

# CARDINOL

10mg, 40mg &160mg tablets

Propranolol hydrochloride

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## Presentation

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Tablets each containing 10mg propranolol hydrochloride BP. Red film coated, biconvex round tablets, 9/32" diameter, imprinted "PL 10" with a bisect on one side.

Tablets each containing 40mg propranolol hydrochloride BP. Red film coated, biconvex round tablets, 11/32" diameter, imprinted "PL 40" with a bisect on one side.

Tablets each containing 160mg propranolol hydrochloride BP. Red film coated, biconvex round tablets, 7/16" diameter, imprinted "PL 160" with a bisect on one side.

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## Uses

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### Actions

Propranolol is a competitive antagonist at both the beta<sub>1</sub> and beta<sub>2</sub>-adrenoreceptors. It has no agonist activity at the beta-adrenoreceptor but has membrane stabilising activity at concentrations exceeding 1 to 3 mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta-adrenoreceptor blockade has been demonstrated in man by a parallel shift to the right in the dose-heart rate response curve to beta-agonists such as isoprenaline.

Propranolol, as with other beta-adrenoreceptor blocking medicines, has negative inotropic effects, and is therefore contraindicated in uncontrolled heart failure.

Propranolol is a racemic mixture and the active form is the S(-) isomer of propranolol. With the exception of inhibition of the conversion of thyroxine to triiodothyronine it is unlikely that any additional ancillary properties possessed by R(+) propranolol, in comparison with the racemic mixture, will give rise to different therapeutic effects.

Propranolol is effective and well-tolerated in most ethnic populations, although the response may be less in Afro-Caribbean black patients.

### Pharmacokinetics

Following intravenous administration the plasma half-life of propranolol is about 2 hours and the ratio of metabolites to parent medicine in the blood is lower than after oral administration. In particular 4-hydroxy propranolol is not present after intravenous administration.

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1 to 2 hours after dosing in fasting patients. The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 6 hours. Propranolol is widely and rapidly distributed throughout the body with highest levels occurring in the lungs, liver, kidney, brain and heart. Propranolol is highly protein bound (80 to 95%).

Since the half-life may be increased in patients with significant hepatic or renal impairment, care should be taken when starting treatment and selecting the initial dose.

### Indications

CARDINOL, a beta-adrenoreceptor blocking medicine, is indicated in the following:

- Control of essential and renal hypertension.

- Management of angina pectoris.
- Long term prophylaxis after recovery from acute myocardial infarction.
- Control of most forms of cardiac dysrhythmias.
- Prophylaxis of migraine.
- Management of essential tremor.
- Control of anxiety and anxiety tachycardia.
- Adjunctive management of thyrotoxicosis and thyrotoxic crisis.
- Management of hypertrophic obstructive cardiomyopathy.
- Management of phaeochromocytoma (with an alpha-adrenoreceptor blocking medicine).

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## Dosage and Administration

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### Adults

Oral Dosage

#### Hypertension

A starting dose of 80mg twice a day may be increased at weekly intervals according to response. The usual dose range is 160 to 320mg per day. With concurrent diuretic or other antihypertensive medicines a further reduction of blood pressure is obtained.

#### Angina, Anxiety, Migraine and Essential Tremor

A starting dose of 40mg two or three times daily may be increased by the same amount at weekly intervals according to patient response. An adequate response in anxiety, migraine and essential tremor is usually seen in the range 80 to 160 mg/day and in angina in the range 120 to 240 mg/day.

#### Dysrhythmias, Anxiety Tachycardia, Hypertrophic Obstructive Cardiomyopathy and Thyrotoxicosis

A dosage range of 10 to 40mg three or four times a day usually achieves the required response.

#### Post Myocardial Infarction

Treatment should start between days 5 and 21 after myocardial infarction, with an initial dose of 40mg four times a day for 2 or 3 days. In order to improve compliance the total daily dosage may thereafter be given as 80mg twice a day.

#### Phaeochromocytoma

(To be used only with an alpha-adrenoreceptor blocking medicine).

#### Pre-Operative

60mg daily for three days is recommended.

#### Non-Operable Malignant Cases

30mg daily.

### Elderly

Evidence concerning the relation between blood level and age is conflicting. With regard to the elderly, the optimum dose should be individually determined according to clinical response.

### Children

Dosage should be individually determined and the following is only a guide.

#### Dysrhythmias, Phaeochromocytoma, Thyrotoxicosis

Oral

0.25 to 0.5 mg/kg three or four times daily as required.

## **Migraine**

Oral

Under the age of 12: 20mg two or three times daily.

Over the age of 12: the adult dose.

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## **Contraindications**

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Propranolol must not be used if there is a history of bronchial asthma or bronchospasm.

Propranolol as with other beta-adrenoreceptor blocking medicines must not be used in patients with any of the following: known hypersensitivity to the substance; bradycardia; cardiogenic shock; hypotension; metabolic acidosis; after prolonged fasting; severe peripheral arterial circulatory disturbances; second or third degree heart block; sick sinus syndrome; untreated phaeochromocytoma; uncontrolled heart failure; Prinzmetal's angina.

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## **Warnings and Precautions**

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The intravenous injection is intended for the emergency treatment of cardiac dysrhythmias and thyrotoxic crisis only.

Special care should be taken with patients whose cardiac reserve is poor. Beta-adrenoreceptor blocking medicines should be avoided in overt heart failure (see Contraindications). However, they may be used in patients whose signs of failure have been controlled.

Propranolol is contraindicated in severe peripheral arterial circulatory disturbances and may also aggravate less severe peripheral arterial circulatory disturbances.

Due to its negative effect on conduction time, caution must be exercised if propranolol is given to patients with first degree heart block.

Propranolol modifies the tachycardia of hypoglycaemia. Caution should be exercised in the concurrent use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

Propranolol may mask the signs of thyrotoxicosis. One of the pharmacological actions of beta-adrenoreceptor blocking medicines is to reduce heart rate. In the rare instance when symptoms may be attributable to the slow heart rate, the dose may be reduced.

In patients suffering from ischaemic heart disease, as with other beta-adrenoreceptor blocking medicines, treatment should not be discontinued abruptly. Either the equivalent dosage of another beta-adrenoreceptor blocking medicine may be substituted or the withdrawal of propranolol should be gradual.

Propranolol may cause a more severe reaction to a variety of allergens, when given to patients with a history of anaphylactic reaction to such allergens. Such patients may be unresponsive to the usual doses of adrenaline used to treat the allergic reactions.

Since the half-life may be increased in patients with significant hepatic or renal impairment, caution must be exercised when starting treatment and selecting the initial dose.

Propranolol must be used with caution in patients with decompensated cirrhosis.

In patients with portal hypertension, liver function may deteriorate and hepatic encephalopathy may develop. Propranolol may increase the risk of hepatic encephalopathy.

### **Anaesthesia**

Caution must be exercised when using anaesthetic agents with propranolol. It may be decided to

discontinue therapy with beta-adrenoreceptor blocking medicines before surgery, in which case a gradual withdrawal is recommended. If it is decided not to discontinue therapy with beta-adrenoreceptor blocking medicines before surgery, care should be taken when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be the agent with as little negative inotropic activity as possible. Use of beta-adrenoreceptor blocking medicines with anaesthetic medicines may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

### **Pregnancy**

As with all other medicines, propranolol should not be given in pregnancy unless its use is essential. There is no evidence of teratogenicity with propranolol. However, beta-adrenoreceptor blocking medicines reduce placental perfusion, which may result in intra-uterine foetal death, immature and premature deliveries. In addition, adverse effects (especially hypoglycaemia and bradycardia in the neonate and bradycardia in the foetus) may occur. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period.

### **Lactation**

Most beta-adrenoreceptor blocking medicines, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breastfeeding is therefore not recommended following administration of these compounds.

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## **Adverse Effects**

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Propranolol is usually well tolerated. In clinical studies, the undesired events reported are usually attributable to the pharmacological actions of propranolol.

The following undesired events, listed by body system, have been reported:

### **Cardiovascular**

Bradycardia; heart failure deterioration; postural hypotension which may be associated with syncope; cold extremities. In susceptible patients: precipitation of heart block; exacerbation of intermittent claudication; Raynaud's phenomenon.

### **CNS**

Confusion; dizziness; mood changes; nightmares; psychoses and hallucinations; sleep disturbances.

### **Endocrine**

Hypoglycaemia in children.

### **Gastrointestinal**

Gastrointestinal disturbance.

### **Haematological**

Purpura; thrombocytopenia.

### **Integumentary**

Alopecia; dry eyes; psoriasiform skin reactions; exacerbation of psoriasis; skin rashes.

### **Neurological**

Paraesthesia.

### **Respiratory**

Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome (see Contraindications).

### **Special Senses**

Visual disturbances.

## Others

Fatigue and/or lassitude (often transient); an increase in ANA (Antinuclear Antibodies) has been observed, however the clinical relevance of this is not clear. Discontinuance of the medicine should be considered if, according to clinical judgement, the well-being of the patient is adversely affected by any of the above reactions. Cessation of therapy with a beta-adrenoreceptor blocking medicine should be gradual. In the rare event of intolerance, manifested as bradycardia and hypotension, the medicine should be withdrawn and, if necessary, treatment for overdosage instituted.

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## Interactions

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Propranolol modifies the tachycardia of hypoglycaemia. Caution must be exercised in the concurrent use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

Care must be exercised in prescribing a beta-adrenoreceptor blocking medicine with Class I antidysrhythmic agents such as disopyramide.

Digitalis glycosides in association with beta-adrenoreceptor blocking medicines may increase atrioventricular conduction time.

Combined use of beta-adrenoreceptor blocking medicines and calcium channel blockers with negative inotropic effects (e.g. verapamil, 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-adrenoreceptor blocking medicine nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridines e.g. nifedipine, may increase the risk of hypotension, and cardiac failure may occur in patients with latent cardiac insufficiency. Concomitant use of sympathomimetic agents e.g. adrenalin, may counteract the effect of beta-adrenoreceptor blocking medicines. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking beta-adrenoreceptor blocking medicines as, in rare cases, vasoconstriction, hypertension and bradycardia may result.

Administration of propranolol during infusion of lignocaine may increase the plasma concentration of lignocaine by about 30%. Patients already receiving propranolol tend to have higher lignocaine levels than controls. The combination should be avoided.

Concomitant use of cimetidine or hydralazine will increase, whereas concomitant use of alcohol will decrease, the plasma levels of propranolol.

Beta-adrenoreceptor blocking medicines may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicines are co-administered, the beta-adrenoreceptor blocking medicine should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-adrenoreceptor blocking medicine therapy, the introduction of beta-adrenoreceptor blocking medicine should be delayed for several days after clonidine administration has stopped (also see prescribing information for clonidine).

Caution is necessary if ergotamine, dihydroergotamine or related compounds are given in combination with propranolol since vasospastic reactions have been reported in a few patients.

Concomitant use of prostaglandin synthetase inhibiting medicines e.g. ibuprofen and indomethacin, may decrease the hypotensive effects of propranolol.

Concomitant administration of propranolol and chlorpromazine may result in an increase in plasma levels of both medicines. This may lead to an enhanced antipsychotic effect for chlorpromazine and an increased antihypertensive effect for propranolol.

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## Overdosage

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The symptoms of overdosage may include bradycardia, hypotension, acute cardiac insufficiency and bronchospasm.

General treatment should include close supervision, treatment in an intensive care ward, the use of gastric lavage, activated charcoal and a laxative to prevent absorption of any medicine still present in the gastrointestinal tract, the use of plasma or plasma substitutes to treat hypotension and shock.

Excessive bradycardia can be countered with atropine 1 to 2mg intravenously and/or a cardiac pacemaker. If necessary, this may be followed by a bolus dose of glucagon 10mg intravenously. If required, this may be repeated or followed by an intravenous infusion of glucagon 1 to 10 mg/hour depending on response. If no response to glucagon occurs or if glucagon is unavailable, a beta-adrenoreceptor stimulant such as dobutamine 2.5 to 10 micrograms/kg/minute by intravenous infusion may be given.

Dobutamine, because of its positive inotropic effect could also be used to treat hypotension and acute cardiac insufficiency. It is likely that these doses would be inadequate to reverse the cardiac effects of beta-adrenoreceptor blockade if a large overdose has been taken. The dose of dobutamine should therefore be increased if necessary to achieve the required response according to the clinical condition of the patient.

Bronchospasm can usually be reversed by beta-2 agonist bronchodilators such as salbutamol; large doses may be required and the dose should be titrated according to the clinical response. Oxygen or artificial ventilation may be required in some cases.

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## Pharmaceutical Precautions

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CARDINOL tablets should be stored below 25°C, protected from light and moisture.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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Tablets 10mg: Bottles of 100's and 500's (not currently marketed).

Tablets 40mg: Bottles of 100's and 500's (not currently marketed).

Tablets 160mg: Bottles of 50's (not currently marketed).

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## Further Information

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## Name and Address

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**Date of Preparation**

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2 February 2009