

# PRODUCT MONOGRAPH

## **Pr**PROPRANOLOL HYDROCHLORIDE INJECTION USP

(Propranolol Hydrochloride)

**1 mg/mL**

**Beta-Adrenergic Receptor Blocking Agent**

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Date of Revision: June 19, 2013

Control No. 154697

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# Pr**PROPRANOLOL HYDROCHLORIDE INJECTION USP**

(Propranolol Hydrochloride)

## **PART I: HEALTH PROFESSIONAL INFORMATION**

### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Nonmedicinal Ingredients</b>
Intravenous	Injectable / 1 mg/mL	citric acid to adjust pH and water for injection

### **INDICATIONS AND CLINICAL USE**

Propranolol Hydrochloride Injection USP is reserved for life-threatening cardiac arrhythmias in the following conditions:

#### **Cardiac Arrhythmias**

##### **Supraventricular arrhythmias:**

- Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with Wolff-Parkinson-White syndrome (see W-P-W Syndrome under WARNINGS AND PRECAUTIONS).
- Persistent sinus tachycardia which is non-compensatory and impairs the well-being of the patient.
- Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short-term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy (see Thyrotoxicosis under WARNINGS AND PRECAUTIONS).
- Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures.
- Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

**Ventricular tachycardia:** Ventricular arrhythmias do not respond to Propranolol Hydrochloride Injection USP as predictably as do the supraventricular arrhythmias.

- With the exception of ventricular tachycardia induced by catecholamines or digitalis, Propranolol Hydrochloride Injection USP is not the drug of first choice. In critical situations when cardioversion techniques or other drugs are not indicated or are not effective, Propranolol Hydrochloride Injection USP may be considered. If after consideration of the risks involved, Propranolol Hydrochloride Injection USP is used, it should be given intravenously in low dosage and very slowly.
- Persistent premature ventricular extrasystoles which do not respond to conventional measures

and impair the well-being of the patient.

**Tachyarrhythmias of digitalis intoxication:** If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with **oral** propranolol hydrochloride. Severe bradycardia may occur (see OVERDOSAGE).

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated (see DOSAGE AND ADMINISTRATION).

**Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia:**

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, Propranolol Hydrochloride Injection USP may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when Propranolol Hydrochloride Injection USP is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. In patients during anesthesia with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore Propranolol Hydrochloride Injection USP should be titrated carefully when administered for arrhythmias occurring during anesthesia.

**Pheochromocytoma**

After primary treatment with an alpha-adrenergic blocking agent has been instituted, Propranolol Hydrochloride Injection USP may be useful as adjunctive therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use Propranolol Hydrochloride Injection USP unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure rise. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed. In the event of hemorrhage or shock, producing both beta and alpha blockade is contraindicated since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

**CONTRAINDICATIONS**

Propranolol Hydrochloride Injection USP is contraindicated in patients who are hypersensitive to propranolol hydrochloride or to any ingredient in the formulation. For a complete listing, see the DOSAGE FORMS, COMPOSITION and PACKAGING section of this Product Monograph.

Propranolol hydrochloride is also contraindicated in:

- Patients with a history of or current reports of bronchial asthma or bronchospasm;
- Sinus bradycardia;
- Greater than first degree atrioventricular (AV) block;

- Cardiogenic shock;
- Right ventricular failure secondary to pulmonary hypertension;
- Congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with propranolol hydrochloride.
- As with other beta-blockers, the drug must not be used in patients with any of the following: bradycardia, hypotension, metabolic acidosis, severe peripheral arterial circulatory disturbance, sick sinus syndrome, untreated phaeochromocytoma, uncontrolled heart failure, Prinzmetal's angina.

## **WARNINGS AND PRECAUTIONS**

### **Cardiovascular**

#### **In Patients with a History of Cardiac Failure**

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure; therefore, inhibition by means of beta-adrenergic blockade is a potential hazard as it may further depress myocardial contractility and precipitate cardiac failure.

Propranolol hydrochloride acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e. that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may appear to be reduced by propranolol hydrochloride's negative inotropic effect. Due to its negative effect on conduction time, caution must be exercised if it is given to patients with first degree heart block. The effects of the drug and digitalis are additive in depressing AV conduction.

Caution must be exercised in patients whose cardiac reserve is poor.

#### **In Patients Without a History of Cardiac Failure**

Continued depression of the myocardium over a period of time can, in some patients, lead to cardiac failure. In rare instances, this has been observed during propranolol hydrochloride therapy. Therefore at the first sign or symptom of impending cardiac failure, patients should be treated appropriately.

#### **Peripheral Arterial Circulatory Disturbances**

Propranolol Hydrochloride Injection USP is contraindicated in severe peripheral arterial circulatory disturbances (see CONTRAINDICATIONS) and it may aggravate less severe peripheral arterial circulatory disturbances.

#### **Wolff-Parkinson-White Syndrome**

Propranolol Hydrochloride Injection USP should be used with caution since several cases have been reported in which, after propranolol hydrochloride treatment, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one patient, this occurred after an initial dose of 5 mg of propranolol hydrochloride.

### **In Patients with Acute Myocardial Infarction**

It has been reported that administration of propranolol hydrochloride tablets to control cardiac arrhythmias in acute myocardial infarction has caused marked reduction in cardiac output. Therefore, the doses of propranolol hydrochloride should be kept to the minimum in patients with severe myocardial infarction. Caution should be exercised when administering propranolol hydrochloride in such situations, especially when a large portion of the myocardium has been damaged due to coronary occlusion, since adequate sympathetic drive should be preserved to maintain ventricular function.

### **Respiratory**

#### **Patients Prone to Nonallergic Bronchospasm**

Propranolol Hydrochloride Injection USP should be administered with caution since it may block the bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-adrenergic receptors. If bronchospasm occurs, appropriate interventions should be instituted.

### **Central Nervous System**

Dizziness and/or fatigue may occasionally occur with beta-blocker administration and this should be taken into account.

### **Endocrine and Metabolism**

#### **Hyperthyroidism**

Propranolol hydrochloride may mask the clinical signs of developing or continuing hyperthyroidism or its complications, and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol hydrochloride may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This may be another instance where propranolol hydrochloride should be withdrawn slowly by reducing dosage. Propranolol hydrochloride does not distort thyroid function tests.

### **Ophthalmologic**

#### **Oculomucocutaneous Syndrome**

Various skin rashes and conjunctival xerosis have been reported in patients treated with beta blockers, including propranolol hydrochloride. A severe oculomucocutaneous syndrome, whose signs include conjunctivitis sicca and psoriasiform rashes, otitis, and sclerosing serositis has occurred with the long-term use of one, no longer available, beta-adrenergic blocking agent. This syndrome has not been observed with propranolol hydrochloride; however, physicians should be alert to the possibility of such reactions and discontinue treatment if they occur.

### **Skin**

Cutaneous reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol (see ADVERSE REACTIONS - Dermatologic).

### **Hypersensitivity, Allergic Reactions**

Anaphylactic/anaphylactoid reactions have been associated with the administration of propranolol hydrochloride (see ADVERSE REACTIONS).

There may be increased difficulty in treating an allergic type reaction in patients on beta-blockers. In these patients, the reaction may be more severe due to pharmacological effects of beta-blockers and problems with fluid changes. Epinephrine should be administered with caution since it may not have its usual effects in the treatment of anaphylaxis. On the one hand, larger doses of epinephrine may be needed to overcome the bronchospasm, while on the other, these doses can be associated with excessive alpha adrenergic stimulation with consequent hypertension, reflex bradycardia and heart-block and possible potentiation of bronchospasm. Alternatives to the use of large doses of epinephrine include vigorous supportive care such as fluids, and the use of beta agonists including parenteral salbutamol or isoproterenol to overcome bronchospasm, and norepinephrine to overcome hypotension.

Some slowing of the heart due to unopposed vagal activity is usual in patients receiving propranolol hydrochloride, however, occasionally severe bradycardia occurs and may lead to vertigo, syncopal attacks or orthostatic hypotension. Patients, especially those with limited cardiac reserve should be monitored for signs of excessive bradycardia. Should the patient become symptomatic, the dose of propranolol hydrochloride should be decreased or, if necessary, the drug should be discontinued. If it is essential to correct the bradycardia, intravenous atropine or isoproterenol should be considered.

### **Special Populations**

**Pregnant Women:** Propranolol can cause fetal harm when administered to a pregnant woman. The safe use of propranolol hydrochloride in pregnancy has not been established. Use of any drug in pregnancy or in women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Post-marketing case reports including perinatal complications, such as small placentas, intrauterine growth retardation and congenital abnormalities have been reported in neonates where the mother took propranolol during pregnancy. Some infants born to mothers treated with propranolol were reported to have hypoglycemia, bradycardia and/or respiratory depression. Adequate facilities for monitoring such infants at birth should be available.

Propranolol hydrochloride should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Women:** Propranolol is excreted in human milk. Breast feeding is therefore not recommended when propranolol hydrochloride is administered to nursing women.

### **Diabetics:**

#### **Patients with Diabetes and in those Subject to Hypoglycemia**

Propranolol hydrochloride, because of its beta-adrenergic blocking activity, may block premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure. Acute increases in blood pressure have occurred after insulin-induced hypoglycemia in patients on propranolol hydrochloride.

**Pediatrics:** Propranolol hydrochloride is not recommended for use in children.

**Geriatrics:** There is no information available for elderly patients. Therefore, the optimum dose should be individually determined according to clinical response.

**Patients with Renal or Liver Impairment:** In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. There have been reports suggesting that treatment with propranolol may increase the risk of hepatic developing encephalopathy.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

The most serious adverse reactions encountered with propranolol hydrochloride are congestive heart failure and bronchospasm (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

The most common adverse effects are gastrointestinal disturbances (anorexia, nausea, vomiting, diarrhea, abdominal pain).

The following adverse reactions have also been reported: hypersensitivity reactions including anaphylactic/anaphylactoid reactions, Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme and urticaria.

Reported adverse effects, by organ systems, are provided below.

**Cardiovascular:** Congestive heart failure (see WARNINGS), heart failure deterioration; precipitation of heart block; secondary effects of decreased cardiac output (which could include: syncope, vertigo, lightheadedness, decreased renal perfusion and rarely, postural hypotension); intensification of AV block and hypotension; severe bradycardia; claudications and cold extremities, Raynaud's phenomenon; dyspnea; palpitations; precordial pain.

**Central Nervous System:** Dizziness, lethargy, weakness, drowsiness, headache, insomnia, fatigue and/or lassitude, anorexia, anxiety, mental depression, poor concentration, reversible amnesia and catatonia, vivid dreams with or without insomnia, nightmares, hallucinations, psychoses, mood changes, confusion, paresthesia, incoordination.

**Nervous System:** Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis.

**Gastrointestinal:** Nausea, vomiting, epigastric distress, anorexia, bloating, mild diarrhea, constipation.

**Respiratory:** Bronchospasm (may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome): laryngospasm and respiratory distress (see

CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

**Blood:** Thrombocytopenia, thrombocytopenic purpura, and agranulocytosis.

**Dermatologic:** A few cases of erythematous rashes and increase of facial acneiform lesions have been reported; urticaria, exfoliative psoriasiform eruption, Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis and erythema multiforme.

**Endocrine:** Hypoglycaemia in elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

**Allergic:** Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions.

**Others:** Reduction or loss of libido, reversible alopecia and rarely, diminution and loss of hearing, tinnitus, visual disturbances, diminished vision, conjunctivitis, dry eyes and pharyngitis, fever combined with aching and sore throat, flushing of the face.

**Clinical Laboratory Test Findings:** Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, and lactate dehydrogenase have been reported. An increase in ANA (antinuclear antibodies) has been observed, however the clinical relevance of this is not clear.

## DRUG INTERACTIONS

### Drug-Drug Interactions

The drug interactions discussed in this section are based on either drug interactions case reports or studies, or potential interaction due to expected magnitude and seriousness of the interaction.

Concomitant use of propranolol and a vasodilator or an antihypertensive drug will cause further reduction in blood pressure than either drug given alone.

### **Interactions with Substrates, Inhibitors or Inducers of Cytochrome P-450 Enzymes**

Because propranolol's metabolism involves multiple pathways in the cytochrome P-450 system (CYP2D6, 1A2, 2C19), administration of propranolol with drugs that are metabolized by, or affect the activity (induction or inhibition) of one or more of these pathways may lead to clinically relevant drug interactions.

- Substrates or inhibitors of CYP2D6: Blood levels of propranolol may be increased by administration of propranolol with substrates or inhibitors of CYP2D6 such as amiodarone, cimetidine, delavirdine, fluoxetine, paroxetine, quinidine and ritonavir. No interaction was observed with either ranitidine or lansoprazole.
- Substrates or inhibitors of CYP1A2: Blood levels of propranolol may be increased by administration of propranolol with substrates or inhibitors of CYP1A2, such as imipramine,

cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton\* (\* not commercially available in Canada), zolmitriptan and rizatriptan.

- Substrates or inhibitors of CYP2C19: Blood levels of propranolol may be increased by administration of propranolol with substrates or inhibitors of CYP2C19 such as fluconazole, cimetidine, ciprofloxacin, fluoxetine, fluvoxamine, tenoposide\* (\* not commercially available in Canada) and tolbutamide. No interaction was observed with omeprazole.
- Inducers of hepatic drug metabolism: Blood levels of propranolol may be decreased by administration of propranolol with inducers such as rifampin and ethanol. Cigarette smoking also induces hepatic metabolism and has been shown to increase up to 100% the clearance of propranolol, resulting in decreased plasma concentrations.

### **Anti-arrhythmic drugs**

- Class I anti-arrhythmic drugs (e.g. disopyramide, lidocaine, propafenone, quinidine) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effects.
  - The AUC of propafenone is increased by more than 200% with co-administration of propranolol.
  - The metabolism of propranolol is reduced by co-administration of quinidine, leading to a 2- to 3-fold increased blood concentrations and greater beta-blockade.
  - The metabolism of lidocaine is inhibited by co-administration of propranolol, resulting in a 25% increase in lidocaine concentrations.
- Other cardiac-depressant anti-arrhythmic drugs: prior administration of other antiarrhythmic drugs, such as procainamide or quinidine may potentiate the cardiac-depressant activity of propranolol hydrochloride. Prior digitalization may be indicated and atropine should be at hand to control bradycardia.

### **Reserpine or Guanethidine**

Patients receiving catecholamine depleting drugs should be closely observed if administered concomitantly with propranolol hydrochloride. The added catecholamine blocking action of these drugs may produce an excessive reduction of the resting sympathetic nervous activity.

### **Migraine Drugs**

The simultaneous administration of rizatriptan and propranolol can increase the rizatriptan AUC and  $C_{max}$  by approximately 70-80%. The increased rizatriptan exposure is presumed to be caused by inhibition of first-pass metabolism of rizatriptan through inhibition of monoamine oxidase-A. If both drugs are to be used, a rizatriptan dose of 5 mg has been recommended.

Administration of zolmitriptan with propranolol resulted in increased concentration of zolmitriptan (AUC increased by 56% and  $C_{max}$  by 37%).

### **Digitalis glycosides**

In association with beta-blockers, digitalis glycosides may increase atrioventricular conduction time.

**Verapamil, Diltiazem**

Beta-blockers combined with calcium channel blockers with negative inotropic effects (such as verapamil and diltiazem) can lead to an exaggeration of these effects, particularly in patients with impaired ventricular function and/or SA or AV conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered within 48 hours of discontinuing the other.

**Nifedipine**

Concomitant therapy with dihydropyridine calcium channel blockers (such as nifedipine) may increase the risk of hypotension and cardiac failure may occur in patients with latent cardiac insufficiency.

The mean values of  $C_{max}$  and AUC of nifedipine are increased by 64% and 79%, respectively, by co-administration of propranolol.

**Epinephrine**

Concomitant use of sympathomimetic agents, such as epinephrine, may counteract the effects of beta-blockers. Caution must be exercised when administering epinephrine parenterally to patients taking beta-blockers as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

**Cimetidine**

Concomitant use of cimetidine will increase plasma levels of propranolol. Co-administration of propranolol with cimetidine increased propranolol concentrations by about 40%.

**Metoclopramide**

Co-administration of metoclopramide with propranolol did not have a significant effect on propranolol's pharmacokinetics.

**Alcohol**

Concomitant use of alcohol may increase the plasma levels of propranolol.

**Clonidine**

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If clonidine is co-administered with a beta-blocker, the beta-blocker should be withdrawn several days before stopping clonidine administration. If replacing clonidine by beta-blocker therapy, the introduction of the beta-blocker should be delayed for several days after clonidine administration has been discontinued.

**Anaesthetic agents**

Use of beta-blockers with anaesthetic agents may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression should be avoided.

**Theophylline**

Co-administration of theophylline with propranolol decreases theophylline clearance by 33% to 52%.

### **Benzodiazepines**

Propranolol can inhibit the metabolism of diazepam, resulting in increased concentrations of diazepam and its metabolites. Diazepam does not alter the pharmacokinetics of propranolol. The pharmacokinetics of oxazepam, triazolam, lorazepam and alprazolam are not affected by co-administration of propranolol.

### **Phenothiazines and other psychotherapeutic agents**

Phenothiazines and propranolol may have additive hypotensive activity, especially when phenothiazines are administered in large doses. Chlorpromazine has been shown to reduce the clearance of propranolol and increase plasma propranolol concentrations (70% increase in propranolol concentrations). Increased plasma concentrations of chlorpromazine also have been reported in patients receiving the drug concomitantly with propranolol. Hypotension and cardiac arrest have occurred during concomitant therapy with propranolol and haloperidol.

### **Lipid lowering drugs**

Co-administration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations.

Co-administration of propranolol with lovastatin or pravastatin decreased 20% to 25% the AUC of both, but did not alter their pharmacodynamics. Propranolol did not have an effect on the pharmacokinetics of fluvastatin.

### **Warfarin**

Concomitant administration of propranolol and warfarin has been shown to increase warfarin bioavailability and increase prothrombin time. Prothrombin time should be monitored in patients receiving warfarin concomitantly with propranolol.

### **Ibuprofen, Indomethacin**

Concomitant use of prostaglandin synthetase inhibiting drugs (e.g. ibuprofen and indomethacin) may decrease the hypotensive effects of propranolol.

### **Drug-Food Interactions**

Interactions with food have not been established.

### **Drug-Herb Interactions**

Interactions with herbal products have not been established.

### **Drug-Laboratory Interactions**

Propranolol hydrochloride does not interfere with thyroid function tests.

Interactions with other laboratory tests have not been established.

## DOSAGE AND ADMINISTRATION

The usual dose is from 1 to 3 mg, administered under careful monitoring, e.g. electrocardiograph, and central venous pressure recording. The rate of administration should not exceed 1 mg (1 mL) per minute to avoid excessive lowering of blood pressure and cardiac arrest. Sufficient time should be allowed for the drug to reach the site of action, especially when a slow circulation is present. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours. Additional Propranolol Hydrochloride Injection USP should not be given once the desired alteration in rate and/or rhythm is achieved. Changeover to oral therapy should be made as soon as possible.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

### Symptoms

The common signs to be expected in overdose include bradycardia, hypotension, bronchospasm, or acute cardiac failure.

### Treatment

If overdose occurs, discontinue therapy with propranolol hydrochloride and observe the patient closely. Appropriate therapeutic measures should be instituted (consult your regional Poison Control Centre).

## ACTION AND CLINICAL PHARMACOLOGY

### Mechanism of Action

Propranolol hydrochloride is a non-selective beta-adrenergic receptor blocking drug. It has no other autonomic nervous system activity. Propranolol is a competitive antagonist which specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta-adrenergic receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Beta-adrenergic blockade is useful in some clinical conditions in which the sympathetic activity is excessive or inappropriate, and therefore detrimental to the patient. Sympathetic stimulation is however vital in some situations, (e.g. in patients with AV block or with a severely damaged heart) and should be preserved. The basic objective of beta-adrenergic blockade is to decrease adverse sympathetic stimulation, but not to the degree that impairs necessary sympathetic support. Beta-blockade may result in bronchial constriction by interfering with endogenously or exogenously induced bronchodilatation (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

The mechanism of the antihypertensive effects of propranolol has not been established. Among

the factors that may be involved are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. It has been suggested, but not established, that propranolol may achieve a better antihypertensive effect in patients with normal or elevated plasma renin activity (PRA) than those with low PRA.

Propranolol may reduce the oxygen requirement of the heart at any level of effort by blocking catecholamine-induced increases in the heart rate, systolic blood pressure and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end-diastolic pressure, and systolic ejection period.

Propranolol exerts antiarrhythmic effects in concentrations producing beta-adrenergic blockade, which appears to be its principal antiarrhythmic mechanism of action. Beta-adrenergic blockade is of unique importance in the management of arrhythmias caused by increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

### **Respiratory Effects**

Propranolol increases airway resistance by reducing the sympathetic tone at the bronchi. This effect is small in most normal individuals, where it can only be demonstrated by measuring forced expiratory volume (FEV<sub>1</sub>). In asthmatics and patients with other bronchospastic diseases however, this effect is marked and potentially dangerous.

Injection of propranolol reduced FEV<sub>1</sub> with dyspnea, cough and dizziness in 2 of 11 patients with chronic obstructive lung disease. When given the drug orally (40 mg q.i.d.) 5 of these 11 patients reported dyspnoea. Propranolol has been reported to potentiate bronchospasm induced by histamine, acetylcholine, methylcholine or allergens. This potentiation is greater in asthmatics than in non-asthmatic individuals.

### **Other Clinical Pharmacological Effects**

Epstein and associates studied 16 human subjects under conditions of maximal and submaximal exercise. Propranolol 0.15 mg/kg intravenously, was sufficient to reduce by tenfold the sensitivity of heart rate to isoproterenol.

Blockade of beta-adrenergic receptors in the peripheral vasculature has little if any effect on circulation or blood pressure. When administered intra-arterially, propranolol causes a brief vasodilation unrelated to beta-adrenergic receptor blockade.

### **Pharmacokinetics and Drug Metabolism**

#### **Distribution**

Propranolol has a distribution half-life (T<sub>1/2</sub> alpha) of 5-10 minutes and a volume of distribution of about 4 to 5 L/kg. Approximately 90% of circulating propranolol is bound to plasma proteins. The binding is enantiomer-selective. The S-isomer is preferentially bound to alpha<sub>1</sub> glycoprotein and the R-isomer is preferentially bound to albumin.

### **Metabolism and Elimination**

The elimination half-life ( $T_{1/2}$  beta) is between 2 and 5.5 hours. Propranolol is extensively metabolized with most metabolites appearing in the urine. The major metabolites include propranolol glucuronide, naphthyloxylactic acid, and glucuronic acid and sulfate conjugates of 4-hydroxy propranolol. Following single-dose intravenous administration, side-chain oxidative products account for approximately 40% of the metabolites, direct conjugation products account for approximately 45-50% of metabolites, and ring oxidative products account for approximately 10-15% of metabolites. Of these, only the primary ring oxidative product (4-hydroxypropranolol) possesses beta-adrenergic receptor blocking activity.

In vitro studies have indicated that the aromatic hydroxylation of propranolol is catalyzed mainly by polymorphic CYP2D6. Side-chain oxidation is mediated mainly by CYP1A2 and to some extent by CYP2D6. 4-hydroxy propranolol is a weak inhibitor of CYP2D6.

### **Special Populations**

**Pediatric:** The pharmacokinetics of propranolol have not been investigated in patients under 18 years of age. Propranolol injection is not recommended for treatment of cardiac arrhythmias in pediatric patients.

**Geriatric:** Elevated propranolol plasma concentrations, a longer mean elimination half-life (254 vs. 152 minutes), and decreased systemic clearance (8 vs. 13 mL/kg/min) have been observed in elderly subjects when compared to young subjects. However, the apparent volume of distribution seems to be similar in elderly and young subjects. These findings suggest that dose adjustment of propranolol injection may be required for elderly patients.

### **Gender**

Intravenously administered propranolol was evaluated in 5 women and 6 men. When adjusted for weight, there were no gender-related differences in elimination half-life, volume of distribution, protein binding, or systemic clearance.

### **Obesity**

In a study of intravenously administered propranolol, obese subjects had a higher AUC (161 versus 109 hr• $\mu$ g/L) and lower total clearance than did non-obese subjects. Propranolol plasma protein binding was similar in both groups.

### **Renal Insufficiency**

The pharmacokinetics of propranolol and its metabolites were evaluated in 15 subjects with varying degrees of renal function after propranolol administration via the intravenous and oral routes. When compared with normal subjects, an increase in fecal excretion of propranolol conjugates was observed in patients with increased renal impairment. Propranolol was also evaluated in 5 patients with chronic renal failure, 6 patients on regular dialysis, and 5 healthy subjects, following a single oral dose of 40 mg of propranolol. The peak plasma concentrations ( $C_{max}$ ) of propranolol in the chronic renal failure group were 2- to 3-fold higher (161 ng/mL) than

those observed in the dialysis patients (47 ng/mL) and in the healthy subjects (26 ng/mL). Propranolol plasma clearance was also reduced in the patients with chronic renal failure. Chronic renal failure has been associated with a decrease in drug metabolism via downregulation of hepatic cytochrome P450 activity.

### **Hepatic Insufficiency**

Propranolol is extensively metabolized by the liver. In a study conducted in 6 normal subjects and 20 patients with chronic liver disease, including hepatic cirrhosis, 40 mg of R-propranolol was administered intravenously. Compared to normal subjects, patients with chronic liver disease had decreased clearance of propranolol, increased volume of distribution, decreased protein-binding, and considerable variation in half-life. Caution should be exercised when propranolol is used in this population. Consideration should be given to lowering the dose of intravenous propranolol in patients with hepatic insufficiency.

### **Thyroid Dysfunction**

No pharmacokinetic changes were observed in hyperthyroid or hypothyroid patients when compared to their corresponding euthyroid state. Dosage adjustment does not seem necessary in either patient population based on pharmacokinetic findings.

## **STORAGE AND STABILITY**

Store between 15°C and 30°C. Discard unused portion.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Each mL contains propranolol hydrochloride 1 mg, citric acid to adjust pH and water for injection. Preservative free.

Propranolol Hydrochloride Injection USP, 1 mg/mL, is available in 1 mL (in a 2mL vial) single use vials, boxes of 10.

**LATEX FREE STOPPER:** Stopper contains no dry natural rubber.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

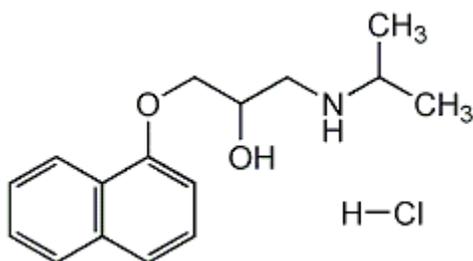
#### Drug Substance

Proper name: (±) -propranolol hydrochloride

Chemical name: (±) 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride

Molecular formula and molecular mass:  $C_{16}H_{21}NO_2 \cdot HCl$  ; 295.81 g/mol

Structural Formula:



Physicochemical properties: Propranolol hydrochloride is a stable, colourless, crystalline solid with a melting point of 163-164°C. It is readily soluble in water and ethanol and insoluble in non-polar solvents.

## **DETAILED PHARMACOLOGY**

Propranolol hydrochloride is a non-selective competitive antagonist of endogenous and exogenous sympathomimetic amines at beta-adrenergic receptors (Beta<sub>1</sub> and Beta<sub>2</sub>). Chemically it is a racemic mixture of equal amounts of levo and dextro isomers. The levo isomer is responsible for most of the beta receptor blocking activity.

### **Cardiovascular Effects**

Intravenous administration of propranolol to cats and dogs produced a fall in heart rate by blocking endogenous sympathetic activity to the heart. In anesthetized dogs, propranolol produced dose-related decrease in heart rate, cardiac contractile force, and small depressions in blood pressure, and cardiac output. These effects have also been demonstrated in man. A reduction in myocardial oxygen consumption and increased right atrial pressure were observed in healthy humans.

Human and animal studies with propranolol have demonstrated competitive and reversible blockage of the increased heart rate and increased force of contraction produced by isoproterenol, epinephrine, norepinephrine and stellate ganglion stimulation. Propranolol reduced the pressor response to norepinephrine, potentiated that of epinephrine, but did not affect the response to phenylephrine.

Amounts of propranolol which completely abolished the increase in heart rate produced by stimulation of the right stellate ganglion in anesthetized cats did not affect the bradycardia produced by vagal stimulation.

Propranolol causes no observable response when it interacts with beta-receptors in the absence of a primary antagonist such as epinephrine or isoproterenol indicating a lack of intrinsic sympathomimetic activity.

Lucchesi et al. demonstrated in dogs that propranolol was effective in reversing or preventing several types of experimentally-induced cardiac arrhythmias.

In animal experiments, at concentrations much higher than those necessary for a complete beta-adrenergic blockade, propranolol exerts a local anesthetic effect. This has also been termed a "membrane stabilizing" or "quinidine-like" effect. This property of propranolol has been demonstrated *in vitro* with human myocardium only at a minimum concentration of 10 mg/L which is about 100 times greater than that required for inhibition of exercise tachycardia or suppression of ectopic beats. This is, therefore, not thought to be an important property and there are not *in vivo* methods for demonstrating this effect in man.

Plasma renin levels are reduced by propranolol.

### **Central Nervous System Effects**

Propranolol readily crosses the blood/brain barrier. In some animal experiments it has been shown to display central muscle relaxant, sedative and anticonvulsant properties. To date, none of

these effects can be directly attributed to blockade of beta-adrenergic receptors in the Central Nervous System. One publication has suggested that the CNS activity of propranolol may be attributable to a glycol metabolite.

### **Metabolic Activity**

Propranolol may produce hypoglycemia but this effect appears to be rare and its mechanism is not clear. Propranolol also impairs the sympathetically mediated rebound response to hypoglycemic symptoms (see WARNINGS AND PRECAUTIONS).

Propranolol inhibits the rise in plasma free fatty acids induced by sympathomimetic amines. It also inhibits the lipolytic action of catecholamines in isolated adipose tissues of several animal species.

## **TOXICOLOGY**

### **Acute Toxicity (LD<sub>50</sub>)**

<b>Species</b>	<b>Dose (mg/kg) IV</b>	<b>Dose (mg/kg) Oral</b>
Mice	30-50	500-800
Rats	25-30	1000-1500
Rabbits	7.5-10.0	approx. 600

### **Subacute Toxicity**

Four-week subacute toxicity studies were performed in rats (doses of 3.0 and 15 mg/kg intraperitoneally), on dogs (doses of 1.5 and 7.5 mg/kg intravenously) and three-month oral toxicity studies were conducted on rats, mice and dogs. No drug-induced histopathologic changes were observed in any of the animals.

### **Chronic Toxicity**

**Rats:** A toxicity study of 18 months' duration was conducted in four groups of rats (one control and three experimental) each consisting of 25 males and 25 females. All animals received medication by tube directly into the stomach for the first 6 months, and thereafter in their diet.

A number of animals receiving the highest dose (150 mg/kg) developed bronchospasm soon after receiving the drug. A variety of pathologic lesions were observed in both the control and experimental groups. Dilatation of both ventricles was noted in a number of animals receiving the high-dose. Spontaneous myocarditis consisting of minor lymphocytic infiltration was observed in both groups. Testicular atrophy and reduction or absence of corpora lutea was seen in both the control and experimental groups.

**Dogs:** A one-year toxicity test was carried out in 32 dogs in both sexes, divided into 4 groups (control, and propranolol 60, 20 and 5 mg/kg). A patchy edema and a slight increase in the size of the lymphoid follicles of the mucosa in the fundus of the stomach were seen and were attributed

to mild irritation caused by prolonged dosing with high doses of propranolol.

### **Tumourigenic Tests**

The carcinogenic potential of propranolol was investigated in mice and rats by chronic administration of the compound in the diet for 78 weeks at varying concentrations to provide dosage levels of 10, 50 and 150 mg/kg/day. Control groups of mice and rats were fed the same diet without the drug. After 78 weeks of dosing, the mice were then kept alive for an additional 2 months, and the rats for an additional 6 months.

At the termination of the experiment, gross and microscopic pathologic investigations revealed that in mice the incidence of benign and malignant neoplasms was similar in control and all treated groups. Therefore, no drug-related tumorigenic effect was observed at any dose level. Similarly, no tumorigenic effect was observed in the rat. The incidence of tumours was lower in female rats treated with 150 mg/kg/day propranolol than in any of the other groups. This was attributed to the markedly decreased body weight gains in this group.

### **Reproductive Studies**

The effects of propranolol on fertility, pregnancy, the developing fetus and newborns at the time of weaning were studied in rats using various dose levels, administered either by gastric intubation or in the feed. The drug was also fed to rabbits in their diet.

In some studies in rats, a non-dose related increase in resorption sites and neonatal deaths were observed. No teratogenic effects were noted in either species. Furthermore, the compound had no adverse effect on fertility, pregnancy, parturition, or lactation.

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24. Daily Med online edition: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=18491>
25. Drugs.com ; Drug Information Online : <http://www.drugs.com/pro/propranolol-injection.html>

**PART III: CONSUMER INFORMATION****Pr** **PROPRANOLOL HYDROCHLORIDE INJECTION USP**  
(Propranolol Hydrochloride)

This leaflet is part III of a three-part "Product Monograph" published when Propranolol Hydrochloride Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Propranolol Hydrochloride Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION****What the medication is used for:**

Propranolol Hydrochloride Injection USP contains propranolol hydrochloride, one of a group of substances called beta-adrenergic receptor-blocking agents (beta blockers). It is used in the following conditions:

- Certain life-threatening cardiac arrhythmias.
- Pheochromocytoma.

**What it does:**

Propranolol hydrochloride acts to reduce blood pressure and correct arrhythmias.

It works by the effects it has on the heart and circulation and also on other parts of the body.

**When it should not be used:**

Do not use Propranolol Hydrochloride Injection USP if you:

- are hypersensitive (allergic) to propranolol hydrochloride or another beta-blocker;
- are hypersensitive to any ingredient in the formulation. For a complete listing, see below What the important nonmedicinal ingredients are;
- have had or currently have bronchial asthma or bronchospasm (a sudden closing of muscles in the throat, making it hard to breathe) ;
- have allergic rhinitis (for example, runny nose during the pollen season);
- have a heart condition known as heart failure (a condition where the heart is unable to pump enough blood);
- have pulmonary hypertension (high blood pressure in blood vessels of the lungs, which lead to heart failure);
- are prone to having hypoglycaemia (episodes of low blood sugar);
- have any of the following heart or cardiovascular conditions:
  - bradycardia (abnormally slow heart beat)
  - hypotension (unusually low blood pressure)
  - metabolic acidosis (when there is too much acid in the body's fluids)
  - poor blood circulation
  - sick sinus syndrome (a group of heart rhythm disorders);
  - untreated pheochromocytoma (a tumour condition in the adrenal glands)

- uncontrolled heart failure
- Prinzmetal's angina (a condition that produces chest pain and pressure while at rest)

**What the medicinal ingredient is:**

Propranolol hydrochloride

**What the important nonmedicinal ingredients are:**

Citric acid to adjust pH and water for injection. Preservative free.

**What dosage forms it comes in:**

Solution containing propranolol hydrochloride at a concentration of 1 mg/mL.

**WARNINGS AND PRECAUTIONS**

Propranolol Hydrochloride Injection USP is reserved for life-threatening arrhythmias or those occurring under anesthesia. Temporary maintenance with oral therapy may be indicated.

**BEFORE Propranolol Hydrochloride Injection USP is used tell your doctor if you:**

- have a heart condition;
- have poor circulation;
- have a history of serious allergies;
- have a history of skin reactions;
- are prone to chronic bronchitis and emphysema not related to allergies;
- have diabetes;
- have a condition involving an over-active thyroid gland
- have or have had a severe allergic condition involving the eyes and skin;
- have liver or kidney problems;
- are pregnant or intending to become pregnant;
- are nursing;
- are taking any other medications.

Propranolol Hydrochloride Injection USP is not recommended for children.

**INTERACTIONS WITH THIS MEDICATION**

If taken with some other medicines, the effects of Propranolol Hydrochloride Injection USP or the other medication may change. Tell your doctor or pharmacist if you are taking or have recently taken any other medications, including non-prescription medicines, vitamins, minerals, natural supplements, or alternative medicines.

Examples of drugs or substances that may interact with Propranolol Hydrochloride Injection USP include:

- Alcoholic beverages
- Diuretics (drugs used to increase urine output, such as hydrochlorothiazide)
- Drugs used to control heart rhythm, e.g., disopyramide, amiodarone, procainamide, quinidine, propafenone
- Warfarin (to thin the blood)

- Insulin
- Drugs used to reduce high blood pressure, e.g., guanethidine, clonidine, calcium channel blockers (verapamil, diltiazem, nifedipine)
- Rizatriptan and zolmitriptan (drugs used to treat migraine headaches)
- Digitalis glycosides (a drug used to control heart rate and rhythm)
- Epinephrine (a drug used to treat severe allergic reactions)
- Cimetidine (a drug used to treat stomach ulcers and pain)
- Chlorpromazine (a drug used to treat psychoses)
- Lidocaine (a drug used as a local anesthetic)
- Pain relief or anti-inflammatory drugs available with or without prescriptions such as ibuprofen
- Theophylline (a drug used for respiratory problems)
- Diazepam (a drug used for anxiety)

Please check with your doctor before taking any other medications with Propranolol Hydrochloride Injection USP.

**PROPER USE OF THIS MEDICATION**

**Usual dose:**

The usual dose is from 1 to 3 mg intravenously. If necessary, a second dose may be given after two minutes. Thereafter, additional drug should not be given in less than four hours.

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Like all medicines, Propranolol Hydrochloride Injection USP can cause side effects, although not everybody gets them.

The most common side effects are abdominal pain, nausea, vomiting, loss of appetite and diarrhea. Other side effects include disturbed sleep and nightmares, cold hands and feet, numbness and spasm in your fingers followed by warmth and pain (Raynaud’s phenomenon).

The most serious side effects with Propranolol Hydrochloride Injection USP are heart failure and bronchospasm (see When it should not be used and WARNINGS AND PRECAUTIONS).

The following table contains a list of side effects that may occur with Propranolol Hydrochloride Injection USP. The table does not include a complete list. Therefore, check with your doctor immediately if you notice or are bothered by any unusual symptoms.

<b>SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM</b>				
<b>Symptom / effect</b>		<b>Talk with your doctor or pharmacist</b>		<b>Stop taking drug and call your doctor or pharmacist</b>
		<b>Only if severe</b>	<b>In all cases</b>	
<b>Frequency unknown</b>	Allergic reactions (skin rash, hives, itching, swelling of the lips, face, tongue, throat, trouble breathing or swallowing, wheezing, blisters of the skin, sores or pain in the mouth or eyes)			✓
	Difficulty breathing and swollen ankles (Congestive heart failure)		✓	
	Abnormally low blood pressure, dizziness (particularly, when standing up), tiredness fainting		✓	
	Bronchospasm		✓	
	Weakness, insomnia, headache, fatigue	✓		
	Changes in mood, hallucinations, memory loss	✓		
	<b>Common</b>	Dry eyes, visual disturbances	✓	
	Abdominal pain, nausea, vomiting, diarrhea, loss of appetite	✓		
<b>Uncommon</b>	ringing in the ears		✓	
	Low level of sugar in the blood (hypoglycemia)	✓		

*This is not a complete list of side effects. For any unexpected effects while taking Propranolol Hydrochloride Injection USP, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Store between 15°C and 30°C. Discard unused portion.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701E  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

***NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.***

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Sandoz Canada Inc., at: 1-800-361-3062

or by written request at:  
145 Jules-Léger  
Boucherville QC  
J4B 7K8

Or by e-mail at :  
[medinfo@sandoz.com](mailto:medinfo@sandoz.com)

This leaflet was prepared by Sandoz Canada Inc.

Last revised: June 19, 2013.