

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Propranolol Injection BP 1 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Propranolol hydrochloride BP 1 mg

3. PHARMACEUTICAL FORM

Solution for Injection

A clear colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardiac Arrhythmias

Intravenous administration is usually reserved for life-threatening arrhythmias or those occurring under anaesthesia.

1. Supraventricular arrhythmias Intravenous propranolol is indicated for the short-term treatment of supraventricular tachycardia, including Wolff-Parkinson-White syndrome and thyrotoxicosis, to decrease ventricular rate. Use in patients with atrial flutter or atrial fibrillation should be reserved for arrhythmias unresponsive to standard therapy or when more prolonged control is required. Reversion to normal sinus rhythm has occasionally been observed, predominantly in patients with sinus or atrial tachycardia.
2. Ventricular tachycardias With the exception of those induced by catecholamines or digitalis, propranolol is not the drug of first choice. In critical situations when cardioversion techniques or other drugs are not indicated or are not effective, propranolol may be considered. If, after consideration of the risks involved, propranolol is used, it should be given intravenously in low dosage and very slowly, as the failing heart requires some sympathetic drive for maintenance of myocardial tone. Some patients may respond with complete reversion to normal sinus rhythm, but reduction in ventricular rate is more likely. Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. Intravenous propranolol is indicated for the treatment of persistent premature ventricular extra systoles that impair the well-being of the patient and do not respond to conventional measures.
3. Tachyarrhythmias of digitalis intoxication Intravenous propranolol is indicated to control ventricular rate in life-threatening digitalis-induced arrhythmias. Severe bradycardia may occur.
4. Resistant tachyarrhythmias due to excessive catecholamine action during anaesthesia Intravenous propranolol is indicated to abolish tachyarrhythmias due to excessive catecholamine action during anaesthesia when other measures fail. These arrhythmias may arise because of release of endogenous catecholamines or administration of catecholamines. All general inhalation anaesthetics produce some degree of myocardial depression. Therefore, when propranolol is used to treat arrhythmias during anaesthesia, it should be used with extreme caution, usually with constant monitoring of the ECG and central venous pressure.

4.2 Dosage and Method of Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

The usual dose is 1 to 3 mg administered under careful monitoring, such as electrocardiography and central venous pressure. The rate of administration should not exceed 1 mg (1 mL) per minute to diminish the possibility of lowering blood pressure and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the site of action even 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 should not be given when the desired alteration in rate or rhythm is achieved.

Transfer to oral therapy as soon as possible.

4.3 Contraindications:

Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; and 4) in patients with known hypersensitivity to propranolol hydrochloride.

4.4 Special warnings and precautions for use

Warnings:

Cardiac Failure

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, some have been shown to be highly beneficial when used with close follow-up in patients with a history of failure who are well compensated and are receiving additional therapies, including diuretics as needed. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

Nonallergic Bronchospasm (e.g., Chronic Bronchitis, Emphysema)

In general, patients with bronchospastic lung disease should not receive beta blockers. Propranolol should be administered with caution in this setting since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

Major Surgery

The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli in propranolol-treated patients might augment the risks of general anesthesia and surgical procedures.

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension.

Diabetes and Hypoglycemia

Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in labile insulin-dependent diabetics. In these patients, it may be more difficult to adjust the dosage of insulin.

Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting, as in preparation for surgery. Hypoglycemia has been reported after prolonged physical exertion and in patients with renal insufficiency.

Thyrotoxicosis

Beta-adrenergic blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T4 and reverse T3, and decreasing T3.

Wolff-Parkinson-White Syndrome

Beta-adrenergic blockade in patients with Wolff-Parkinson-White syndrome and tachycardia has been associated with severe bradycardia requiring treatment with a pacemaker. In one case this resulted after an initial 5 mg dose of intravenous propranolol.

Precautions:

General

Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol is not indicated for the treatment of hypertensive emergencies.

Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should be told that propranolol might interfere with the glaucoma screening test. Withdrawal may lead to a return of elevated intraocular pressure.

Risk of anaphylactic reaction. While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Angina Pectoris

There have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of propranolol therapy. Therefore, when discontinuance of propranolol is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without a physician's advice. If propranolol therapy is interrupted and exacerbation of angina occurs, it is usually advisable to reinstitute propranolol therapy and take other measures appropriate for the management of angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

4.5 Interaction with other Medicinal products and other forms of Interaction

Caution should be exercised when propranolol is administered with drugs that have an effect on CYP2D6, 1A2, or 2C19 metabolic pathways. Co-administration of such drugs with propranolol may lead to clinically relevant drug interactions and changes in its efficacy and/or toxicity.

Cardiovascular Drugs

Antiarrhythmics

Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol.

Quinidine increases the concentration of propranolol and produces a greater degree of clinical beta-blockade and may cause postural hypotension.

Disopyramide is a Type I antiarrhythmic drug with potent negative inotropic and chronotropic effects and has been associated with severe bradycardia, asystole and heart failure when administered with propranolol.

Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with propranolol.

The clearance of lidocaine is reduced when administered with propranolol. Lidocaine toxicity has been reported following coadministration with propranolol.

Caution should be exercised when administering propranolol with drugs that slow A-V nodal conduction, e.g. digitalis, lidocaine and calcium channel blockers.

Calcium Channel Blockers

Caution should be exercised when patients receiving a beta-blocker are administered a calcium-channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction.

There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers.

Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high degree heart block, and heart failure.

ACE Inhibitors

When combined with beta-blockers, ACE inhibitors can cause hypotension, particularly in the setting of acute myocardial infarction.

ACE inhibitors have been reported to increase bronchial hyperreactivity when administered with propranolol.

The antihypertensive effects of clonidine may be antagonized by beta-blockers. Propranolol should be administered cautiously to patients withdrawing from clonidine.

Alpha-blockers

Prazosin has been associated with prolongation of first dose hypotension in the presence of beta-blockers.

Postural hypotension has been reported in patients taking both beta-blockers and terazosin or doxazosin.

Reserpine

Patients receiving catecholamine-depleting drugs, such as reserpine, with propranolol should be closely observed for excess reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension. Administration of reserpine with propranolol may also potentiate depression.

Inotropic Agents

Patients on long-term therapy with propranolol may experience uncontrolled hypertension if administered epinephrine as a consequence of unopposed alpha-receptor stimulation. Epinephrine is therefore not indicated in the treatment of propranolol overdose.

Isoproterenol and Dobutamine

Propranolol is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. Also, propranolol may reduce sensitivity to dobutamine stress echocardiography in patients undergoing evaluation for myocardial ischemia.

Non-Cardiovascular Drugs**Non-Steroidal Anti-Inflammatory Drugs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been reported to blunt the antihypertensive effect of beta-adrenoreceptor blocking agents.

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and heart rate.

Antidepressants

The hypotensive effects of MAO inhibitors or tricyclic antidepressants may be exacerbated when administered with beta-blockers by interfering with the beta blocking activity of propranolol.

Anesthetic Agents

Methoxyflurane and trichloroethylene may depress myocardial contractility when administered with propranolol.

Warfarin

Administration of propranolol with warfarin increases the concentration of warfarin. Therefore, the prothrombin time should be monitored.

Neuroleptic Drugs

Hypotension and cardiac arrest have been reported with the concomitant use of propranolol and haloperidol.

Thyroxine

Thyroxine may result in a lower than expected T3 concentration when used concomitantly with propranolol.

Carcinogenesis and Mutagenesis and Impairment of Fertility

In dietary administration studies in which mice and rats were treated with propranolol hydrochloride for up to 18 months at doses of up to 150 mg/kg/day, there was no evidence of drug-related tumorigenesis. On a body surface area basis, this dose in the mouse and rat is, respectively, about equal to and about twice the maximum recommended human oral daily dose (MRHD) of 640 mg propranolol hydrochloride. In a study in which both male and female rats were exposed to propranolol hydrochloride in their diets at concentrations of up to 0.05% (about 50 mg/kg body weight and less than the MRHD), from 60 days prior to mating and throughout pregnancy and lactation for two generations, there were no effects on fertility. Based on differing results from Ames Tests performed by different laboratories, there is equivocal evidence for a genotoxic effect of propranolol hydrochloride in bacteria (*S. typhimurium* strain TA 1538).

4.6 Pregnancy and Lactation

Pregnancy

Pregnancy Category C

In a series of reproductive and developmental toxicology studies, propranolol hydrochloride was given to rats by gavage or in the diet throughout pregnancy and lactation. At doses of 150 mg/kg/day, but not at doses of 80 mg/kg/day (equivalent to the MRHD on a body surface area basis), treatment was associated with embryotoxicity (reduced litter size and increased resorption rates) as well as neonatal toxicity (deaths). Propranolol hydrochloride also was administered (in the feed) to rabbits (throughout pregnancy and lactation) at doses as high as 150 mg/kg/day (about 5 times the maximum recommended human oral daily dose). No evidence of embryo or neonatal toxicity was noted.

There are no adequate and well-controlled studies in pregnant women. Intrauterine growth retardation has been reported for neonates whose mothers received propranolol hydrochloride during pregnancy. Neonates whose mothers received propranolol hydrochloride at parturition have exhibited bradycardia, hypoglycemia, and respiratory depression. Adequate facilities for monitoring such infants at birth should be available. Propranolol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Propranolol is excreted in human milk. Caution should be exercised when propranolol is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of propranolol in pediatric patients have not been established.

Geriatric Use

Clinical studies of intravenous propranolol did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly subjects have decreased clearance and a longer mean elimination half-life. These findings suggest that dose adjustment of propranolol injection may be required for elderly patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Insufficiency

Propranolol is extensively metabolized by the liver. Compared to normal subjects, patients with chronic liver disease have decreased clearance of propranolol, increased volume of distribution, decreased protein-binding and considerable variation in half life. Consideration should be given to lowering the dose of intravenously administered propranolol in patients with hepatic insufficiency.

4.7 Effects on ability to drive and use machines

None Know

4.8 Undesirable effects

The following adverse events have been reported with use of formulations of sustained- or immediate-release oral propranolol and may be expected with intravenous propranolol.

Cardiovascular

Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System

Lightheadedness; mental depression manifested by insomnia; lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations, vivid dreams, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose-related.

Gastrointestinal

Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic

Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory

Bronchospasm.

Hematologic

Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Autoimmune

In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous

Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta-blocker (practolol) have not been associated with propranolol.

4.9 Overdose

Propranolol is not significantly dialyzable. In the event of overdosage or exaggerated response, the following measures should be employed:

Hypotension and bradycardia have been reported following propranolol overdose and should be treated appropriately. Glucagon can exert potent inotropic and chronotropic effects and may be particularly useful for the treatment of hypotension or depressed myocardial function after a propranolol overdose. Glucagon should be administered as 50 to 150 mcg/kg intravenously followed by continuous drip of 1 to 5 mg/hour for positive chronotropic effect. Isoproterenol, dopamine, or phosphodiesterase inhibitors may also be useful. Epinephrine, however, may provoke uncontrolled hypertension. Bradycardia can be treated with atropine or isoproterenol. Serious bradycardia may require temporary cardiac pacing.

The electrocardiogram, pulse, blood pressure, neurobehavioral status and intake and output balance must be monitored. Isoproterenol and aminophylline may be useful for bronchospasm.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

As propranolol concentration increases, so does its beta-blocking effect, as evidenced by a reduction in exercise-induced tachycardia (n=6 normal volunteers).

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•mcg/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.

5.2 Pharmacokinetic properties

Distribution

Propranolol has a distribution half-life (T_{1/2} alpha) of 5 to 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 alpha₁ glycoprotein and the R-isomer is preferentially bound to albumin.

Metabolism and Elimination

The elimination half-life (T_{1/2} alpha) 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 to 50% of metabolites, and ring oxidative products account for approximately 10 to 15% of metabolites. Of these, only the primary ring oxidative product (4-hydroxypropranolol) possesses beta-adrenergic receptor blocking activity.

5.3 Preclinical safety data

Not known

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, Water for Injection

6.2 Incompatibilities

Not known

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container and special equipment for use, administration or implantation

10 x 1 ml Amber ampoule USP type-I ampoule packed in a carton with literature.

6.6 Special precautions for disposal <and other handling>

None.

7. MARKETING AUTHORISATION HOLDER

Ciron Drugs & Pharmaceuticals Pvt. Ltd.
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Jay Coach Junction, Western Express Highway, Goregaon (East)
Mumbai- 400 063, India.

8. MARKETING AUTHORISATION NUMBER(S)

08158/07645/NMR/2019

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/11/2022

10. DATE OF REVISION OF THE TEXT

14/07/2023

11. Reference

<https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=f14ea537-dd5c-4c78-9037-9a85e9e610ef&type=display#:~:text=Propranolol%20Hydrochloride%20Injection%2C%20USP%20is,4.0%20with%20citric%20acid%20monohydrate>