NEW ZEALAND DATA SHEET

CARDINOL LA

1. Product Name

CARDINOL LA, 160mg, modified release capsule.

2. Qualitative and Quantitative Composition

Each modified release capsule contains 160mg of propranolol hydrochloride BP.

Excipient with known effect: Sugars

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

CARDINOL LA is presented as size 1 gelatin capsules with a clear colourless body and opaque, green cap containing cream and white pellets.

CARDINOL LA capsules contain spheroids of the beta-blocker propranolol hydrochloride which have a sustained release coating to provide long action.

4. Clinical Particulars

4.1 Therapeutic indications

CARDINOL LA is indicated for the following:

1. Control of hypertension.

2 Management of angina pectoris.

3. Long term prophylaxis after recovery from acute myocardial infarction.

4.2 Dose and method of administration

Adults

Hypertension

The starting dose is one capsule daily, taken either morning or evening. An adequate response is seen in most patients at this dosage. If necessary, it can be increased to two capsules and a further reduction in blood pressure can be attained if a diuretic or other antihypertensive agent is given in addition to CARDINOL LA.

Angina

An adequate response is usually obtained with one capsule daily either morning or evening, dependant on patient convenience.

Post Myocardial infarction

Treatment should start between days 5 and 21 after myocardial infarction with one 40 mg propranolol tablet four times a day for 2 or 3 days.

In order to achieve maximum compliance, the total daily dosage of 160 mg propranolol may thereafter be given as a single CARDINOL LA capsule. Compliance is extremely important as beta-blockade may have to be continued indefinitely.

Special populations

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

CARDINOL LA is not recommended for use in children.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

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

Bronchospasm can usually be reversed by $beta_2$ agonist bronchodilators such as salbutamol. Large doses of the $beta_2$ agonist bronchodilator may be required to overcome the beta blockade produced by propranolol and the dose should be titrated according to the clinical response; both intravenous and inhalational administration should be considered. The use of intravenous aminophylline and/or the use of ipratropium (given by nebuliser) may also be considered. Glucagon (1 to 2 mg given intravenously) has also been reported to produce a bronchodilator effect in asthmatic patients. Oxygen or artificial ventilation may be required in severe cases.

Propranolol as with other beta-blockers must not be used in patients with any of the following conditions: 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.

Propranolol must not be used in patients prone to hypoglycaemia, i.e., patients after prolonged fasting or patients with restricted counter-regulatory reserves. Patients with restricted counter-regulatory reserves may have reduced autonomic and hormonal responses to hypoglycaemia which includes glycogenolysis, gluconeogenesis and/or impaired modulation of insulin secretion. Patients at risk for an inadequate response to hypoglycaemia includes individuals with malnutrition, prolonged fasting, starvation, chronic liver disease, diabetes and concomitant use of drugs which block the full response to catecholamines.

4.4 Special warnings and precautions for use

Propranolol as with other beta-blockers:

- although contraindicated in uncontrolled heart failure, may be used in patients whose signs of heart failure have been controlled. Caution must be exercised in patients whose cardiac reserve is poor.

- should not be used in combination with calcium channel blockers with negative inotropic effects (e.g. verapamil, diltiazem), as it 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 intravenously within 48 hours of discontinuing the other.

- although contraindicated in severe peripheral arterial circulatory disturbances, 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.

- may block/modify the signs and symptoms of hypoglycaemia (especially tachycardia). Propranolol occasionally causes hypoglycaemia, even in non-diabetic patients, e.g., neonates, infants, children, elderly patients, patients on haemodialysis or patients suffering from chronic liver disease and patients suffering from overdose. Severe hypoglycaemia associated with propranolol has rarely presented with seizures and/or coma in isolated patients. Caution must be exercised in the concurrent use of propranolol and hypoglycaemic therapy in diabetic patients. Propranolol may prolong the hypoglycaemic response to insulin.

- may mask the signs of thyrotoxicosis.

- should not be used in untreated phaeochromocytoma. However, in patients with phaeochromocytoma, an alpha-blocker may be given concomitantly.

- will reduce heart rate as a result of its pharmacological action. In the rare instances when a treated patient develops symptoms that may be attributable to a slow heart rate, the dose may be reduced.

- 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.

Abrupt withdrawal of beta-blockers is to be avoided. The dosage should be withdrawn gradually over a period of 7 to 14 days. An equivalent dosage of another beta-blocker may be substituted during the withdrawal period to facilitate a reduction in dosage below that of CARDINOL LA 160 mg. Patients should be followed during withdrawal especially those with ischaemic heart disease.

When a patient is scheduled for surgery and a decision is made to discontinue beta-blocker therapy, this should be done at least 24 hours prior to the procedure. The risk/benefit of stopping beta blockade should be made for each patient.

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. There have been reports suggesting that treatment with propranolol may increase the risk of developing hepatic encephalopathy.

Interference with laboratory tests: Propranolol has been reported to interfere with the estimation of serum bilirubin by the diazo method and with the determination of catecholamines by methods using fluorescence.

4.5 Interaction with other medicines and other forms of interaction

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.

Simultaneous administration of rizatriptan and propranolol can cause an increased rizatriptan AUC and C_{max} by approximately 70 - 80%. The increased rizatriptan exposure is presumed to be caused by inhibition of first-passage 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.

Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have potentiating effect on atrial-conduction time and induce negative inotropic effect.

Digitalis glycosides in association with beta blockers may increase atrioventricular conduction time.

Combined use of beta-blockers 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 sino-atrial or atrio-ventricular conduction abnormalities. This may result in severe hypotension, bradycardia and cardiac failure. Neither the beta-blocker nor the calcium channel blocker should be administered intravenously within 48 hours of discontinuing the other.

Concomitant therapy with dihydropyridine calcium channel blockers 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. adrenaline, may counteract the effect of beta-blockers. Caution must be exercised in the parenteral administration of preparations containing adrenaline to patients taking beta-blockers 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 plasma levels of propranolol, and concomitant use of alcohol may increase the plasma levels of propranolol.

Beta-blockers may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. If the two medicines are co-administered, the beta-blocker should be withdrawn several days before discontinuing clonidine. If replacing clonidine by beta-blocker therapy, the introduction of beta-blockers should be delayed for several days after clonidine administration has stopped.

Caution must be exercised 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 indometacin, 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.

Caution must be exercised when using anaesthetic agents with propranolol. The anaesthetist should be informed and the choice of anaesthetic should be an agent with as little negative inotropic activity as possible. Use of beta-blockers with anaesthetic drugs may result in attenuation of the reflex tachycardia and increase the risk of hypotension. Anaesthetic agents causing myocardial depression are best avoided.

Pharmacokinetic studies have shown that the following agents may interact with propranolol due to effects on the enzyme systems in the liver which metabolise propranolol and these agents: quinidine, propafenone, rifampicin, theophylline, warfarin, thioridazine, and dihydropyridine calcium channel blockers such as nifedipine, nisoldipine, nicardipine, isradipine and lacidipine. Owing to the fact that blood concentrations of either agent may be affected, dosage adjustments may be needed according to clinical judgement (see also the interaction above concerning concomitant therapy with dihydropyridine calcium channel blockers).

4.6 Fertility, pregnancy and lactation

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-blockers 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.

Breast-feeding

Most beta-blockers, particularly lipophilic compounds, will pass into breast milk although to a variable extent. Breast feeding is therefore not recommended following administration of these compounds.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

The use of propranolol is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable effects

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. The following definitions of frequencies are used:

Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ class	Frequency	Undesirable Effect
Blood and lymphatic system disorders	Rare	Thrombocytopaenia
Endocrine disorders	Not known	Hypoglycaemia in neonates, infants, children, elderly patients, patients on haemodialysis, patients on concomitant antidiabetic therapy, patients with prolonged fasting and patients with chronic liver disease has been reported, seizure linked to hypoglycaemia
Nervous system disorders	Common	Sleep disturbances, nightmares
	Rare	Hallucinations, psychoses, mood changes, confusion, memory loss, paraesthesia
	Very rare	Isolated reports of myasthenia gravis like syndrome or exacerbation of myasthenia gravis have been reported
Eye disorders	Rare	Dry eyes, visual disturbances

Cardiovascular disorders	Common	Bradycardia, cold extremities, Raynaud's phenomenon
	Rare	Heart failure, deterioration, precipitation of heart block, postural hypotension, which may be associated with syncope, exacerbation of intermittent claudication
Respiratory, thoracic and mediastinal disorders	Rare	Bronchospasm may occur in patients with bronchial asthma or a history of asthmatic complaints, sometimes with fatal outcome
Gastrointestinal disorders	Uncommon	Gastrointestinal disturbances, such as nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Rare	Purpura, alopecia, psoriasiform skin reactions, exacerbation of psoriasis, skin rashes
General disorders and administration site conditions	Common	Fatigue and/or lassitude (often transient)
	Rare	Dizziness
Investigations	Very rare	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-blocker 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Propranolol is known to cause severe toxicity when used in overdose. Patients should be informed of the signs of overdose and advised to seek urgent medical assistance if an overdose of propranolol has been taken.

Clinical features:

Cardiac

Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. QRS complex prolongation, ventricular tachycardia, first to third degree AV block, ventricular fibrillation or asystole may also occur. Development of cardiovascular complications is more likely if other cardioactive drugs, especially calcium channel blockers, digoxin, cyclic antidepressants or neuroleptics have also been ingested. Older patients and those with underlying ischaemic heart disease are at risk of developing severe cardiovascular compromise.

CNS

Drowsiness, confusion, seizures, hallucinations, dilated pupils and in severe cases coma may occur. Neurological signs such as coma or absence of pupil reactivity are unreliable prognostic indicators during resuscitation.

Other features

Bronchospasm, hyperkalaemia and occasionally CNS-mediated respiratory depression may occur.

Management

In cases of overdose or extreme falls in heart rate or blood pressure, treatment with propranolol must be stopped. Management should include general symptomatic and supportive measures including a clear airway and monitoring of vital signs until stable. In symptomatic patients, or patients with an abnormal ECG, early discussion with critical care should be considered.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: beta blocking agents, ATC code: C07AA05

Mechanism of action

Propranolol is a competitive antagonist at both the $beta_1$ and $beta_2$-adrenoceptors. It has no agonist activity at the beta-adrenoceptor, but has membrane stabilising activity at concentrations exceeding 1 to 3 mg/litre, though such concentrations are rarely achieved during oral therapy. Competitive beta 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-blockers, 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. 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.

Clinical efficacy and safety

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

The sustained release preparation of propranolol maintains a higher degree of $beta_1$-blockade 24 hours after dosing compared with conventional propranolol.

5.2 Pharmacokinetic properties

Absorption

Propranolol is completely absorbed after oral administration and peak plasma concentrations occur 1 to 2 hours after dosing in fasting patients. Following oral dosing with the sustained release preparation of propranolol the blood profile is flatter than after conventional propranolol but the half-life is increased to between 10 and 20 hours.

Distribution

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%).

Elimination

The liver removes up to 90% of an oral dose with an elimination half-life of 3 to 6 hours.

5.3 Preclinical safety data

Propranolol is a drug on which extensive clinical experience has been obtained. All relevant information for the prescriber is provided elsewhere in this data sheet.

6. Pharmaceutical Particulars

6.1 List of excipients

- sucrose
- maize starch
- talc
- shellac
- gelatin capsule.

Contains sugars and sulfites.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blister pack: 2 years.

Bottle pack: 2 years.

6.4 Special precautions for storage

Blister pack: store at or below 30°C.

Bottle pack: store at or below 25°C.

6.5 Nature and contents of container

Blister pack of 30 capsules.

HDPE bottle with a tamper evident PP cap. Pack-size of 100 capsules.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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AUCKLAND
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Telephone 0800 168 169

9. Date of First Approval

22 February 1984

10. Date of Revision of the Text

18 July 2022

Summary table of changes

Section	Summary of new information
Header	Logo updated
2	Addition of excipient with known effect
6.1	Removal of gluten and lactose free statement Addition of sugar and sulfites allergen declaration statement
9	Sponsor details updated