Patient Listing submitted

5.4	**Literature References**	
	Possible Study Types:	
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FASTING AND FED ON 425 MG See OGD#05-0755 issued 11/8/2005 attachment below 1. Study(ies) meets BE criteria (90% CI of 80-125, C max, AUC) **Fasted biostudy of metabolite 5-hydroxypropafenone Cmax falls outside the range (108 – 130) . This is a DBE review issue. See DBE memo to file in DFS signed off by Barbara Davit on 12/28/2006.** 2. EDR Email: Data Files Submitted: YES SENT TO EDR 3. In-Vitro Dissolution:	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** NO 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria: 90% CI of the proportional difference in success rate between test and reference must be within (-0.20, +0.20) for a binary/dichotomous endpoint. For a continuous endpoint, the test/reference ratio of the mean result must be within (0.80, 1.25). 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted	☐
Study Type	**IN-VITRO BE STUDY(IES)** (i.e., in vitro binding assays) NO 1. Study(ies) meets BE criteria (90% CI of 80-125) 2. EDR Email: Data Files Submitted: 3. In-Vitro Dissolution:	☐
Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** NO 1. Solutions (Q1/Q2 sameness): a. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) 2. Suspensions (Q1/Q2 sameness): a. In-Vivo PK Study 1. Study(ies) meets BE Criteria (90% CI of 80-125, C max, AUC) 2. EDR Email: Data Files Submitted b. In-Vivo BE Study with Clinical End Points 1. Properly defined BE endpoints (eval. by Clinical Team) 2. Summary results meet BE criteria (90% CI within +/- 20% or 80-125) 3. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) 4. EDR Email: Data Files Submitted c. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐

Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** NO 1. Pilot Study (determination of ED50) 2. Pivotal Study (study meets BE criteria 90%CI of 80-125)	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** NO 1. In-Vivo PK Study 1. Study(ies) meet BE Criteria (90% CI of 80-125, C max, AUC) 2. In-Vitro Dissolution 3. EDR Email: Data Files Submitted 2. Adhesion Study 3. Skin Irritation/Sensitization Study	☐

Updated 10/10/2006 C. Bina

Search results from the "OB_Rx" table for query on "021416."

Active Ingredient:	PROPAFENONE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	RYTHMOL SR
Applicant:	RELIANT PHARMS
Strength:	225MG
Application Number:	021416
Product Number:	001
Approval Date:	Sep 4, 2003
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	PROPAFENONE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	RYTHMOL SR
Applicant:	RELIANT PHARMS
Strength:	325MG
Application Number:	021416
Product Number:	002
Approval Date:	Sep 4, 2003
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	PROPAFENONE HYDROCHLORIDE
Dosage Form;Route:	CAPSULE, EXTENDED RELEASE; ORAL
Proprietary Name:	RYTHMOL SR
Applicant:	RELIANT PHARMS
Strength:	425MG
Application Number:	021416
Product Number:	003
Approval Date:	Sep 4, 2003
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through November, 2006
Patent and Generic Drug Product Data Last Updated: December 19, 2006

Patent and Exclusivity Search Results from query on Appl No 021416 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021416	001	5681588	OCT 28,2014			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021416	001	NDF	SEP 04,2006

Patent and Exclusivity Search Results from query on Appl No 021416 Product 003 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021416	003	5681588	OCT 28,2014			

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021416	003	NDF	SEP 04,2006

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV - 8 2005

Par Pharmaceutical, Inc.
Attention: Achyut J. Bhatt
One Ram Ridge Road
Spring Valley, NY 10977

Reference Number: OGD #05-0755

Dear Mr. Bhatt:

This letter is in response to your correspondence dated June 21, 2005. You request that the Office of Generic Drugs (OGD) provide bioequivalence recommendations regarding Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg, and 425 mg. OGD provides the following comments:

1. The following studies are recommended to establish bioequivalence of Propafenone Extended Release Capsules:

    a. A single-dose fasting *in-vivo* bioequivalence study comparing Propafenone Hydrochloride Extended Release Capsules, 425 mg, to the reference listed drug (RLD), Rythmol® SR, (Propafenone Hydrochloride) Extended Release Capsules, 425 mg.

    b. A single-dose fed *in-vivo* bioequivalence study comparing Propafenone Hydrochloride Extended Release Capsules, 425 mg, to the RLD.

2. Please measure both the parent compound, propafenone and its metabolite, 5-OH propafenone. Please analyze propafenone using the 90% confidence interval approach. For 5-OH propafenone, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

3. Propafenone Hydrochloride Extended Release Capsules, 225 mg and 325 mg may be considered for a waiver of *in-vivo* bioequivalence testing based on (1) acceptable bioequivalence studies on the 425 mg strength, (2) acceptable dissolution testing of the 225 mg, 325 mg and 425 mg strengths, and (3) proportional similarity in the formulations of the 225 mg, 325 mg and 425 mg strengths.

4. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual capsule data as well as the mean, range, and standard deviation at each time point for twelve capsules. In addition, please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the following FDA method:

Apparatus:	USP Apparatus II (paddle)
Speed:	50 rpm
Medium:	0-2 Hours: 900 mL of 0.08 M HCl 2-12 Hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours.
Sampling Times:	1, 2, 4, and every 2 hours and until at least 80% of the labeled content is dissolved.

Dissolution specifications will be determined upon review of the data.

5. Please provide a table that identifies every missing sample in the study. Also, for every reassayed sample, please provide a table identifying the reason(s) for reassay, as well as the original and reassayed values of the sample. Please identify which value was selected for the PK analysis. Please provide the Standard Operating Procedures (SOPs) for all types of reassays including those that describe criteria for identifying and reassaying pharmacokinetically anomalous samples. The SOP(s) should clearly state objective criteria for defining pharmacokinetic anomalies, the method of reassay, and acceptance criteria for selecting which value to report for the reassayed sample. This SOP should be in place prior to the start of the study; otherwise, the Division of Bioequivalence may not accept reassayed values of samples. Finally, please conduct all pharmacokinetic and statistical analyses using both the original as well as reassayed values.

6. The bioequivalence data to be submitted in an ANDA should be provided in a diskette or CD in SAS Transport format in two separate files as described below:

   a. SUBJ SEQ PER TRT AUCT AUCI CMAX TMAX KE Thalf
   b. SUBJ SEQ PER TRT C1 C2 C3 ..... Cn

   Please separate each field with a blank space and indicate missing values with a period (.).

Please refer to the Guidance for Indust
Electronic Format-ANDAs" for infor
www.fda.gov/cder/guidance/index.htm

If you have any questions, please call Steven M
of Bioequivalence at (301) 827-5847. In future
please include a copy of this letter.

Sincerely

Dale P. C
Director
Division o
Office of
Center for

OGD # 05-0755

Appears this way on original.

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

/s/

Martin Shimer

1/10/2007 08:01:13 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-540

Par Pharmaceutical, Inc.
Attention: Janis A. Picurro
One Ram Ridge Road
Spring Valley, NY 10977

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated December 20, 2006.

NAME OF DRUG: Propafenone Hydrochloride Extended-release Capsules, 225 mg and 425 mg

DATE OF APPLICATION: October 10, 2006

DATE (RECEIVED) ACCEPTABLE FOR FILING: October 11, 2006

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

  2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the

patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a copy of a court order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing

agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Martin Shimer, Chief, Regulatory Support Branch, at (301)827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Cheryl Wiseman
Project Manager
301-827-5806

Sincerely yours,

{See appended electronic signature page}

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Martin Shimer
1/10/2007 07:12:21 AM
Signing for Wm Peter Rickman

BIOEQUIVALENCY AMENDMENT

ANDA 78-540

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Par Pharmaceutical, Inc. TEL: 845-639-5121

ATTN: Janis Picurro FAX: 845-639-5201

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on October 10, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Propafenone Hydrochloride Extended-Release Tablets, 225 mg, 325 mg, and 425 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __2__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

The Division of Bioequivalence has developed new data summary tables in a concise format consistent with the Common Technical Document (CTD). Please provide complete tables and send them with the rest of the bioequivalence submission. The tables are available in Word and PDF format under the title "Model Bioequivalence Data Summary Tables" in our website at http://www.fda.gov/cder/ogd/index.htm. To improve the efficiency of the Division, these tables should be provided in future ANDA submissions.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-540 APPLICANT: Par Pharmaceutical, Inc.

DRUG PRODUCT: Propafenone Hydrochloride Extended-Release Capsules, 225, 325, and 425 mg

The Division of Bioequivalence (DBE) has completed its review of the dissolution testing portion of your submission(s) acknowledged on the cover sheet. The review of the bioequivalence studies and waiver requests will be conducted later. The following deficiencies have been identified:

1. Please provide acknowledgement for your acceptance of the following dissolution method and specifications:

Medium:	0 to 2 hours: 900 mL of 0.08N HCl 2 to 12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours
Temperature:	37°C ± 0.5°C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling times:	1, 2, 4, and every 2 hours thereafter

The test product should meet the following specifications:

1 hr:	(b) (4)
4 hrs:	
12 hrs:	NLT (b) (4)

2. For future applications, please provide the *in vitro* dissolution summary table as shown in Attachment 1 in a word file (.doc) and pdf format.

3. For this application, please clearly define the SAS data files (.xpt) so that they correspond to the appropriate bioequivalence study. The SAS data files provided by the firm are labeled Propafenone HCL 425mg ER Cap **Fast**-D-1.XPT, Propafenone HCL 425mg ER Cap **Fast**-M-1.XPT, and Propafenone HCL 425mg ER Cap **Fast**-D-2.XPT, Propafenone HCL 425mg ER Cap **Fast**-M-2.XPT. According to the file name, it is unclear to the DBE as to which datasets are for the fasting BE study No. BA0667005 and fed BE study No. BA0667006. The DATADEF .pdf file does not provide sufficient information to clear up this discrepancy.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment 1

Table 4. Summary of In Vitro Dissolution Studies

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions and Proposed Specification	No. of Dosage Units	Collection Times Mean of %Drug Dissolved (Range) [%CV]				Study Report Location
					min	min	min	min	
Diss. study report #	Test prod name/ #	mg Tab./Cap./Susp.	Conditions of Dissolution Testing: Apparatus: Speed of Rotation: rpm Medium: Volume: mL Temperature: °C+ Proposed Specification:	12					
Diss. study report #	Ref prod name/ #	mg Tab./Cap/Susp.		12					

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

/s/

Dale Conner

2/1/2007 04:19:23 PM

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2

ORIG AMENDMENT
N1 AB.

February 7, 2007

Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

Bioequivalence Amendment

RE: ANDA 78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Staff:

Reference is made to our abbreviated new drug application dated October 10, 2006 and the subsequent amendment of November 6, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg. Reference is also made to the February 1, 2007 correspondence from the Division of Bioequivalence. A copy of the February 1, 2007 correspondence is appended in Attachment 1.

Par Pharmaceutical is addressing the Agency's deficiencies with this bioequivalence amendment to ANDA 78-540. The Agency's comments and our response follow.

Comment 1

Please provide acknowledgement for your acceptance of the following dissolution method and specifications:

Medium:	0 to 2 hours: 900 mL of 0.08N HCl 2 to 12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours
Temperature:	37° C ± 0.5° C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling Times:	1, 2, 4 and every 2 hours thereafter

The test product should meet the following specifications:

1 hr:	(b) (4)%
4 hrs:	%
12 hrs:	NLT (b) (4)%

Response

The dissolution testing is conducted using the FDA-recommended method as follows:

Medium:	0 to 2 hours: 900 mL of 0.08N HCl 2 to 12 hours: Phosphate buffer, pH 6.8 The pH is changed by adding a buffer concentrate to the initial medium (HCl) after 2 hours
Temperature:	37° C ± 0.5° C
USP Apparatus:	II (Paddle)
Rotational Speed:	50 rpm
Sampling Times:	1, 2, 4 and every 2 hours thereafter

RECEIVED
FEB 0 8 2007
OGD / CDER

Par also acknowledges and accepts the Agency's recommended dissolution specification of:

1 hr:	(b) (4)%
4 hrs:	%
12 hrs:	NLT (b) (4)%

The finished product/stability monograph will be updated accordingly and will be submitted to the application.

Comment 2
For future applications, please provide the *in-vitro* dissolution summary table as shown in Attachment 1 in a word file (.doc) and pdf format.

Response
For future applications, Par commits to provide the *in-vitro* dissolution summary table as shown in Attachment 1, in both, a word file (.doc) and pdf format.

Comment 3
For this application, please clearly define the SAS data files (.xpt) so that they correspond to the appropriate bioequivalence study. The SAS data files provided by the firm are labeled Propafenone HCL 425 mg ER Cap Fast-D-1.XPT, Propafenone HCL 425 mg ER Cap Fast-M-1.XPT, and Propafenone HCL 425 mg ER Cap Fast-D-2.XPT, Propafenone HCL 425 mg ER Cap Fast-M-2.XPT. According to the file name, it is unclear to the DBE as to which datasets are for the fasting BE study No. BA0667005 and fed BE study No. BA0667006. The DATADEF.pdf file does not provide sufficient information to clear up this discrepancy.

Response
Please refer to our Table of Contents for Module 5 submitted in electronic format on the CD Rom with the original application. Section 5.3, Clincal Study Reports, Subsection 5.3.1.2 Comparative BA and Bioequivalence (BE) Reports lists Study #BA0667005 Fasting Study and Study #BA0667006 Non-Fasting Study. Within each study, the associated SAS dataset files are provided after Appendix 16.6. For ease of review, a hard copy of the Table of Contents for Module 5 is provided in Attachment 2.

This concludes our bioequivalence amendment to ANDA 78-540 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

If you have any questions or require additional information, please do not hesitate to contact me at (845) 639-5128, by fax (845) 639-5201 or by e-mail *jszozda@parpharm.com.*

Sincerely yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Senior Associate, Regulatory Affairs

78-540

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1 ✓
Copy 2

February 22, 2007

Martin Shimer, Branch Chief, Regulatory Support Branch
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

PATENT AMENDMENT

RE: Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg Notice of Paragraph IV Certification (CTD Module 1.3.5)

Dear Mr. Shimer:

Reference is made to our abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg and the amendment of November 6, 2006 which provided for the addition of the 325 mg strength.

With respect to the 225 mg, 325 mg and 425 mg strengths, Par declares the following:

- In accordance with 21 CFR 314.95(b), Par Pharmaceutical, Inc. certifies that notice was provided by U.S. registered mail, return receipt requested, to each person identified under CFR 314.95(a) on January 10, 2007 and the notice met the content requirements under 314.95(c).
- A copy of the Patent Certification Notice letter for U.S. Patent 5,681,588, referencing the 225 mg, 325 mg and 425 mg strengths, is provided.

This concludes our Notice of Paragraph IV Certification for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg. If additional information is required, please do not hesitate to contact me directly at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Senior Associate, Regulatory Affairs

Enclosure

Telephone Fax

ANDA 78-540

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
240-276-8987

TO: PAR PHARMACEUTICAL, INC TEL: 845-639-5121

ATTN: JANIS PICURRO FAX: 845-639-5201

FROM: ADOLPH VEZZA

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for _Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg and 425 mg.

Pages (including cover): 6

SPECIAL INSTRUCTIONS:

Labeling Comments

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

ANDA Number: **78-540** Dates of Submissions: **October 10 and November 6, 2006**

Applicant's Name: **Par Pharmaceutical, Inc.**

Established Name: **Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg and 425 mg**

Labeling Deficiencies:

1. CONTAINER 60s, 100s, 500s and 1000s

    a. Established name

        i. Increase the prominence of the established name and strength so that they appear as the most prominent information on the label.

        ii. Decrease the prominence of "PAR".

        Iii. "Hydrochloride" rather than "HCl"

    b. Differentiate your product strengths by boxing, contrasting colors, or some other means.

    c. Storage temperature recommendation

        i. "15^{o} to" rather than "15^{o}to"

        ii. "Controlled Room Temperature" [upper case "C", "R" and "T"]

    d. 225 mg LABELS – "Contains FD&C Yellow No.5 (tartrazine) as a color additive." or "Contains color additives including FD&C Yellow No.5 (tartrazine)."

    e. 425 mg LABELS – 100s, 500s and 1000s

        i. "Each capsule contains" – "hydrochloride … 425 mg"

        ii. USUAL DOSAGE – "One capsule every 12 hours. See …"

2. INSERT

    a. GENERAL COMMENTS

        i. "Propafenone ER capsules" rather than "Propafenone HCl ER" and "Propafenone HCl ER capsules" throughout the text of the insert.

        ii. "mcg" rather than "µg" throughout the insert

b. TITLE

Place “Rx only” beneath the title.

c. CLINICAL PHARMACOLOGY

i. Hemodynamics, second line –

A). Place “2.61” and “L/min/m^2” on same line of text.

B). “L/min/m^2” rather than “L/min/m2”

ii. Pharmacokinetics and Metabolism

A). Absorption/Bioavailability, second paragraph

1). “ER” rather than (b) (4) [three instances

2). Fourth line – “… an increase of overall …” rather than “an increase in overall …”

B). Distribution, second paragraph – Place “0.5 – 2” and “mcg/mL” on same line of text.

C). Metabolism, first paragraph

1). Third line – “5-hydroxypropafenone” [spelling]

2). Sixth line – Place “10-32” and “hours” on the same line of text.

iii. Clinical Trials

A). RAFT

1). First paragraph, seventh line – “beta-blockers” [add hyphen]

2). Improve the clarity/legibility of the graph

B). ERAFT, second paragraph, last sentence – “propafenone” [lower case “p”]

d. WARNINGS

i. Proarrhythmic Effects, last paragraph, second sentence – “4%” [delete the terminal zero]

ii. Congestive Heart Failure

A). First sentence – “beta-blockade” [add hyphen]

B). Second sentence – “1%” [delete the terminal zero]

iii. Conduction Disturbances, last paragraph, last sentence – Place “(rate <50” and “beats/min)” on the same line of text.

e. PRECAUTIONS

i. Hepatic Dysfunction

A). Place the subsection title immediately beneath the section title.

B). "… propafenone HCl immediate release tablets …" [delete (b) (4) – two instances]

ii. Information for Patients

A). Add the following sub-subsection immediately beneath the "Dosing Schedule" sub-subsection:

Elevated ANA Titers:
Positive ANA titers have been reported in patients receiving propafenone. They have been reversible upon cessation of treatment and may disappear even in the face of continued propafenone therapy. These laboratory findings were usually not associated with clinical symptoms, but there is one published case of drug-induced lupus erythematosus (positive rechallenge); it resolved completely upon discontinuation of therapy. Patients who develop an abnormal ANA test should be carefully evaluated and, if persistent or worsening elevation of ANA titers is detected, consideration should be given to discontinuing therapy.

B) Add the following to the end of this subsection:

"The 225 mg capsules contain FD&C Yellow No.5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No.5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity>"

iii. Drug Interactions

A). Rifampin – "C_{max}" rather than "Cmax" [three instances]

B). Fluoxetine - "C_{max}" rather than "Cmax" [two instances]

f. ADVERSE REACTIONS

i. First paragraph, first sentence – "U.S." rather than "US."

ii. Table 2

A). Title – "($\geq$ 2%" rather than "(b) (4)

B). "MeDRA" rather than "MedDRA"

C). First column – Place the title "**Investigations**" immediately above the "Blood alkaline phosphatase increased" row.

iii. Cardiac disorders, second line "…block; bundle branch block left; …"

iv. "*Investigations:*" [*italics*]

v. Table 3 – "**Propafenone ER**" [**bold print**]

vi. Table 4, last column – "N=100" rather than (b) (4)

g. HOW SUPPLIED

i. Place "225" and "mg" on the same line of text.

ii. Place "325" and "mg" on the same line of text.

iii. Place "425" and "mg" on the same line of text.

Please revise your labeling as described above and submit in final print. Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format - ANDA". The immediate container labels may be submitted either electronically or in hard copy. However, for ease of review, we ask that you submit electronically.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

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

{See appended electronic signature page}

_____

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Lillie Golson
5/9/2007 03:11:08 PM
Lillie Golson for Wm. Peter Rickman

PAR PHARMACEUTICAL

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2

June 01, 2007

Mr. Adolph Vezza
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North 2
7500 Standish Place, Room 150
Rockville, Maryland 20855

LABELING AMENDMENT

RE: ANDA #78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Vezza:

Reference is made to the Agency's telephone facsimile of May 10, 2007 regarding labeling deficiencies related to our abbreviated new drug application dated October 10, 2006 and the subsequent amendment dated November 11, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg. A copy of the Agency's May 10, 2007 correspondence is provided.

Par's labeling has been revised as instructed. In accordance with 21 CFR 314.94(a)(8)(iv) and to facilitate review, a side-by-side comparison of our proposed final printed labeling with the previously submitted labeling with all differences annotated and explained is included electronically on the enclosed CD ROM.

This concludes our labeling amendment to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules. If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

Enc.

PAR PHARMACEUTICAL

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Copy 1 ✓
Copy 2
Copy 3 (Field)*

July 19, 2007

U|XP

Martin Shimer, Branch Chief, Regulatory Support Branch
Food and Drug Administration
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

PATENT AMENDMENT

RE: ANDA 78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Shimer:

Reference is made to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg, dated October 11, 2006 and the subsequent amendment dated November 10, 2006 which provided for the addition of the 325 mg strength.

In conjunction with the above, Par is amending ANDA 78-540 with the following:

Pursuant to 21 CFR 314.95(b), Par is certifying that notice has been provided to each person identified under 314.95(a) and the notice met the content requirements under 314.95(c).

Pursuant to 21 CFR 314.95(e), Par is providing documentation of receipt of notice by providing a photostatic copy of the United States Track & Confirm delivery receipt.

Please be advised that litigation relative to United States Patent Numbers 5.681,588 was initiated prior to the expiration of the 45 day period as described in Section 505(j)(4)(B)(iii) of the Act.

A copy of the complaint filed in the United States District Court for the District of Delaware is attached for reference.

We certify that the field copy of this amendment was submitted to the FDA New York District Office.

If you have any questions or require additional information regarding the above matter, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

*Mr Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

MINOR AMENDMENT

ANDA 78-540

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Par Pharmaceutical, Inc. TEL: 845-425-7100

ATTN: Julie Szozda FAX: 845-639-5201

FROM: Ted Palat PROJECT MANAGER: (301) 594-0338

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated October 10, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Propafenone Hydrochloride, 225 mg, 325 mg, and 425 mg

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (_two_ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540 APPLICANT: Par Pharmaceuticals, Inc

DRUG PRODUCT: Propafenone HCl Extended Release Capsules, 225 mg, 325 mg, and 425 mg

Chemistry Deficiencies:

1. (b) (4)

2.

3.

4.

(b) (4)

5.

6.

7.

8.

9. The specification for dissolution in the release and stability of the finished product is not consistent with the recommended specification by the Division of Bioequivalence. Please submit updated specifications. Submit data to support the 24 months expiration dating.

10. Please submit available controlled room temperature stability data.

Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Ubrani Venkataram

7/25/2007 03:32:34 PM

PAR PHARMACEUTICAL

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fax 845 425 7907
www.parpharm.com

Copy 1
Copy 2
Copy 3 (field)*

ORIG AMENDMENT
N/AM

November 28, 2007

Ted Palat
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
7500 Standish Place, Room 150
Rockville, Maryland 20855

MINOR AMENDMENT

RE: ANDA #78-540 Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Palat:

Reference is made to the Agency's correspondence of July 26, 2007 regarding our abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg and the subsequent amendment which provided for the addition of the 325 mg strength.

Par Pharmaceutical is addressing the Agency's deficiencies with this minor amendment to ANDA 78-540. The Agency's comments and our responses follow.

Chemistry Deficiencies:

Comment 1

(b) (4)

Response

(b) (4)

RECEIVED
NOV 29 2007
OGD

Following this page, 5 pages withheld in full - (b)(4)

Comment 9
The specification for dissolution in the release and stability of the finished product is not consistent with the recommended specification by the Division of Bioequivalence. Please submit updated specifications. Submit data to support the 24 months expiration dating.

Response
The dissolution specifications for release and stability of the finished product have been updated in accordance with the Division of Bioequivalence recommendation. All results obtained after Par accepted the new limits for dissolution were within specifications. Updated finished product/stability monographs are provided in Attachment 7. All available stability data are provided to support our proposed 24 month expiration dating. Please refer to our response to Comment 10.

Comment 10
Please submit available controlled room temperature stability data.

Response
The stability summary reports have been updated to include the test for (b) (4). The available controlled room temperature stability data is appended in Attachment 8.

We certify that the field copy of this minor amendment was submitted to the FDA New York District Office.

If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *jszozda@parpharm.com.*

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

*Mr. Matthew Spataro
NYDO NDA/ANDA File Room
Food and Drug Administration
158-15 Liberty Avenue
Jamaica, New York 11433

MINOR AMENDMENT

ANDA 78-540

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Par Pharmaceutical, Inc. TEL: 845-639-5128

ATTN: Julie Szozda FAX: 845-639-5201

FROM: Nitin Patel FDA CONTACT PHONE: (240) 276-8548

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 10, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Propafenone Hydrochloride Extended-Release Tablets, 225 mg, 325 mg, and 425 mg.

Reference is also made to your amendment dated November 28, 2007.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__**1**__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-540 APPLICANT: Par Pharmaceuticals, Inc

DRUG PRODUCT: Propafenone HCl Extended Release Capsules, 225 mg, 325 mg, and 425 mg

A. Chemistry Deficiencies

1. (b) (4)

2.

3.

4.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval. Please refer to the letter posted on the Office of Generic Drugs website for further information and submit the necessary revisions to your application.

Sincerely yours,

{see appended electronic signature page}

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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

/s/

Ubrani Venkataram
6/13/2008 02:54:05 PM
For Florence Fang

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

July 30, 2008

Nitin Patel, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Central Document Room
7500 Standish Place, Room 150
Rockville, Maryland 20855

RE: ANDA #78-540 Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Patel:

Reference is made to the Agency's correspondence of June 13, 2008 regarding our abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg and the subsequent amendment which provided for the addition of the 325 mg strength.

Par Pharmaceutical is addressing the Agency's deficiencies with this minor amendment to ANDA 78-540. The Agency's comments and our responses follow.

A. Chemistry Deficiencies:

Comment 1

(b) (4)

Please discuss.

Response

(b) (4)

product does not vary significantly but compares well across all dosage strengths.

Comment 2

(b) (4)

dissolution method. Please revise the documents to be consistent with that recommended by the DBE and resubmit.

Following this page, 1 page withheld in full - (b)(4)

Effective July 1, 2008, all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval. Please refer to the letter posted on the Office of Generic Drugs website for further information and submit the necessary revisions to your application.

Response

We note and acknowledge that effective July 1, 2008 all Abbreviated New Drug Applications must demonstrate that the subject drug product is in compliance with USP Residual Solvents <467> prior to receiving Approval or Tentative Approval.

As such, Propafenone Hydrochloride Extended Release Capsules manufactured by Par is in compliance with USP Residual Solvents <467> requirements, the Residual Solvents Report, Document #MS08-037-1 is provided electronically for your review in Attachment 3, Residual Solvents, which demonstrates that our product meets USP <467> acceptance criteria.

This amendment is being provided electronically as PDF documents on the enclosed CD ROM. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions, please don't hesitate to contact me at (845) 639-5128 or by e-mail at *julie.szozda@parpharm.com.*

Very truly yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

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Spring Valley, NY 10977
tel 845 425 7100
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April 23, 2009

Martin Shimer, Branch Chief, Regulatory Support Branch
Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, Maryland 20855

PATENT AMENDMENT

RE: ANDA 78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Shimer:

Reference is made to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg, dated October 11, 2006 and all subsequent amendments thereto.

In conjunction with the above, Par is amending ANDA 78-540 with the following:

Please be advised that all claims, counterclaims and defenses in litigation relative to United States Patent Number 5.681,588 has been dismissed with prejudice pursuant to Rule 41(a) of the Federal Rules of Civil Procedure. A copy of the amended complaint and stipulation of dismissal filed in the United States District Court for the District of Delaware is attached for reference.

This amendment is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If additional information is required regarding the above matter, please don't hesitate to contact the undersigned via the new phone number (845) 573-5780 or by e-mail at *julia.szozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
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May 19, 2009

Nitin Patel, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT

RE: ANDA #78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Patel:

Reference is made to the April 28, 2009 telephone call from Dr. Shankar Saha, Chemist at FDA regarding our Minor Amendement submitted on July 30, 2008 related to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par Pharmaceutical is addressing the Agency's deficiencies with this telephone amendment to ANDA 78-540. The Agency's comments and our responses follow.

Comment 1

(b) (4)

Response

(b) (4)

Comment 2

(b) (4) Please clarify and provide the report for the out of specification result.

Response

(b) (4)

Representative samples of the 225 mg, 325 mg and 425 mg strengths of the finished product for visualization purposes have been forwarded to your attention under separate cover as requested by Dr. Shankar Saha.

This amendment is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA. If you need any additional information, please contact me at the information provided below.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780 or by e-mail *julia.szozda@parpharm.com.*

Sincerely yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
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tel 845 425 7100
fax 845 425 7907
www.parpharm.com

June 25, 2009

Nitin Patel, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT

RE: ANDA #78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Patel:

Reference is made to the June 15, 2009 telephone call from Dr. Shankar Saha, Chemist at FDA regarding our Minor Amendement submitted on July 30, 2008 related to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par Pharmaceutical is addressing the Agency's deficiencies with this telephone amendment to ANDA 78-540. The Agency's comment and our response follow.

Comment

(b) (4)

Response

(b) (4)

This amendment is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780 or by e-mail *julia.szozda@parpharm.com.*

Sincerely yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

PAR PHARMACEUTICAL

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www.parpharm.com

July 16, 2009

Nitin Patel, Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, Maryland 20855

TELEPHONE AMENDMENT

RE: ANDA #78-540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Patel:

Reference is made to the July 08, 2009 telephone call from Dr. Shankar Saha, Chemist at FDA regarding the residual solvents specification in the finished product monographs previously submitted to our abbreviated new drug application for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg. Dr. Saha requested that the residual solvents statement be updated to include the relevant option.

As per Dr. Saha's request, Par Pharmaceutical has updated the residual solvents statement on the specification page of our finished product monographs to include the relevant option. The updated monographs are provided.

This telephone amendment is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780 or by e-mail *julia.szozda@parpharm.com.*

Sincerely yours,
PAR PHARMACEUTICAL, INC.

Julie Szozda

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
tel 845 425 7100
fax 845 425 7907
www.parpharm.com

October 6, 2009

Gary J. Buehler
Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, Maryland 20855

GENERAL CORRESPONDENCE
Withdrawal of 04/23/09 Patent Amendment

RE: ANDA 078540
Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application dated October 10, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg and 425 mg and the amendment of November 6, 2006 which provided for the addition of the 325 mg strength.

Par is amending our ANDA 078540 to withdraw the April 23, 2009 Patent Amendment. Based on our pre-existing PIV certification, Par is requesting Tentative Approval be granted of our ANDA for Propafenone Hydrochloride Extended Release Capsules. Notwithstanding the foregoing, this amendment in no way constitutes an amendment or withdrawal of our patent certification under 21 U.S.C. §355(j)(2)(A)(viii)(IV).

This amendment is being submitted through the Electronic Submissions Gateway (ESG). Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency on June 22, 2005 by Par Pharmaceutical Inc. In addition, our request for a waiver of eCTD specification was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If additional information is required, please do not hesitate to contact me directly at (845) 573-5780 or by e-mail at *julia.szozda@parpharm.com.*

Sincerely,
PAR PHARMACEUTICAL, INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
Tel: 845-425-7100
Fax: 845-573-5795
www.parpharm.com

Submitted through the Electronic Submissions Gateway (ESG)

March 16, 2010

Gary J. Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
OGD Document Room
7500 Standish Place
Rockville, Maryland 20855

Minor Amendment - Final Approval Requested

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Mr. Buehler:

Reference is made to our abbreviated new drug application dated October 11, 2006 and all subsequent amendments relative to Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

We herewith submit this minor amendment to request final approval of our application, ANDA 078540 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg. Please be advised that all claims, counterclaims and defenses in litigation relative to United States Patent Number 5,681,588 have been dismissed with prejudice pursuant to Rule 41(a) of Federal Rules of Civil Procedure. A copy of the amended complaint and stipulation of dismissal filed in the United States District Court for the District of Delaware is attached for reference.

Please note there are no text changes to the labeling since the submission of the labeling amendment dated June 1, 2007. Final printed labeling is provided electronically in SPL, pdf and MSWord format.

In accordance with the Agency's guidance on melamine contamination, we provide certifications from the suppliers of lactose anhydrous, povidone and gelatin used, stating that there is no melamine contamination risk in their product. In addition, please be advised that there have been no changes to this application.

Par also acknowledges that Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg may not be marketed without final Agency approval. Introduction or delivery into interstate commerce of the drug product will not occur before the effective date of approval of this application.

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Submitted through the Electronic Submissions Gateway (ESG)

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
Tel: 845-425-7100
Fax: 845-573-5795
www.parpharm.com

June 3, 2010

Dr. Shankar Saha
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
OGD Document Room
7500 Standish Place
Rockville, MD 20855

Telephone Amendment

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Dr. Saha:

Reference is made to the Agency's correspondence dated April 23, 2010 to our abbreviated new drug application dated October 11, 2006 and all subsequent amendments relative to Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg. Please note that our request for waiver of the 10-day "clock" and an extension to June 3, 2010 for submission of this telephone amendment was granted.

We herewith submit this telephone amendment in response to the Agency letter dated April 23, 2010.

Comment

1. Regarding solubility of the API in water: according to the MSDS from (b) (4) and other literature, the API is soluble in hot water but slightly soluble in cold water. The package insert information is correct but the information in description section is incomplete – it does not specify solubility in hot water. Please revise the information in the description section.

Response

The description for solubility in the original submission, Module 3, General Properties section, Table 3.2.S.1.3-1 mistakenly indicated "Soluble in water (20ºC), chloroform and ethanol". We have revised the information for solubility to read "Soluble in hot water, slightly soluble in cold water (20ºC), chloroform and ethanol" to be in line with the API manufacturers information in their Drug Master File. A copy of the updated General Properties Table, Table 3.2.S.1.3-1 is provided. We apologize for any inconvenience incurred.

The RLD labeling posted on the FDA website, Drugs@FDA is dated 09/04/2003 and the current approved version is unavailable at this time. Please be advised that our package insert will be updated as soon as the current version becomes available.

Following this page, one page withheld in full - (b)(4)

Response

(b) (4)

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
Tel: 845-425-7100
Fax: 845-573-5795
www.parpharm.com

Submitted through the Electronic Submissions Gateway (ESG)

June 7, 2010

Dr. Shankar Saha
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
OGD Document Room
7500 Standish Place
Rockville, MD 20855

Telephone Amendment

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Dr. Saha:

Reference is made to your telephone call requesting that Par provide the analytical reports for the 3 lots of raw material used to establish the particle size specifications, as stated in the Telephone Amendment dated 06/03/2010 relative to our abbreviated new drug application dated October 11, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

We herewith submit this amendment in response to today's telephone request.

The established particle size specifications were based on 3 lots of the raw material provided by the API manufacturer, (b) (4) Lot #0000149639, Lot #0000107987 and Lot #0000090518. A copy of these analytical reports is provided as requested.

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
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Spring Valley, NY 10977
Tel: 845-425-7100
Fax: 845-573-5795
www.parpharm.com

Submitted through the Electronic Submissions Gateway (ESG)

June 22, 2010

Dr. Shankar Saha
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
OGD Document Room
7500 Standish Place
Rockville, MD 20855

Telephone Amendment

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Dr. Saha:

Reference is made to the June 8, 2010 telephone call regarding the telephone amendments dated June 3, 2010 and June 7, 2010 relative to our October 11, 2006 abbreviated new drug application dated for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par is submitting this amendment to ANDA 078540 to provide additional information as requested by the Agency on June 8, 2010.

Comment
The particle size specifications listed in the cover letter of the June 3, 2010 Telephone Amendment does not match the specifications listed in the raw material monograph RM-RA100152-006. Please explain.

Response
Please note that a typographical error is noted in the particle size specifications on the cover letter of the June 3, 2010 telephone amendment. However, the particle size specifications for $D_{10,}$ $D_{50,\ and}$ D_{90} have since been revised based on data generated on additional lots of API.

D_{10}	(b) (4)
D_{50}	
D_{90}	

We apologize for any inconvenience incurred.

Comment
Particle size data included in the June 7, 2010 Telephone Amendment is on 3 separate lots of API. However, the data should be based on the API lots used in the exhibit batches. Please generate particle size data on the lots of API used in the exhibit batches and submit.

Response

Based on the data obtained on the three lots of API used in the exhibit batches, Lot #502949, Lot #504159 and Lot #505340, the particle size specifications for $D_{10,}$ $D_{50,\ and}$ D_{90} have been revised as follows:

D_{10}	(b) (4)
D_{50}	
D_{90}	

Please refer to Section 3.2.S.4.1 in Module 3 for the updated certificates of analysis for the API lots used in the exhibit batches and the updated raw material monograph. Particle Size Method Verification Report, MS10-014-01 is provided in Section 3.2.S.4.3.

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
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July 26, 2010

Tina Nhu, Project Manager
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
OGD Document Room
7500 Standish Place
Rockville, MD 20855

Fax: (240)-276-8405

Telephone Amendment

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Ms Nhu:

Reference is made to Dr. Saha's July 14, 2010 telephone conversation with Karen Rocco of Par regarding the proposed particle size specification submitted in telephone amendment dated June 22, 2010 relative to our October 11, 2006 abbreviated new drug application dated for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par is submitting this amendment to ANDA 078540 to provide revised particle size specifications as requested by the Agency.

Comment

Particle size specifications provided in the June 22, 2010 Telephone Amendment for the drug substance are not acceptable. Please revise your particle size specifications based on the data generated.

Response

Par has worked with the drug substance manufacturer, (b) (4) to evaluate the reproducibility of the (b) (4) particle size test method. It was determined that the (b) (4) (b) (4) affected the test results, causing variability. Thus the method was revised to establish these test parameters. The resulting data generated by Par and (b) (4) demonstrate the reliability and reproducibility of the revised method.

According to this method, particle size data has been generated on the three lots of API used in the exhibit batches, Lot #502949, Lot #504159 and Lot #505340 and five additional lots of API. The following revised particle size specifications have been mutually agreed upon by Par and the API manufacturer, (b) (4) for D_{10}, D_{50} and D_{90}:

D_{10}	(b) (4)
D_{50}	
D_{90}	

Please refer to attached page for Section 3.2.S.4.3 of Module 3 for the data generated from eight lots of API. The raw material monograph will be updated accordingly and submitted in an appropriate submission at a later time.

Representative sample of the 425 mg strength (bio strength) of the reference listed drug, Rythmol SR for visualization purposes has been forwarded to your attention under separate cover as requested by Dr. Shankar Saha.

If the revised particle size specifications and RLD sample evaluation are acceptable to the Agency, we believe that all outstanding issues with this application are resolved. Therefore, we look forward to our Final Approval and Thank the Agency for their efforts in this regard.

This amendment is submitted electronically on the enclosed CD Rom. Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

cc: Dr. Shankar Saha Fax: (240) 276-8582

TELEPHONE CONFERENCE FAX

ANDA 78540

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Par Pharmaceutical, Inc. TEL: 845-573-5780

ATTN: Julie Szozda FAX: 845-573-5795

FROM: Shankar Saha FDA CONTACT PHONE: (240) 276-8548

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated October 11, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Propafenone HCl ER capsules, 225 mg, 325 mg, and 425 mg.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" within ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Tina Nhu at (240) 276-8548. Please submit documentation by fax to the attention of Shankar Saha at 240-276-8582. Please also submit official hard copies of any faxed documentation to the Document Room.

1. The manufacturing of Propafenone HCl ER capsules 225 mg, 325 mg, and 425 mg drug product includes (b) (4)

You have noted that the (b) (4) are critical for drug release. The manufacturing process is designed to produce (b) (4)

In this regard:

a. Please explain the release mechanism of the drug product.
b. Please clearly define the term (b) (4) in this case. Additionally, how did you measure the (b) (4)
c. Please explain the impact of (b) (4) on the release profile and performance of the drug product. Please submit supportive data.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA

Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
ANDA-78540	ORIG-1	PAR PHARMACEUTICAL	PROPAFENONE HYDROCHLORIDE

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

/s/

SHANKAR L SAHA
08/11/2010

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
Tel: 845-425-7100
Fax: 845-573-5795
www.parpharm.com

Submitted through the Electronic Submissions Gateway (ESG)

August 17, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Correction to Telephone Amendment Cover Letter

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Dr. Webber:

Reference is made to our July 26, 2010 Telephone Amendment submitted to the abbreviated new drug application dated October 11, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par is amending the July 26, 2010 Telephone Amendment to provide a correction to the particle size specifications listed in the cover letter. The particle size specification for D_{10} in the cover letter has been corrected to reflect the proposed limits referenced in the particle size distribution sheet for data generated from the eight lots of API. The updated cover letter is attached.

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

We apologize for any inconvenience incurred. If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

Par Pharmaceutical, Inc.
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Tel: 845-425-7100
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www.parpharm.com

Submitted through the Electronic Submissions Gateway (ESG)

August 24, 2010

Keith Webber, Ph.D., Acting Director
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, MD 20855

Telephone Amendment

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Dr. Webber:

Reference is made to the Agency's Telephone Fax dated August 11, 2010 relevant to our abbreviated new drug application dated October 11, 2006 for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par Pharmaceutical is addressing the Agency's deficiencies with this telephone amendment to ANDA 078540. The Agency's comments and our responses follow.

Comment

1. *The manufacturing of Propafenone HCl ER Capsules 225 mg, 325 mg and 425 mg drug product includes* (b) (4) .

   You have noted that the (b) (4) *are critical for drug release. The manufacturing process is designed to produce* (b) (4) *. In regard:*

   a. Please explain the release mechanism of the drug product.

   b. Please clearly define the term (b) (4) *in this case. Additionally, how did you measure the* (b) (4) *?*

   c. Please explain the impact of (b) (4) *on the release profile and performance of the drug product. Please submit supportive data.*

Response

a. The drug substance is released from the final product through (b) (4) .

Following this page, one page withheld in full - (b)(4)

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*. We truly appreciate the Agency's consideration and efforts toward the review and approval of this application.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

cc: Dr. Shankar Saha
Fax: (240) 276-8582

Par Pharmaceutical, Inc.
One Ram Ridge Road
Spring Valley, NY 10977
Tel: 845-425-7100
Fax: 845-573-5795
www.parpharm.com

September 08, 2010

Tina Nhu, Project Manager
Office of Generic Drug
Center for Drug Evaluation and Research
Food and Drug Administration
OGD Document Room
7500 Standish Place
Rockville, MD 20855

Telephone Amendment

RE: ANDA #078540, Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg

Dear Ms Nhu:

Reference is made to the 09/08/2010 telephone conversation with Dr. Saha regarding our October 11, 2006 abbreviated new drug application dated for Propafenone Hydrochloride Extended Release Capsules, 225 mg, 325 mg and 425 mg.

Par is submitting this amendment to ANDA 078540 to include the raw material monograph, which has been updated to reflect the revised particle size specifications as submitted in the 07/26/10 telephone amendment. The particle size specifications are as follows:

D_{10} (b) (4)
D_{50}
D_{90}

A copy of the updated raw material monograph, Document #RM-RA100152-008 is provided.

We believe that all outstanding issues with this application are resolved and we look forward to our Final Approval and Thank the Agency for their efforts in this regard.

Please be advised that a "Letter of Non-Repudiation Agreement" was submitted to the Agency by Par Pharmaceutical, Inc on June 22, 2005. In addition, our request for a waiver of the eCTD specifications requirements was granted and provided in an e-mail dated March 04, 2008 from Virginia Ventura of the FDA.

If you have any questions or require additional information, please contact the undersigned by phone at (845) 573-5780, by fax (845) 573-5795 or by e-mail *julia.szozda@parpharm.com*.

Very truly yours,
PAR PHARMACEUTICAL INC.

Julie Szozda
Submissions Manager, Regulatory Affairs

cc: Dr. Shankar Saha Fax: (240) 276-8582

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-540 Applicant Par Pharmaceutical, Inc.
Drug Propafenone Hydrochloride Extended-release Capsules, 225 mg, 325 mg, and 425 mg
Strength(s) _____

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER:	**DRAFT Package**	**FINAL Package**
1. **Martin Shimer**	Date 10 August 2009	Date 10/18/10
Chief, Reg. Support Branch	Initials MHS	Initials rlw

Contains GDEA certification: Yes ☒ No ☐ (required if sub after 6/1/92)
Patent/Exclusivity Certification: Yes ☒ No ☐
If Para. IV Certification- did applicant Notify patent holder/NDA holder Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☒ No ☐
Has case been settled: Yes ☒ No ☐
Is applicant eligible for 180 day Generic Drugs Exclusivity for each strength: Yes ☒ No ☐
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.

Determ. of Involvement? Yes ☐ No ☒
Pediatric Exclusivity System
RLD = Rythmol SR NDA# 21-416
Date Checked 10/18/10
Nothing Submitted ☒
Written request issued ☐
Study Submitted ☐
Date settled:

Comments: ANDA submitted on 10/11/2006, BOS=Rythmol SR NDA 21-416, PIV to '588. ANDA ack for filing with PIV for the 225 mg and 425 mg strengths on 10/11/2006 (LO dated 1/10/2007). On 11/7/2006 the sponsor submitted a NSA to include the 325 mg strength, same BOS, PIV to the '588. XP submitted on 11/13/2006-Par provided notice for the 325 mg strength at the same time that they submitted their NSA for the '588 patent-RR from Reliant in Liberty Corner NJ dated 11/8/2006 (OGD notes that this notice was sent prematurely as OGD had yet to issue an ACK letter). XP sent on 2/23/2007-RR from Liberty Corner NJ signed and dated 1/11/2007 (notice sent on 1/10/2007)-this notice was sent for all 3 strengths. Letter submitted from Kirkland and Ellis that CA06-774 was filed in the D of DE on 12/19/2006 for infringement of the '588 with respect to the '325 mg strength-this suit was filed pursuant to the premature notice on the 325 mg strength. XP submitted by sponsor on 7/20/2007-CA 06-774-JJF filed in the D of DE on 1/26/2007 for infringement of the '588 for all strengths. 30 month stay of approval=7/10/2009. On 4/23/2009, the sponsor submitted a patent amendment which included a copy of a Stipulation of Dismissal which was entered in CA 06-774, the dismissal was entered on 4/17/2009 by the court.

Applicant was the first to submit a substantially complete ANDA with PIV certs to listed patents and therefore is eligible for 180 day exclusivity. However, the sponsor did not secure TA within 30 months and therefore would be subject to MMA forfeiture provisions under 505(j)(5)(D)(IV).

Final recommendation-ANDA is eligible for Full Approval. It is noted that there are no other ANDAs pending within OGD for these drug products. Therefore, the approval language should not state that the applicant is awarded 180 day exclusivity and include the disclaimer language that OGD will further evaluate this issue in the future if it is warranted.

2. **Project Manager**, Simon Eng Team 8	Date _____	Date _____
Review Support Branch	Initials sse	Initials _____

Original Rec'd date 10/10/09
Date Acceptable for Filing 10/11/09
Patent Certification (type) IV
Date Patent/Exclus.expires 10-28-2014
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☒
Bio Review Filed in DFS: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 8/15/07
Date of Office Bio Review 6-15-07
Date of Labeling Approv. Sum 6/19/07
Date of Sterility Assur. App. n/a
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☒
Modified-release dosage form: Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☒

Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement

Reviewer: Labeling Team Leader:
Date_____ Date 10/18/10
Name/Initials_____ Name/Initials rlw/for

Comments:
Final-printed labeling (FPL) found acceptable for approval 3/24/10. Today, I confirmed with Adolph Vezza, labeling reviewer, that Par's FPL remains acceptable for approval./rlw

From: Golson, Lillie D
Sent: Monday, August 10, 2009 2:33 PM
To: Eng, Simon; Golson, Lillie D
Subject: FW: 78540/PAR/Propafenone HCl Extended-release Caps Labelings Endorsement

Hi Simon,

Please sign on behalf of Adolph and me.

Thanks

Lillie

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 8/17/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials SL
Comments:Revised version saved to the V drive. 9/22/2010 - Slight modification made to AP letter.

5. Div. Dir./Deputy Dir. Date 9/17/10
Chemistry Div. II Initials FF

Comments:A series of amendments submitted. cmc ok.

6. Frank Holcombe **First Generics Only** Date 10/18/10
Assoc. Dir. For Chemistry Initials rlw/for
Comments: (First generic drug review)
With her endorsement of this approval package, the CMC division director has confirmed that there are no precident setting issues associated with the review and approval of this ANDA. Thus, no further CMC review is necessary.

7. Vacant Date_____
Deputy Dir., DLPS Initials_____
RLD = Rhythmol SR Capsules, 225 mg, 325 mg and 425 mg
GlaxoSmithKline NDA 21-416

8. Peter Rickman Date 10/18/10
Director, DLPS Initials rlw/for
Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Bioequivalence studies (fasting and non-fasting) on the 425 mg capsule strength found acceptable. In-vitro dissolution testing for all three capsule strengths also found acceptable. Waivers granted to the 225 mg and 325 mg capsule strengths under 21 CFR 320.22(d)(2). Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 6/15/07.

Final-printed labeling (FPL) found acceptable for approval 3/24/10.

CMC found acceptable for approval (Chemistry Review #4) 10/1/10.

OR

8. Robert L. West Date 10/18/10
Deputy Director, OGD Initials RLWest
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 10/14/10 (Verified 10/18/10). No "OAI" Alerts noted.

Par submitted a paragraph IV certification to the '588 patent and was sued within the 45-day period. Subsequently, the litigation was dismissed. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

This first-generic ANDA is recommended for approval.

9. Gary Buehler Date 10/18/10
Director, OGD Initials rlw
Comments: for Keith Webber, Ph.D. Deputy Director, OPS
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, SELECT PM NAME Team 8 Date 10/18/2010

Review Support Branch Initials tn
_____Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
1300Time notified of approval by phone
1300Time approval letter faxed

FDA Notification:
10/18/2010Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
10/18/2010Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

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/s/

TINA T NHU
10/18/2010