PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]APO-PROPAFENONE

Propafenone Hydrochloride Tablets

Film-coated tablets, 150 mg and 300 mg, Oral

Apotex Standard

Antiarrhythmic Agent

ATC-Code: C01BC03

APOTEX INC.
150 Signet Drive
Toronto, Ontario
M9L 1T9

Date of Initial Authorization:
FEB 08, 2001

Date of Revision:
APR 03, 2023

Submission Control Number: 269487

RECENT MAJOR LABEL CHANGES

NA

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

APO-PROPAFENONE (propafenone hydrochloride) is indicated for:

- the treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia prevention.

APO-PROPAFENONE may also be used for the treatment of patients with documented symptomatic ventricular arrhythmias when the symptoms are of sufficient severity to require treatment. Because of the proarrhythmic effects of APO-PROPAFENONE, its use should be reserved for patients in whom, in the opinion of the physician, the benefit of treatment clearly outweighs the risks.

For patients with sustained ventricular tachycardia, APO-PROPAFENONE therapy should be initiated in the hospital. Initiation in hospital may also be required for certain other patients depending on their cardiac status and underlying cardiac disease.

The effects of propafenone hydrochloride in patients with recent myocardial infarction have not been adequately studied and, therefore, its use in this condition cannot be recommended.

There is no evidence from controlled clinical trials that the use of propafenone hydrochloride favourably affects survival or the incidence of sudden death.

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical trials and experience suggests that use in elderly patients is associated with differences in safety (see 7 WARNINGS AND PRECAUTIONS, Special population, 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

- APO-PROPAFENONE is contraindicated in the following conditions:
    - Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
    - Known Brugada Syndrome.
    - Incident of myocardial infarction within the last 3 months.

- Severe or uncontrolled congestive heart failure (see 7 WARNINGS AND PRECAUTIONS).
- Cardiogenic shock.
- Sinoatrial, atrioventricular and intraventricular disorders of impulse conduction and sinus node dysfunction (e.g. sick sinus syndrome) in the absence of an artificial pacemaker.
- Severe bradycardia (less than 50 beats/min).
- Severe hypotension.
- Bronchospastic disorders.
- Severe disorders of electrolyte balance.
- Severe hepatic failure (see 7 WARNINGS AND PRECAUTIONS).
- Severe obstructive pulmonary disease.
- Myasthenia gravis.
- Concomitant treatment with ritonavir (see 9.4 Drug-Drug Interactions).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- No antiarrhythmic drug has been shown to reduce the incidence of sudden death in patients with asymptomatic ventricular arrhythmias. Most antiarrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increased incidence of sudden death. In light of the above, physicians should carefully consider the risks and benefits of antiarrhythmic therapy for all patients with ventricular arrhythmias.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The dose of APO-PROPAFENONE must be individually determined on the basis of patient's response and tolerance. The usefulness of monitoring plasma levels for optimization of therapy has not been established. The recommended dose titration regimen can be used for both fast and slow metabolizers (see 10 CLINICAL PHARMACOLOGY).

4.2 Recommended Dose and Dosage Adjustment

- The initial dose of APO-PROPAFENONE is 150 mg given every 8 hours (450 mg/day). Dosage may be increased at three to four day intervals to 300 mg every 12 hours (600 mg/day). Should a further increase in dosage be necessary a maximum dose of 300 mg every 8 hours (900 mg/day) may be given.

- In those patients in whom widening of the QRS complex (>0.12 seconds) or prolongation of PR interval (>0.24 seconds) occurs, the dosage of APO-PROPAFENONE should be reduced.
- In patients with mild to moderate hepatic insufficiency APO-PROPAFENONE therapy should be initiated with 150 mg given once daily (150 mg/day) (see 7 WARNINGS AND PRECAUTIONS). The dosage may be increased at a minimum of 4 day intervals to 150 mg twice daily (300 mg/day) then to 150 mg every 8 hours (450 mg/day) and, if necessary, to 300 mg every 12 hours (600 mg/day).
- There is no information on dosing with propafenone hydrochloride in patients with renal impairment. APO-PROPAFENONE should be used cautiously in these patients and only after consideration of the benefit/risk ratio. These patients should be carefully monitored for signs of toxicity. Lower doses may be required (see 7 WARNINGS AND PRECAUTIONS).
- In elderly patients, impaired hepatic or renal function may cause the effective dose of APO-PROPAFENONE to be lower, therefore, these patients should be carefully monitored (see 7 WARNINGS AND PRECAUTIONS).
- There is no information on the appropriate regimen for the transfer from lidocaine to propafenone hydrochloride.
- Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Administration of APO-PROPAFENONE with food is recommended. Owing to the bitter taste and surface anesthetic action of propafenone, the film-coated tablets should be swallowed whole (without chewing) with liquid.

4.5 Missed Dose

If you forget to take one tablet, take another as soon as you remember, unless it is almost time for your next dose. If it is, do not take the missed tablet at all. Never double-up on a missed dose.

5 OVERDOSAGE

The symptoms of overdose may include bradycardia, conduction disturbances, which may include PR prolongation, QRS widening, suppression of sinus node automaticity, AV block, ventricular tachycardia, ventricular flutter, ventricular fibrillation and cardiac arrest. Reduction of contractility (negative inotropic effect) can cause hypotension which, in severe cases, can lead to cardiovascular shock.

Non-cardiac signs and symptoms: Metabolic acidosis, headache, dizziness, blurred vision, paraesthesia, tremor, nausea, constipation, dry mouth and convulsions have been reported on overdose. Death has also been reported.

In severe cases of poisoning, clonic-tonic convulsions, paraesthesia, somnolence, coma and respiratory arrest may occur.

If ingestion is recent, perform gastric lavage or induce emesis.

In addition to general emergency measures, the patient's vital parameters should be monitored in an intensive care setting, and rectified, as appropriate.

Defibrillation as well as infusion of dopamine and isoproterenol have been effective in controlling rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam.

Supportive measures such as mechanical respiratory assistance and cardiac massage may be necessary.

Defibrillation and the use of a temporary pacemaker, as well as infusion of isoproterenol and dopamine have been effective in controlling cardiac rhythm and blood pressure. Convulsions have been alleviated with intravenous diazepam.

Detoxification measures such as forced diuresis, hemoperfusion and hemodialysis have not proven useful.

Treatment

Owing to high protein binding (> 95%) and the large volume of distribution, hemodialysis is ineffective and attempts to achieve elimination via hemoperfusion are of limited efficacy.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Film-coated tablets 150 mg, 300 mg	Colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol and titanium dioxide.

APO-PROPAFENONE 150 mg: Each round, white, film-coated, biconvex, tablet engraved ‘APO’ over ‘P150’ on one side contains 150 mg propafenone hydrochloride. Available in bottles of 100 and 500.

APO-PROPAFENONE 300 mg: Each round, white, film-coated, biconvex, tablet scored and engraved ‘APO’ over ‘P300’ on one side contains 300 mg propafenone hydrochloride. Available in bottles of 100 and 500.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses. However, due to the bitter taste it is recommended to be swallowed whole.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Gender

No data are available to Health Canada to suggest that gender is associated with differences in pharmacokinetics, safety or effectiveness of propafenone hydrochloride, when administered as APO-PROPAFENONE.

Race

No data are available to Health Canada to suggest that race is associated with differences in pharmacokinetics, safety or effectiveness of propafenone hydrochloride, when administered as APO-PROPAFENONE.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Mortality

The results of the Cardiac Arrhythmia Suppression Trials (CAST) in post-myocardial infarction patients with asymptomatic ventricular arrhythmias showed a significant increase in mortality and in the non-fatal cardiac arrest rate in patients treated with flecainide or encainide compared with a matched placebo-treated group. CAST was continued using a revised protocol with the moricizine and placebo arms only. The trial was prematurely terminated because of a trend towards an increase in mortality in the moricizine treated group.

The applicability of these results to other populations or other antiarrhythmic agents is uncertain, but at present it is prudent to consider these results when using any antiarrhythmic agent in patients with structural heart disease.

Brugada Syndrome

A Brugada Syndrome may be unmasked or Brugada-like electrocardiogram (ECG) changes may be provoked after exposure to propafenone in previously asymptomatic carriers of the syndrome. After initiating therapy with propafenone, an ECG should be performed to rule out changes suggestive of Brugada Syndrome.

Proarrhythmic Effects

APO-PROPAFENONE (propafenone hydrochloride) like other antiarrhythmics, may cause proarrhythmic effects, i.e., it may cause new or worsen pre-existing arrhythmias (see 8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions). Such proarrhythmic effects range from an increase in frequency of premature ventricular contractions (PVCs) to the development of more severe ventricular tachycardia, ventricular fibrillation or torsade de pointes. Some of these arrhythmias can be life-threatening and may require resuscitation to prevent a potentially fatal outcome. It is therefore essential that each patient administered propafenone

hydrochloride be evaluated clinically and electrocardiographically prior to, and during therapy to determine whether the response to propafenone supports continued treatment.

Overall in clinical trials with propafenone hydrochloride, 4.7% of all patients had new or worsened ventricular arrhythmia possibly representing a proarrhythmic event [0.7% was an increase in PVCs, 4.0% a worsening, or new appearance, of ventricular tachycardia (VT) or ventricular fibrillation (VF)]. Of the patients who had worsening of VT (4%), 92% had a history of VT and/or VT/VF, 71% had coronary artery disease, and 68% had a prior myocardial infarction. The incidence of proarrhythmia in patients with less serious or benign arrhythmias which include patients with an increase in frequency of PVCs, was 1.6%. Although most proarrhythmic events occurred during the first week of therapy, late events also were seen and the CAST study suggests that a risk is present throughout treatment (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Mortality).

Congestive Heart Failure

During treatment with oral propafenone hydrochloride in patients with depressed baseline function (mean EF = 33.5%), no significant decreases in ejection fraction (EF) were seen. In clinical trial experience, new or worsened congestive heart failure (CHF) has been reported in 3.7% of patients; of those 0.9% were considered probably or definitely related to propafenone hydrochloride. Of the patients with CHF probably related to propafenone hydrochloride, 80% had preexisting heart failure and 85% had coronary artery disease. CHF attributable to propafenone hydrochloride developed rarely (< 0.2%) in patients who had no previous history of CHF. Propafenone hydrochloride exerts both beta blockade and a dose related direct negative inotropic effect on myocardium. Therefore, APO-PROPAFENONE should not be prescribed in patients with uncontrolled congestive heart failure where left ventricular output is less than 35%. Caution should be exercised when using APO-PROPAFENONE in patients with minimal cardiac reserve or in those who are receiving other drugs with negative inotropic potential.

Effects on Cardiac Conduction

Propafenone hydrochloride slows cardiac conduction which may result in a dose-related prolongation of PR interval and QRS complex, development of first or higher degree AV block, bundle branch block and intraventricular conduction delay (see 8.2 Clinical Trial Adverse Reactions). Therefore, development of signs of increasing depression of cardiac conductivity during APO-PROPAFENONE therapy requires a reduction in dosage or a discontinuation of APO-PROPAFENONE unless the ventricular rate is adequately controlled by a pacemaker.

Effects on Pacemaker Threshold

Patients with permanent pacemakers should have their existing thresholds re-evaluated after initiation of or change in APO-PROPAFENONE therapy because of a possible increase in endocardial stimulation threshold.

Driving and Operating Machinery

Blurred vision, dizziness, fatigue and postural hypotension may affect the patient's speed of reaction and impair the individual's ability to operate machinery and motor vehicles.

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Hematologic Disturbances

Agranulocytosis has been reported infrequently in patients taking propafenone hydrochloride. The onset is generally within four to six weeks and presenting symptoms have included fever, fatigue, and malaise. Agranulocytosis occurs in less than 0.1% of patients taking propafenone hydrochloride. Patients should be instructed to immediately report fever, fatigue, malaise or any signs of infection, especially in the first three months of therapy. Prompt discontinuation of APO-PROPAFENONE therapy is recommended when a decreased white blood cell count or other signs and symptoms warrant consideration of agranulocytosis/granulocytopenia. Cessation of propafenone hydrochloride therapy is usually followed by recovery of blood counts within two weeks.

Hepatic/Biliary/Pancreatic

Use in Patients with Impaired Hepatic Function

Since propafenone hydrochloride is highly metabolized by the liver it should be administered cautiously to patients with impaired hepatic function (see 2 CONTRAINDICATIONS). Administration of propafenone hydrochloride to these patients results in an increase in bioavailability to approximately 70% compared to 3 to 40% for patients with normal liver function, prolongation of the half-life, a decrease in the systemic clearance, and a reduction in the serum protein binding of the drug. As a result, the dose of APO-PROPAFENONE given to patients with impaired hepatic function should be reduced (see 4 DOSAGE AND ADMINISTRATION). It is important to monitor electrocardiographic intervals for signs of excessive pharmacological effects (see 5 OVERDOSAGE) and/or adverse reactions, until an individualized dosage regimen has been determined.

A number of patients with liver abnormalities associated with propafenone hydrochloride therapy have been reported in foreign post-marketing experience. Some appeared due to be hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome.

Increased hepatic enzymes (alkaline phosphatase, serum transaminases) (0.2%), hepatitis (0.03%) and cholestasis (0.1%) have also been observed. See 8 ADVERSE REACTIONS, 8.3 Less Common Clinical Trial Adverse Reactions).

Immune

Elevated ANA Titres

In long-term studies, positive antinuclear antibody (ANA) titres have been reported in 21% of patients receiving propafenone hydrochloride. However, it is impossible to determine what exact percentage of patients had a new positive ANA titre as a result of propafenone hydrochloride therapy. This laboratory finding has not been associated with clinical symptoms. One case of Lupus-like syndrome has been reported which resolved upon discontinuation of

therapy. Laboratory evaluation for antinuclear antibodies should be performed initially and at regular intervals. It is recommended that patients in whom an abnormal ANA test has occurred be evaluated regularly. If worsening elevation of ANA titres or clinical symptoms are detected, APO-PROPAFENONE should be discontinued.

Renal

There is limited experience with use of oral propafenone hydrochloride in patients with impaired renal function. In patients whose kidney function is impaired, there may be drug accumulation after standard therapeutic doses. In patients with renal impairment, exposure to propafenone and 5-hydroxypropafenone was similar to that in healthy controls, while accumulation of glucuronide metabolites was observed. Since a considerable percentage of propafenone metabolites are excreted in the urine (18.5 to 38% of the dose/48 hours), APO-PROPAFENONE should be used cautiously in patients with renal impairment and only after consideration of the benefit/risk ratio. These patients should be carefully monitored for signs of toxicity (see 5 OVERDOSAGE). The dose in these patients has not been determined.

Reproductive Health: Female and Male Potential

- **Fertility**

  Impaired Spermatogenesis

  Clinical evaluation of spermatogenesis was undertaken in 11 normal subjects, given oral propafenone hydrochloride 300 mg twice daily for four days which was then increased to 300 mg three times daily for an additional four days. Patients were followed for 128 days post-treatment and demonstrated a 28% reduction in semen sample volume following the last dose (Day 8) and a 27% reduction in sperm count, on Day 72. Follicle-stimulating hormone (FSH) and testosterone levels were also slightly decreased. Neither the decrease in sperm count nor the decrease in sample volume were sustained beyond the single visit in which they occurred, and both values remained within the laboratories normal reference range. Reduced spermatogenesis was also observed in animal experiments. The significance of these findings is uncertain.

Respiratory

Nonallergic Bronchospasm (e.g. chronic bronchitis, emphysema)

Patients with bronchospastic disease should, in general, not receive APO-PROPAFENONE or other agents with beta-adrenergic blocking activity (see 2 CONTRAINDICATIONS).

Propafenone hydrochloride should be used with caution in patients with obstruction of the airways eg. asthma.

7.1 Special Populations

7.1.1 Pregnant Women

Propafenone hydrochloride has been shown to be embryotoxic in the rat when given in doses of 600 mg/kg (about six times the maximum recommended human dose on a mg/m^2 basis) and in the rabbit when given in doses of 150 mg/kg (about three times the maximum recommended human dose on a mg/m^2 basis). In a perinatal and postnatal study in rats, propafenone hydrochloride produced dose-dependent increases in maternal and neonatal mortality, decreased maternal and pup body weight gain and reduced neonatal physiological development.

There are no adequate and well controlled studies in pregnant women. APO-PROPAFENONE should be used during pregnancy only when the potential benefit outweighs the risk to the fetus. Propafenone hydrochloride is known to pass the placental barrier in humans. The concentration of propafenone hydrochloride in the umbilical cord has been reported to be about 30% of that in the maternal blood.

Labour and Delivery

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

7.1.2 Breast-feeding

Propafenone and 5-hydroxypropafenone are excreted in human milk. Because of possible serious adverse reactions in nursing infants, an alternative method of infant feeding should be considered when the use of APO-PROPAFENONE is considered essential.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): A slight increase in the incidence of dizziness was observed in elderly patients. Because of the possible increased risk of impaired hepatic or renal function in this age group, APO-PROPAFENONE should be used with caution. The effective dose may be lower in these patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most frequent and very common adverse reactions related to propafenone therapy are dizziness, cardiac conduction disorders and palpitations.

Adverse reactions were dose related and occurred most frequently during the first month of therapy.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The adverse events listed in Table 1 were observed in greater than one percent of patients.

Table 1 - Adverse Events Observed in Greater than 1% of Patients Treated with Propafenone Hydrochloride Tablets

	Incidence by Total Daily Dose (%)			Overall Incidence at Any Dose (%) (N=2127)	% of Patients who Discontinued
	450 mg	600 mg	900 mg		
Cardiovascular System					
Dyspnea	2.2	2.3	3.6	5.3	1.6
Proarrhythmia	2.0	2.1	2.9	4.7	4.7
Angina	1.7	2.1	3.2	4.6	0.5
Congestive Heart Failure	0.8	2.2	2.6	3.7	1.4
Ventricular Tachycardia	1.4	1.6	2.9	3.4	1.2
Palpitations	0.6	1.6	2.6	3.4	0.5
First Degree AV Block	0.8	1.2	2.1	2.5	0.3
Syncope	0.8	1.3	1.4	2.2	0.7
QRS Duration, Increased	0.5	0.9	1.7	1.9	0.5
Bradycardia	0.5	0.8	1.1	1.5	0.5

PVC's	0.6	0.6	1.1	1.5	0.1
Edema	0.6	0.4	1.0	1.4	0.2
Bundle Branch Block	0.3	0.7	1.0	1.2	0.5
Atrial Fibrillation	0.7	0.7	0.5	1.2	0.4
Intraventricular Conduction Delay	0.2	0.7	0.9	1.1	0.1
Hypotension	0.1	0.5	1.0	1.1	0.4
Central Nervous System					
Dizziness	3.6	6.6	11.0	12.5	2.4
Headaches	1.5	2.5	2.8	4.5	1.0
Blurred Vision	0.6	2.4	3.1	3.8	0.8
Ataxia	0.3	0.6	1.5	1.6	0.2
Insomnia	0.3	1.3	0.7	1.5	0.3
Tremor(s)	0.3	0.8	1.1	1.4	0.3
Drowsiness	0.6	0.5	0.7	1.2	0.2
Gastrointestinal System					
Nausea and/or Vomiting	2.4	6.1	8.9	10.7	3.4
Unusual Taste	2.5	4.9	6.3	8.8	0.7
Constipation	2.0	4.1	5.3	7.2	0.5
Dyspepsia	1.3	1.7	2.5	3.4	0.9
Diarrhea	0.5	1.6	1.7	2.5	0.6
Dry Mouth	0.9	1.0	1.4	2.4	0.2
Anorexia	0.5	0.7	1.6	1.7	0.4
Abdominal Pain/Cramping	0.8	0.9	1.1	1.7	0.4
Flatulence	0.3	0.7	0.9	1.2	0.1
Other					
Fatigue	1.8	2.8	4.1	6.0	1.0
Rash	0.6	1.4	1.9	2.6	0.8
Weakness	0.6	1.6	1.7	2.4	0.7
Atypical Chest Pain	0.5	0.7	1.4	1.8	0.2

Anxiety	0.7	0.5	0.9	1.5	0.6
Diaphoresis	0.6	0.4	1.1	1.4	0.3
Pain, Joints	0.2	0.4	0.9	1.0	0.1

In 2127 patients treated with propafenone hydrochloride in North American controlled and open clinical trials, the most common adverse reactions reported were dizziness (12.5%), nausea and/or vomiting (10.7%), unusual taste (8.8%) and constipation (7.2%). The adverse effects judged to be most severe were aggravation or induction of arrhythmia (4.7%), congestive heart failure (3.7%) and ventricular tachycardia (3.4%). The incidences for these three adverse reactions in patients with a previous history of myocardial infarction (MI) were 6.9, 5.3 and 5.5%, respectively, while in patients without a history of MI the incidences were 3.0, 2.4 and 1.8%, respectively. Approximately 20% of patients had propafenone hydrochloride discontinued due to adverse reactions.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions were reported less frequently than 1% in clinical trials. Causality and relationship to propafenone hydrochloride therapy cannot necessarily be judged from these events.

Cardiovascular: Atrial flutter, AV dissociation, cardiac arrest, flushing, hot flashes, sick sinus syndrome, sinus pause or arrest, supraventricular tachycardia, Torsades de Pointes, ventricular fibrillation.

Gastrointestinal: Gastroenteritis, abdominal distension.

Hepatic: A number of patients with liver abnormalities associated with propafenone hydrochloride therapy have been reported in foreign post-marketing experience. Some appeared due to hepatocellular injury, some were cholestatic and some showed a mixed picture. Some of these reports were simply discovered through clinical chemistries, others because of clinical symptoms. One case was rechallenged with a positive outcome.

Cholestasis (0.1%), elevated liver enzymes (alkaline phosphatase, serum transaminases) (0.2%), hepatitis (0.03%).

Immune System: Allergic reactions.

Nervous System: Abnormal dreams/nightmares, abnormal speech, abnormal vision, confusion, depression, memory loss, numbness, paresthesias, psychosis/mania, seizures (0.3%), tinnitus, unusual smell sensation, vertigo.

Other: Eye irritation, impotence, increased glucose, positive ANA (0.7%), muscle cramps, muscle weakness, nephrotic syndrome, pain.

Skin and subcutaneous tissue: Alopecia, erythema and pruritus.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Hematologic: Agranulocytosis (see 7 WARNINGS AND PRECAUTIONS), anemia, bruising, granulocytopenia, leukopenia, purpura, thrombocytopenia.

8.5 Post-Market Adverse Reactions

Cardiovascular:	Ventricular fibrillation, cardiac conduction disorders (eg. sinoatrial block, intraventricular block), postural or orthostatic hypotension, cardiac failure (an aggravation of preexisting cardiac insufficiency may occur), heart rate reduced.
Gastrointestinal:	Jaundice, bitter taste, abdominal pain, retching.
Hematologic:	Increased bleeding time.
Nervous System:	Apnea, coma, convulsion, extrapyramidal symptoms, restlessness.
Other:	Hyponatremia/inappropriate ADH secretion, lupus erythematosis, chest pain, kidney failure, sperm count decreased, pyrexia.
Skin and subcutaneous tissue disorders:	Acute generalized exanthematous pustulosis, urticaria.

There have been post-marketing reports of patients experiencing conversion of paroxysmal atrial fibrillation to atrial flutter with accompanying 2:1 conduction block or 1:1 conduction. However, the clinical significance has not been established.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drugs that inhibit CYP2D6 (e.g. quinidine), CYP1A2 (e.g. cimetidine) and CYP3A4 (e.g. ketoconazole, cimetidine, erythromycin and grapefruit juice) might lead to increased plasma levels of propafenone. When propafenone hydrochloride is administered with inhibitors of these enzymes, the patients should be closely monitored and the dose adjusted accordingly.

Coadministration of APO-PROPAFENONE with drugs metabolized by CYP2D6 (e.g. venlafaxine) might lead to increased levels of these drugs and/or of propafenone.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Digitalis	CT, T	Propafenone hydrochloride has been shown to produce dose-related increases in serum digoxin levels ranging from approximately 35% at 450 mg/day to 85% at 900 mg/day of propafenone hydrochloride without affecting digoxin renal clearance. Elevations of digoxin levels were maintained for up to 16 months during concomitant administration.	Plasma digoxin levels of patients on concomitant therapy should be measured, and digoxin dosage should ordinarily be reduced when propafenone hydrochloride is started, especially if a relatively large digoxin dose is used or if plasma concentrations are relatively high.
Beta-agonists	CT, T	In a study involving healthy subjects, concomitant administration of propafenone hydrochloride and propranolol resulted in substantial increases in propranolol plasma concentration and elimination t½ with no change in propafenone plasma levels from control values. Similar observations have been reported with metoprolol. Propafenone appears to inhibit the hydroxylation pathway for the two beta-antagonists (just as quinidine inhibits propafenone metabolism). Increased plasma concentrations of	While the therapeutic range for beta-blockers is wide, a reduction in dosage may be necessary during concomitant administration with propafenone hydrochloride.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		metoprolol could overcome its relative cardioselectivity. In propafenone hydrochloride clinical trials, patients who were receiving beta-blockers concurrently did not experience an increased incidence of side effects.	
Anticoagulants	CT	In a study of eight healthy subjects receiving propafenone hydrochloride and concomitant warfarin, mean steady-state warfarin plasma concentrations increased 39% with a corresponding prolongation in prothrombin times of approximately 25%.	It is therefore recommended that in patients treated with propafenone hydrochloride and anticoagulants (e.g. warfarin, acenocoumarol) concomitantly, prothrombin time should be carefully monitored and the dose of anticoagulant adjusted as necessary.
Cimetidine	CT	Concomitant administration of propafenone hydrochloride tablets and cimetidine resulted in a 20% increase in steady-state plasma concentrations of propafenone with no detectable changes in electrocardiographic parameters beyond that measured on propafenone hydrochloride alone.	Therefore, patients should be carefully monitored and the dose of propafenone hydrochloride adjusted when appropriate.
Lidocaine	T	No clinically significant effects on the pharmacokinetics of propafenone or lidocaine have been seen following	Therefore, the combination of propafenone hydrochloride and lidocaine should be used with caution.

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		their concomitant use in healthy volunteers. However, the concomitant use of propafenone hydrochloride and intravenous lidocaine has been reported to increase the frequency and severity of central nervous system side effects of lidocaine.	
Desipramine	C, T	Concomitant administration of propafenone hydrochloride and desipramine may result in elevated serum desipramine levels.	Both desipramine, a tricyclic antidepressant, and propafenone are cleared by oxidative pathways of demethylation and hydroxylation carried out by the hepatic P-450 cytochrome.
Cyclosporin	C, T	Propafenone hydrochloride therapy may increase levels of cyclosporin.	
Theophylline	C, T	Propafenone hydrochloride may increase theophylline concentration during concomitant therapy with the development of theophylline toxicity.	
Rifampin	T	Rifampin may accelerate the metabolism and decrease the plasma levels and antiarrhythmic efficacy of propafenone.	
Ritonavir, Lopinavir/ritonavir	T	Concomitant administration of propafenone hydrochloride and ritonavir, ritonavir/lopinavir may	Concomitant use of propafenone hydrochloride and ritonavir alone or in combination with lopinavir is contraindicated. (see 2 CONTRAINDICATION)

Proper/ Common name	Source of Evidence	Effect	Clinical comment
		result in elevated serum propafenone levels.	
Amiodarone	T	Combination therapy of amiodarone and propafenone hydrochloride can affect conduction and repolarization and lead to abnormalities that have the potential to be proarrhythmic.	Dose adjustments of both compounds based on therapeutic response may be required.
Phenobarbital	T	Phenobarbital is a known inducer of CYP3A4.	Response to propafenone hydrochloride therapy should be monitored during concomitant chronic phenobarbital use.
Fluoxetine, Paroxetine and Fluvoxamine	C, T	Elevated levels of plasma propafenone may occur when propafenone hydrochloride is used concomitantly with SSRI's, such as fluoxetine and paroxetine. Concomitant administration of propafenone hydrochloride 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%.	Lower doses of propafenone may be sufficient to achieve the desired therapeutic response. In poor metabolizers, concomitant administration of propafenone hydrochloride and fluvoxamine may require a dose reduction of propafenone.
Legend: C = Case Study; CT = Clinical Trial; T = Theoretical			

9.5 Drug-Food Interactions

Co-administration of APO-PROPAFENONE with grapefruit juice might lead to increased plasma levels of propafenone.

9.6 Drug-Herb Interactions

Caution should be exercised when administering APO-PROPAFENONE with cytochrome P450 modulating herbal products such as St. John's wort.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Propafenone hydrochloride is an antiarrhythmic agent which possesses class 1C properties in the modified electrophysiological classification of Vaughan-Williams. Propafenone hydrochloride has a direct stabilizing action on myocardial cell membranes. The electrophysiological effect of propafenone hydrochloride manifests itself as a reduction of the upstroke velocity (Phase 0) of the monophasic action potential, while Phase 4 spontaneous automaticity is depressed. Diastolic excitability threshold is increased and effective refractory period prolonged. In Purkinje fibers, and to a lesser extent myocardial fibers, propafenone hydrochloride reduces the fast inward sodium current.

In addition to a local anesthetic effect, approximately equal to procaine, propafenone hydrochloride has weak beta-blocking activity. Clinical trials employing isoproterenol challenge and exercise testing suggest that the affinity of propafenone hydrochloride for beta-adrenergic receptors, as calculated from dose ratios and drug concentrations, is about 1/40 that of propranolol. Propafenone hydrochloride also inhibits the slow calcium influx at high concentrations, however, this action is weak (approximately 1/100 of verapamil) and does not contribute to its antiarrhythmic effect.

10.2 Pharmacodynamics

Electrophysiology

Electrophysiology studies have shown that propafenone hydrochloride prolongs atrioventricular conduction and in some instances significantly lengthens sinus nodal recovery times with a non-significant effect on sinus cycle length. Both atrioventricular (AV) nodal conduction time (AH interval) and His-Purkinje conduction time (HV interval) are prolonged. Propafenone hydrochloride increases atrial, AV nodal and ventricular effective refractory periods. Propafenone hydrochloride causes a dose-dependent increase in the PR interval and QRS complex duration. Non-significant increases in the QTc interval and occasional slowing of the heart rate have also been observed.

Hemodynamics

Propafenone hydrochloride can exert a negative inotropic effect on the myocardium. Increases in pulmonary capillary wedge pressure and systemic and pulmonary vascular resistance, with a concurrent mild depression of cardiac output and cardiac index, have occurred following

propafenone hydrochloride administration. Decreases in left ventricular function have been recorded in patients with depressed baseline function.

10.3 Pharmacokinetics

Table 3 - Summary of Propafenone Hydrochloride Pharmacokinetic Parameters in patients with premature heart beat (single-dose)

Group	N	Dose	C_{max} (± SD)	AUC∞ ng.hr/ml (± SD)	T_{max} (h) (± SD)	T½ (h) (± SD)	CL	V_d
1	7	150 mg	170 (94)	989 (704)	2.1 (1.2)	3.81 (2.01)	0.67 to 0.81 L/h/ kg	1.9 to 3.0 L/kg
2	11	300 mg	410 (178)	3162 (81511)	3.1 (1.5)	3.75 (1.92)		

Absorption:

Due to a genetically determined presence or deficiency of one metabolizing pathway (CYP2D6), patients may be categorized into fast (over 90% of all patients) or slow metabolizers of propafenone hydrochloride, resulting in low or high plasma concentrations respectively. Following oral administration in fast metabolizers, propafenone hydrochloride is nearly completely absorbed and undergoes extensive first-pass hepatic metabolism resulting in a dose-dependent absolute bioavailability ranging from 3 to 40%. Peak plasma concentrations occur within two to three hours. In fast metabolizers, the saturable hydroxylation pathway (CYP2D6) results a non-linear pharmacokinetics (increase in drug plasma concentration and bioavailability with increase in dosage), presumably due to saturation of first pass hepatic metabolism. This departure from dose linearity occurs when single doses above 150 mg are given. A 300 mg dose gives plasma levels six times that of a 150 mg dose. Similarly, for a 3-fold increase in daily dose from 300 to 900 mg/day there is a 10-fold increase in steady-state plasma concentration. In slow metabolizers, as opposed to fast metabolizers, a linear relationship between propafenone hydrochloride dose and plasma concentration was observed.

Slow metabolizers had higher propafenone plasma concentrations which they required for suppression of arrhythmia since they did not produce the active metabolite 5-hydroxypropafenone (5-OHP). These higher propafenone plasma concentrations may lead to clinically evident beta-blockade.

Despite these differences in pharmacokinetics, steady-state conditions are achieved after three to four days of dosing in all patients (fast and slow metabolizers).

Therapeutic plasma levels of propafenone appear to be in the range of 0.5 to 2.0 mcg/mL.

Distribution:

Propafenone distributes rapidly. The steady-state volume of distribution is 1.9 to 3.0 L/kg. The degree of plasma protein binding of propafenone is concentration dependent and decreased from 97.3% at 0.25 mcg/mL to 81.3% at 100 mcg/mL.

Metabolism:

In fast metabolizers, propafenone undergoes extensive hepatic metabolism with less than 1% excreted as unchanged drug. The major active metabolites are 5-hydroxypropafenone (5-OHP) which is formed by CYP2D6 and N-depropylpropafenone (NDPP) which is formed by CYP3A4 and CYP1A2; both metabolites occurring in concentrations less than 20% of the parent compound. *In vitro* preparations and animal studies have shown that the 5-OHP metabolite possesses antiarrhythmic and beta-adrenoreceptor blocking activity comparable to propafenone.

Propafenone is 97% bound to plasma proteins.

Elimination:

For fast metabolizers of propafenone hydrochloride, the elimination $t_{1/2}$ ranges from 2 to 10 hours; for slow metabolizers, the elimination $t_{1/2}$ ranges from 10 to 32 hours. Clearance of propafenone is 0.67 to 0.81 L/h/kg.

Influence of Food: Bioavailability is enhanced by administration of the drug with food.

Special Populations and Conditions

- **Pediatrics:** Propafenone hydrochloride pharmacokinetics have not been evaluated in patients less than 18 years of age.
- **Geriatrics:** Propafenone hydrochloride pharmacokinetics have not been evaluated in elderly patients greater than 65 years of age. However, a slight increase in the incidence of dizziness was observed in elderly patients. Because of the possible increased risk of impaired hepatic or renal function in this age group, propafenone hydrochloride should be used with caution. The effective dose may be lower in these patients.

11 STORAGE, STABILITY AND DISPOSAL

Store APO-PROPAFENONE (propafenone hydrochloride) at room temperature 15°C to 30°C (59°F to 86°F). Do not use beyond the expiry date indicated on the label.

12 SPECIAL HANDLING INSTRUCTIONS

There are no further special handling instructions for this product (see 11 STORAGE, STABILITY AND DISPOSAL).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

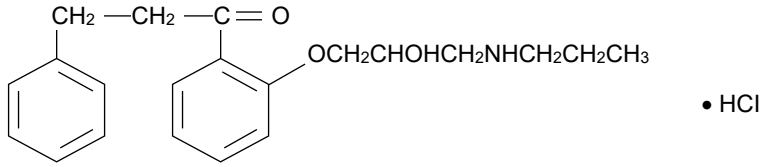
Drug Substance

Proper name: propafenone hydrochloride

Chemical name: 2'-(2-hydroxy-3-propylamino-propoxy)-3-phenylpropriophenone hydrochloride

Molecular formula and molecular mass: $C_{21}H_{27}NO_3 \cdot HCl$, 377.92 g/mol

Structural formula:



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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 4 - Summary of patient demographics for clinical trials in patients with severe ventricular arrhythmias

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)
I	Double-blind, crossover, placebo controlled evaluation in patients with severe ventricular arrhythmias	150 mg b.i.d. 150 mg t.i.d. 300 mg b.i.d. 300 mg t.i.d. Oral dose. 4 weeks.	64 treated
II	Double-blind, randomized, placebo-controlled, crossover, In-hospital evaluation in patients with severe ventricular arrhythmias.	150 mg b.i.d. 150 mg t.i.d. 300 mg b.i.d. 300 mg t.i.d. Oral dose. 6 days	37 treated
Definitions: b.i.d. = twice daily; t.i.d. = three times daily			

Study I was designed to evaluate the safety and efficacy of chronic propafenone hydrochloride administration in patients with severe ventricular arrhythmias. The study consisted of a one-week placebo run-in phase to establish eligibility followed by a four-week dose-ranging phase (300, 450, 600 and 900 mg/day) to establish each patient's optimal therapeutic dose of propafenone hydrochloride. A double-blind, randomized, crossover phase consisting of two two-week periods comparing propafenone hydrochloride to placebo followed. Each two-week period was proceeded by a one-week placebo washout period. Holter recordings were made at weekly intervals throughout the study and analyzed to determine efficacy. Results of this study are summarized in Table 5.

14.2 Study Results

Table 5 - Efficacy Results of Study I in Patients with severe ventricular arrhythmias

Efficacy Parameters	Treatment	Combined Double-Blind Period							
		N	Pre-treatment		Post-treatment				
			Mean ± S.D.	p-value[a]	Mean ± S.D.	Mean (Median) Change	p-value[b]	p-value[a]	p-value[c]
Average # of VPB's per hour	Propafenone	43	469.3 ± 510.8	N.S.	74.5 ± 177.2	-394.7 (-217.3)	<0.01	<0.01	<0.01
	Placebo	42	428.6 ± 402.0		503.5 ± 460.0	74.9 (52.8)	N.S.		
Average # of single VPB's per hour	Propafenone	43	425.5 ± 451.0	N.S.	71.6 ± 173.4	-354.0 (-210.6)	<0.01	<0.01	<0.01
	Placebo	42	398.8± 377.7		451.8 ± 395.3	53.0 (44.6)	N.S.		
Average # of paired VPB's per hour	Propafenone	43	40.6 ± 85.2	N.S.	1.6 ± 4.7	-39.0 (-3.8)	<0.01	<0.01	<0.01
	Placebo	42	26.8 ± 54.7		45.9 ± 106.6	19.1 (0.0)	N.S.		
Average # of VT beats per 24 hours	Propafenone	43	75.3 ± 221.7	N.S.	33.7 ± 216.3	-41.7 (-9.7)	<0.01	<0.01	<0.01
	Placebo	42	71.6 ± 204.7		139.5 ± 371.2	67.9 (0.0)	N.S.		
Average # of VT events per 24 hours	Propafenone	43	22.3 ± 64.7	N.S.	1.1 ± 5.6	-21.2 (-2.9)	<0.01	<0.01	<0.01
	Placebo	42	22.5 ± 64.3		40.7 ± 115.4	18.2 (0.0)	N.S.		

VPB's = Ventricular Premature Beats
Paired VPB's = The number of VPB's occurring in pairs or couplets (not the number of pairs).
VT beats or Ventricular Tachycardia beats = Ventricular Premature Beats occurring in events of 3 or more.
VT events = 3 or more VPB's.
N.S. = Not statistically significant at the 0.05 significance level.

[a] Between treatment p-value for current period values.
[b] Within treatment p-value for change from baseline.
[c] Between treatment p-value for change from baseline.

Propafenone hydrochloride was clinically and statistically ($p < 0.01$) superior to placebo in reducing the number of ventricular premature beats (total ventricular premature beats [VPB's], single VPB's, paired VPB's), ventricular tachycardia beats, and ventricular tachycardia events. In

addition to the above combined period analysis, the first period was analyzed alone (results not shown) and propafenone hydrochloride was significantly superior to placebo for all efficacy parameters.

Study II was also designed to evaluate the safety and efficacy of chronic propafenone hydrochloride administration in patients with severe ventricular arrhythmias. The study began with a two-day placebo run-in phase during which patients must have 60 VPB's/hour or sustained VT or “R on T” etc. Patients fulfilling the entrance criteria were entered into an eight-day dose-ranging phase. A double-blind, randomized, crossover phase consisting of two three-day periods comparing propafenone hydrochloride to placebo followed. Each three-day period was preceded by a two- to three-day placebo washout period. Nine, 24-hour Holter recordings were obtained throughout the study for each completed patient.

Propafenone hydrochloride was shown clinically and statistically ($p < 0.0l$) superior to placebo in reducing all ventricular ectopy parameters as shown in the following Table 6.

Table 6 - Efficacy Results of Study II in Patients with severe ventricular arrhythmias

Efficacy Parameters	**Treatment**	**Combined Double-Blind Period**							
		N	**Pre-treatment**		**Post-treatment**				
			Mean ± S.D.	p-value[a]	Mean ± S.D.	Mean (Median) Change	p-value[b]	p-value[a]	p-value[c]
Average # of VPB’s per hour	Propafenone	19	633.2 ± 635.6	0.02[d,e]	66.9 ± 81.9	-566.3 (-452.1)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	542.7 ± 581.1		682.0 ± 789.7	139.3 (-2.4)	N.S.[d]		
Average # of single VPB’s per hour	Propafenone	19	499.5 ± 433.8	<0.01[d,e]	62.5 ± 77.2	-437.0 (-438.9)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	399.2 ± 428.4		483.9 ± 475.5	84.7 (-10.4)	N.S.[d]		
Average # of paired VPB’s per hour	Propafenone	19	77.9 ± 152.0	N.S.[d]	4.1 ± 13.5	-73.8 (-8.0)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	93.3 ± 184.8		121.4 ± 250.9	28.1 (0.0)	N.S.[d]		
Average # of VT beats per 24 hours	Propafenone	19	1340.3 ± 3851.4	N.S.[d]	7.0 ± 21.2	-1333.3 (-32.5)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	1204.7 ± 2550.2		1839.3 ± 5257.5	634.7 (0.0)	N.S.[d]		

Efficacy Parameters	Treatment	Combined Double-Blind Period							
		N	Pre-treatment		Post-treatment				
			Mean ± S.D.	p-value[a]	Mean ± S.D.	Mean (Median) Change	p-value[b]	p-value[a]	p-value[c]
Average # of VT events per 24 hours	Propafenone	19	317.0 ± 780.9	N.S.[d]	2.3 ± 7.0	-314.7 (-10.5)	<0.01[d]	<0.01[d]	<0.01[d]
	Placebo	19	343.7 ± 708.0		476.3 ± 1301.1	132.6 (0.0)	N.S.[d]		

VPB's = Ventricular Premature Beats
Paired VPB's = The number of VPB's occurring in pairs or couplets (not the number of pairs).
VT beats or Ventricular Tachycardia beats = Ventricular Premature Beats occurring in events of 3 or more.
VT events = 3 or more VPB's.
N.S. = Not statistically significant at the 0.05 significance level.

[a] Between treatment p-value for current period values.
[b] Within treatment p-value for change from baseline.
[c] Between treatment p-value for change from baseline.
[d] This test was performed on transformed data.
[e] Indicates a difference in the behaviour of the two treatment sequences, possibly due to the inconsistent results during the placebo periods.

14.3 Comparative Bioavailability Studies

A randomized, double-blinded, three period, three sequence, single dose, partial replicate, crossover comparative oral bioavailability study comparing APO-PROPAFENONE 300 mg tablets (Apotex Inc.) to RYTHMOL® 300 mg tablets (Abbott Laboratories, Limited) was conducted in healthy, adult, Asian subjects under fasting conditions. Comparative bioavailability data from 51 volunteers (28 males and 23 females) that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Propafenone (1 x 300 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T[3] (ng·h/mL)	2257.6 3700.6 (137.6)	2399.7 3697.6 (115.7)	94.1	87.4 – 101.3
AUC_I[4] (ng·h/mL)	2206.8 3733.8 (142.1)	2411.5 3771.4 (116.3)	91.5	85.3 - 98.1

Propafenone (1 x 300 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
C_{max}[3] (ng/mL)	463.9 601.9 (62.6)	497.0 622.7 (58.9)	93.3	85.1- 102.4
T_{max}[3,5] (h)	2.6 (38.3)	2.2 (40.1)		
$T_{1/2}$[4,5] (h)	5.4 (39.9)	5.6 (34.9)		

[1] APO-PROPAFENONE (propafenone hydrochloride) film-coated tablets, 300 mg (Apotex Inc.)
[2] RYTHMOL® (propafenone hydrochloride) film-coated tablets, 300 mg (Abbott Laboratories, Limited)
[3] Test N=51, Reference N=101
[4] Test N=49, Reference N=99
[5] Expressed as the arithmetic mean (CV%) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Electrophysiology

The antiarrhythmic effect of propafenone hydrochloride has been demonstrated in a number of different animal models. Electrically-induced ventricular fibrillation was controlled by propafenone hydrochloride (2 mg/kg intravenous) in the guinea pig and rabbit. Chloroform- and adrenaline-induced arrhythmias were reduced or abolished by propafenone hydrochloride in the cat (1 mg/kg intravenous, 2 to 10 mg/kg intravenous) and dog (1 mg/kg intravenous, 10 mg/kg oral) as were arrhythmias induced by calcium chloride, glycoside and coronary ligature in the dog (1 to 4 mg/kg intravenous). Aconitine-induced arrhythmias were also controlled by propafenone hydrochloride in the rabbit (3 mg/kg intravenous).

Propafenone can be classified as an antiarrhythmic drug with a membrane stabilizing effect.

Hemodynamics

In the dog, the force of ventricular contraction and blood pressure were not affected by doses of 3 mg/kg intravenous. However, after higher doses of 12 mg/kg intravenous or in hearts predamaged by coronary ligature, or when administering beta-blockers concomitantly, a fall in blood pressure, a reduction in the heart rate and contractility, and an increase in ECG-intervals (PR and QRS) have been seen.

Other

Structural similarities between propafenone and propranolol prompted several animal investigations into the possible beta-blocking effects of propafenone. A $beta_1$-sympatholytic action on isolated heart preparations (guinea pigs) and a $beta_2$-sympatholytic action on the coronary arteries and tracheal muscles (bovine) have been demonstrated *in vitro*. *In vivo* studies in rats showed that the antiarrhythmic effect occurred with intravenous doses seven times lower than necessary for the beta-blocking effect (ED_{50} at 0.437 mg/kg and 3.25 mg/kg respectively). However, the *in vitro* beta-blocking effect of propafenone occurred in the same dose range as the antiarrhythmic effect.

In *in vitro* studies of bovine coronary arteries, propafenone (56.0 mg/L) yielded a relaxing effect weaker than that of etafenone, papaverine, hexobendine, fendiline and oxifedrine but stronger than that of theophylline, aminophylline and carbocromen. In bovine tracheal muscle, and guinea pig colon, the potency of propafenone was the same as that of papaverine. *In vivo*, canine duodenum tone decreased slightly after intravenous propafenone, 0.5 to 4.0 mg/kg, with a marked decrease of the amplitude of peristalsis following propafenone, 1.0 to 4.0 mg/kg.

The local anesthetic activity of propafenone was demonstrated in the cornea of conscious guinea pigs with a 0.5% solution of propafenone.

Acute Toxicity

Table 7 - LD_{50} Values Observed in the Acute Toxicity Studies

Species	Route	Sex	LD_{50}	(95% Confidence Interval)
Mouse	oral	male	650	(445-888) mg/kg
		female	605	(434-840) mg/kg
	i.v.	male	29.3	(26.6-32.7) mg/kg
		female	31.1	(28.3-35.7) mg/kg
Rat (Adult)	oral	male	1,316	(978-1,729) mg/kg
		female	1,250	(263-5,934) mg/kg*
	i.v.	male	18.6	(16.8-22.0) mg/kg
		female	16.8	(14.4-19.4) mg/kg
Rat (Juvenile)	oral	male	3,556	(2,731-4,885) mg/kg
		female	2,902	(2,090-4,484) mg/kg
	i.v.	male	23.0	(16.0-32.0) mg/kg
		female	23.1	(16.1-31.8) mg/kg
*90% confidence interval				

In an acute oral dose tolerance study in dogs with two animals per dose level, no dogs died at 350 mg/kg, one dog died at 500 mg/kg and both dogs died at 650 mg/kg. In a similar study in cats, no animals died at 60 mg/kg and both cats died at the 100 mg/kg dose level.

Primary symptoms of toxicity were ataxia, attenuated reflexes and tonic-clonic convulsions.

Subacute and Chronic Toxicity

The studies are summarized in Table 8. For all studies, animals in each group were equally divided by sex.

Table 8 - Summary of Subacute and Chronic Toxicity Studies

Species	Route of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. of Animals Per Dose Group	No. of Deaths Per Dose Group	Toxic Effects
Rabbit	i.v.	3 weeks	0 0.3 0.5 1.0	4 4 4 4	0 0 0 0	Dose related reduction in body weight increases and elevated SPGT values were observed in the high dose group. High dose group had significantly increased heart weights, with focal muscle cell degeneration. Reduced spermatogenesis was found on histological examination in all groups.
Rat (Wistar)	i.v.	4 weeks	0 0.35 1.75 3.5	30 30 30 30	0 0 0 0	Changes were observed in the 3.5 mg/kg group. Sedation, tremor and reduced alertness were noted as well as reduction in body weight gain and food and water consumption. Clinical laboratory tests revealed decreases in erythrocyte count and serum urea, sodium and phosphorus values. Increases in serum chloride were also noted.
Rat (Wistar)	oral (gavage)	4 weeks	0 30 150 300	20 20 20 20	0 0 0 0	A decrease in serum sodium values was observed in rats receiving 300 mg/kg.

Table 8 - Summary of Subacute and Chronic Toxicity Studies

Species	Route of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. of Animals Per Dose Group	No. of Deaths Per Dose Group	Toxic Effects
Rat (Wistar)	oral (gastric tube)	6 months	0 90 270 (180) 600 (360)	30 30 30 30	0 0 3 11	Due to high mortality, the intermediate and high doses were reduced after eight weeks. Death was preceded by weight loss or reduced weight gain. Intermediate doses produced sedation and reduced reflexes. Sedation, apathy, ataxia, impaired coordination, shaggy skin, loose stool and intermittent tonic-clonic convulsions occurred in the high dose group. Histopathology revealed a dose related increase in fatty liver cells and kidney protein cylinders in the tubuli. Nephritis was observed in the high dose group. Focal to complete degeneration of the tubular epithelial cells in the testes was observed equally in all dose groups.
Rat (Sprague-Dawley)	oral (gavage)	26 weeks	0 90 180 500 (360)	52 52 52 52	0 0 14 27	Due to high mortality, the high dose was decreased after 6 weeks. Primarily in the high dose group, observations included unkempt coat, sedation, ataxia and apathy. Inhibition of body weight gain occurred in all groups. Inflammatory renal lesions (nephritis and nephrohydrosis) caused by precipitations of propafenone in the upper tubules was noted in several high dose and one intermediate dose animal.

Table 8 - Summary of Subacute and Chronic Toxicity Studies

Species	Route of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. of Animals Per Dose Group	No. of Deaths Per Dose Group	Toxic Effects
Dog (Beagle)	i.v.	4 weeks	0 0.3 1.0 5.0	6 6 6 6	0 0 0 0	The 5 mg/kg animals showed a reduction in body weight and food consumption, and increased restlessness, timidity, anxiety and shaggy coats. Tremor, reduced responses and spontaneous defecation were observed immediately post injection. ECG tracings taken at the end of the study revealed significant heart rate reduction. Laboratory evaluations revealed significantly lowered LDH, BUN, Na, Cl, and inorganic phosphorus. Complete cessation of spermatogenesis was observed on histopathology.
Dog (Beagle)	i.v.	4 weeks	0 1.0 2.2 5.0	6 6 6 6	0 0 0 0	The 5 mg/kg group showed a decrease in serum potassium.
Dog (Mongrel)	oral	4 weeks	0 20 50 100	2 2 2 2	0 0 0 0	Reduction in body weight and increased heart and liver weights were observed in the high dose group.

Table 8 - Summary of Subacute and Chronic Toxicity Studies

Species	Route of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. of Animals Per Dose Group	No. of Deaths Per Dose Group	Toxic Effects
Dog (Beagle)	oral	6 months	0 30 120 240 (180) (210) (240)	6 6 6 6	0 0 0 1	The following effects were observed in the 120 mg/kg group: sedation, intermittent tremor, reduced body weight gain and food consumption. Prothrombin time was also shortened. Due to one death and the marked deterioration of remaining animals in the 240 mg/kg group, the dose was reduced to 180 mg/kg at 9 weeks and gradually increased to 240 mg/kg at the thirtieth week. At this dose, animals exhibited apathy, sedation, ataxia, convulsions, vomiting, salivation, diarrhea, reduced body weight gain and food intake, reduced prothrombin time, decreased LDH values and increased uric acid.
Dog (Beagle)	oral	52 weeks	0 30 60 120	10 10 10 10	0 0 1 3	Vomiting was observed in the 60 mg/kg dosed dogs. The 120 mg/kg dogs exhibited vomiting, ataxia and tremor with tonic-clonic spasm. Biochemical analysis showed decreased total protein and globulins. One animal at 60 mg/kg and 3 animals at 120 mg/kg died. Probable cause of death: circulatory collapse.

Table 8 - Summary of Subacute and Chronic Toxicity Studies

Species	Route of Dosing	Duration of Dosing	Daily Dose (mg/kg)	No. of Animals Per Dose Group	No. of Deaths Per Dose Group	Toxic Effects
Monkey (Rhesus)	i.v.	4 weeks	0 2.0 5.0	4 4 4	0 0 0	A dose related decrease in body weight gain was reported. All animals treated showed a decrease in the ejaculation volume and sperm count. Death of all spermatozoa was observed in the high dose group. The following was observed on histopathology: inhibition of spermatogenesis in the 2.0 mg/kg group and more severe disorders of spermatogenesis (including absence of spermatozoa maturation, severe degree of atypical nuclei with hyperchromasia and an increased number of nucleus pycnosis) in the 5.0 mg/kg dose group. Sperm counts returned to normal within 8 weeks post study.

Carcinogenicity:

Mutagenicity Study

The mutagenic potential of propafenone was investigated in bacteria *in vitro* (Salmonella / microsome assay) as well as in Chinese hamsters, rats and mice *in vivo*. No indication of mutagenic activity was detected in any of these studies.

Carcinogenicity Studies

Propafenone hydrochloride was administered in doses of 60, 180 and 540 (360) mg/kg to NMR mice for 104 weeks. After 21 weeks, the maximum dose was reduced to 360 mg/kg for the remainder of the study. Sprague-Dawley rats were given doses of 30, 90 and 270 mg/kg in the food for 30 months. In these studies propafenone hydrochloride was not carcinogenic.

Reproductive and Developmental Toxicology:

Fertility and General Reproductive Performance

SPF albino rats (24/sex/dose) received 0, 30, 90and 270 mg/kg/day of propafenone hydrochloride (gavage). Males were treated for 70 days prior to mating and females began treatment 14 days prior to mating. Both continued treatment for a maximum of 14 days during the mating period. Propafenone hydrochloride did not produce any adverse effects on fertility but increased the time required for mating.

Male Wistar rats (20/group) and male albino rabbits (10/group) received oral propafenone hydrochloride at doses of 0 or 150 mg/kg (rats) and 0 or 120 mg/kg (rabbits) over 10 weeks (6 days/week). On the last day of treatment in the rat and after termination of treatment in the rabbit, each male was paired with two non-treated females. There was no effect in either species on fertility, mating behaviour, or litter size.

Teratology Studies

Female Wistar rats (20/group) received oral propafenone hydrochloride (gavage) at doses of 0, 90, 270 or 600 mg/kg from the 5th to the 15th day of pregnancy. There was no evidence of teratogenicity at any dose. An embryotoxic effect (i.e. increased resorption rates and decreased fetal weights) was detected at the highest dose level. This dose was already toxic to dams as evidenced by reduced weight gain.

White pregnant female New Zealand rabbits received oral (gavage) propafenone hydrochloride at doses of 0, 15, 30 or 150 mg/kg/day from the 6th to the 18th day of pregnancy. Fetuses of the intermediate and high dose group showed variations (retarded ossification of the skull, the coccygeal vertebra and end-phalanx). The number of resorption and dead fetuses was increased in the high dose group. This dose was toxic to the dam as evidenced by reduced weight gain and increased mortality.

Spermatogenesis

Intravenous administration of propafenone hydrochloride in doses of 0.3, 0.5 and 1.0 mg/kg for three weeks to NZ-rabbits (two per dose) resulted in reduced spermatogenesis. The dose of 1.0 mg/kg produced degenerated spermatogenic epithelium in the testes of all animals.

Additional studies of spermatogenesis were performed in the monkey, dog and rabbit. After intravenous administration of 2 and 5 mg/kg propafenone hydrochloride per day to monkeys for four weeks, decreased spermatogenesis occurred, but was reversible eight weeks after discontinuation of propafenone hydrochloride. Minor alterations in the spermatogram (oligospermia) were observed in dogs administered 5 mg/kg intravenous for four weeks and rabbits administered 3.5 and 5 mg/kg intravenous for six days. The phenomenon was reversible four weeks after discontinuation of propafenone hydrochloride. No injury to the parenchyma of the testes occurred, nor did electron microscopy demonstrate any changes in the spermatogenic epithelium of rabbits.

17 SUPPORTING PRODUCT MONOGRAPHS

1. RYTHMOL® film-coated tablets, 150 and 300 mg, submission control, 251371, Product Monograph, BGP Pharma ULC. (AUG 26, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]APO-PROPAFENONE

Propafenone Hydrochloride Tablets

Read this carefully before you start taking **APO-PROPAFENONE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **APO-PROPAFENONE**.

Serious Warnings and Precautions

- APO-PROPAFENONE is intended for use only in patients with life-threatening irregular heartbeats (arrhythmias). Most anti-arrhythmic drugs have the potential to cause dangerous arrhythmias; some have been shown to be associated with an increase of sudden death. Your doctor will tell you about the risk and benefits of anti-arrhythmic therapy.

What is APO-PROPAFENONE used for?

APO-PROPAFENONE is used in adults to treat certain types of irregular heartbeat conditions known as ventricular arrhythmias.

How does APO-PROPAFENONE work?

APO-PROPAFENONE is a heart rate regulating agent. It acts on the metabolism of the heart muscles to block some of the irregular heartbeats. It also acts as a local anaesthetic, blocks the sodium current and slows down the potential of heart muscles reacting fast.

What are the ingredients in APO-PROPAFENONE?

Medicinal ingredients: propafenone hydrochloride.

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methylcellulose, polyethylene glycol and titanium dioxide.

APO-PROPAFENONE comes in the following dosage forms:

Film-coated tablets: 150 mg and 300 mg.

Do not use APO-PROPAFENONE if:

- you are allergic to propafenone hydrochloride or any of the other ingredients in APO-PROPAFENONE;
- you have certain severe heart conditions (e.g., Brugada Syndrome, congestive heart failure, cardiogenic shock, bradycardia, or heart conduction disorders);
- you have had a heart attack within the last 3 months;
- you have severe liver failure;
- you have lung problems (e.g., bronchospastic disorders, or severe obstructive pulmonary disease);
- you have myasthenia gravis (an autoimmune disorder that causes muscle weakness);
- you have severe hypotension (low blood pressure);
- you have severe electrolyte imbalance problems;
- you are taking ritonavir (an antiviral medication used to treat human immunodeficiency virus (HIV)).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take APO-PROPAFENONE. Talk about any health conditions or problems you may have, including if you:

- you have a family history of sudden cardiac death;
- you are pregnant or plan to become pregnant;
- are breast-feeding or plan to breastfeed. APO-PROPAFENONE is excreted into your breast milk. If you are breastfeeding, your healthcare professional will discuss alternative methods to feed your infant;
- have any heart problems;
- have abnormal blood cell counts;
- have liver problems;
- have a neuromuscular disease (e.g., myasthenia gravis);
- have kidney problems;
- have a permanent pacemaker;
- have a blockage in any part of the airway (e.g., asthma).

Other warnings you should know about:

Taking APO-PROPAFENONE may cause the following:

- **Heart problems:** APO-PROPAFENONE can cause other heart problems. This includes abnormal heartbeat rhythms (e.g., arrhythmias, severe ventricular tachycardia, ventricular fibrillation or torsade de pointes) and cardiac conduction reduction (problems related to the electrical system that controls your heart beat). These can be life-threatening and may require resuscitation to prevent a potentially fatal outcome. Your healthcare professional will assess your heart throughout your treatment. They may decide to reduce or stop your treatment as necessary.
- **Agranulocytosis (low level of white blood cells):** APO-PROPAFENONE can cause agranulocytosis, usually within four to six weeks of treatment. Tell your healthcare professional if you notice or develop a fever, fatigue, discomfort, or any signs of infection. Your healthcare professional may stop your treatment with APO-PROPAFENONE.
- **Liver problems:** APO-PROPAFENONE can cause liver problems such as liver cell damage, increase in liver enzymes, and inflammation of the liver (hepatitis). Your healthcare professional will monitor your health and may adjust your dose of APO-PROPAFENONE.
- **Immune problems:** APO-PROPAFENONE can cause an abnormal blood test called Antinuclear Antibody Test or ANA Test. Your healthcare professional will monitor and assess your antinuclear antibodies (a type of antibodies produced by the immune system) at the start and during regular intervals of your treatment. They may reduce or stop your treatment.
- **Fertility problems (male):** APO-PROPAFENONE can cause a reduction in your semen, follicle-stimulating hormone (FSH), and testosterone levels. Talk to your healthcare professional to see how APO-PROPAFENONE can affect you.

Driving and using machines: APO-PROPAFENONE can cause blurred vision, dizziness, fatigue, and low blood pressure. Before you drive or do tasks that require special attention, wait until you know how you respond to APO-PROPAFENONE.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with APO-PROPAFENONE:

- medications known as beta-blockers used to treat high blood pressure (e.g., propranolol and metoprolol);
- quinidine, ketoconazole, and erythromycin (medications known to decrease the activity of class of enzymes (such as CYP3A4 and CYP2D6) responsible for breakdown and removal of many drugs and toxins);

- cimetidine (used to relieve symptoms of acid reflux, heart burn and stomach ulcer by decreasing the activity of proton pump (enzyme CYP1A2);
- medications known as anticoagulants used to prevent blood clotting such as warfarin or acenocoumarol;
- certain local anesthetics (e.g., lidocaine);
- desipramine, fluoxetine, paroxetine, fluvoxamine and venlafaxine (medications known as antidepressants used to treat depression);
- cyclosporine (used to supress immune system function);
- theophylline (used to treat lung diseases);
- rifampin (used to treat or prevent tuberculosis and other bacterial infections);
- ritonavir and lopinavir/ritonavir products (an antiviral medication typically used to treat HIV);
- amiodarone, digoxin (used to treat or heart problems);
- phenobarbital (used to control seizures);
- St. John's Wort (herbal compound commonly used to treat depression and mood disorders);
- grapefruit juice.

How to take APO-PROPAFENONE:

- APO-PROPAFENONE tablets should be swallowed whole with liquid. Do not chew your tablets.
- APO-PROPAFENONE should be taken with food.

Usual dose:

Your doctor will determine the right dose of APO-PROPAFENONE is for you. The initial adult dose of APO-PROPAFENONE is 150 mg every 8 hours. Your doctor may decide on a different dosage depending on your situation.

Overdose:

If you think you, or a person you are caring for, have taken too much APO-PROPAFENONE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget or miss a dose, take it as soon as you remember. But if it is almost time for your next dose do not take the missed dose. Instead take the next scheduled dose. Do not try to make up for a missed dose by taking a double dose.

What are possible side effects from using APO-PROPAFENONE?

These are not all the possible side effects you may have when taking APO-PROPAFENONE. If you experience any side effects not listed here, tell your healthcare professional.

Some side effects include:

- gastrointestinal problems such as abdominal pain/cramping or discomfort, constipation, diarrhea, dry mouth, flatulence, loss of appetite, and unusual taste;
- nervous system problems such as anxiety, difficulty in sleeping (insomnia), and sweating;
- pain in the joints.

Check with your healthcare professional if you experience any unexpected effects, or are concerned by the above side effects.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Arrhythmia (abnormal heart rhythms): rapid, slow or irregular heartbeat		√	
Heart problems (disorders affecting your heart muscle, valves or rhythm): chest pain, chest discomfort, high blood pressure, irregular heart rhythm, shortness of breath, fainting, swelling of the legs, ankles and feet, or weakness		√	
COMMON			
Angina (not enough oxygen to the heart muscle): discomfort in the shoulder, arm,		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
back, throat, jaw or teeth, or pain or pressure in the chest			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, or fatigue (may occur when you go from lying or sitting to standing up)		√	
Syncope (fainting): a temporary loss of consciousness due to a sudden drop in blood pressure		√	
Liver problems: yellowing skin or eyes, vomiting, nausea, right upper stomach area pain or swelling, unusual dark urine, or unusual tiredness		√	
Bleeding problem: excessive bruising, or easy bleeding		√	
Edema: unusual swelling of the arms, hands, legs, feet, ankles, face or airway passages		√	
UNCOMMON			
Ataxia (lack of muscle coordination): difficulty with fine motor tasks such as eating, writing or buttoning shirt, difficulty walking, loss of balance, or slurring speech		√	
UNKNOWN			
Convulsions: seizures, spasms, shaking, or fits		√	
Movement disorders: tremor, bradykinesia, muscle rigidity, restlessness, or uncontrolled movements		√	
Allergic reaction: difficulty swallowing or breathing, wheezing, drop in blood pressure, feeling sick to your stomach and throwing up,		√	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
hives, rashes, or swelling of the face, lips, tongue or throat			
Acute generalized exanthematous pustulosis (AGEP; a severe skin reaction): sudden skin eruptions, small red bumps, fever, or rashes		√	
Nervous system problems: weakness or paralysis of limbs or face, difficulty speaking, severe headache, seeing, feeling or hearing things that are not there, loss of consciousness, confusion, disorientation, or trembling		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

APO-PROPAFENONE tablets should be stored at room temperature 15°C to 30°C (59°F to 86°F).

Do not take your tablets after the expiry date shown on the label.

It is important to keep the APO-PROPAFENONE tablets in the original package.

Keep out of reach and sight of children.

If you want more information about APO- PROPAFENONE:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html,) the manufacturer's website (http://www.apotex.ca/products), or by calling 1-800-667-4708.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

Last Revised: April 3, 2023