PRODUCT MONOGRAPH

[Pr] LUPIN-PROPRANOLOL LA

(Propranolol Hydrochloride)

Extended-Release Capsules USP
60 mg, 80 mg, 120 mg and 160 mg

Beta-Adrenergic Receptor Blocking Agent

Date of Preparation: August 28, 2019

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Control No. 204042

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Oral	**Extended-release Capsules** 60 mg 80 mg 120 mg 160 mg	*D & C Red 28, Ethylcellulose, FD & C Blue 1, Gelatin, Hypromellose, Povidone, Sodium Lauryl sulphate, Sugar spheres, Talc, Titanium dioxide, Triethyl Citrate.*

INDICATIONS AND CLINICAL USE

LUPIN-PROPRANOLOL LA (propranolol hydrochloride) extended-release capsules are indicated as maintenance therapy in the treatment of hypertension and for the prophylaxis of angina pectoris.

As with conventional propranolol hydrochloride tablets, LUPIN-PROPRANOLOL LA capsules are compatible with thiazide-like diuretics and/or peripheral vasodilators. Combinations of propranolol hydrochloride extended-release capsules with thiazide-like diuretics and/or peripheral vasodilators have been shown to be generally more effective than LUPIN-PROPRANOLOL LA alone.

Initial treatment and individual titration of dosage must always be carried out with conventional propranolol hydrochloride tablets. The long-acting formulation may then be used for maintenance therapy, provided the dosage requirement is suitable.

LUPIN-PROPRANOLOL LA is not indicated for the emergency treatment of hypertensive crises.

Geriatrics: There is no information available for elderly patients.

Pediatrics: LUPIN-PROPRANOLOL LA is not recommended for use in children (see **WARNINGS AND PRECAUTIONS, Special Populations**).

CONTRAINDICATIONS

LUPIN-PROPRANOLOL LA capsules are contraindicated in patients who are hypersensitive to LUPIN-PROPRANOLOL LA (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.

LUPIN-PROPRANOLOL LA is also contraindicated in:

- Patients with a history of or current reports of bronchial asthma or bronchospasm;
- Allergic rhinitis during the pollen season;
- Sinus bradycardia and greater than first degree 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;
- Patients prone to hypoglycaemia, i.e. after prolonged fasting or patients with impaired capacity to counter-regulate a possible hypoglycaemic event.
- As with other beta-blockers, LUPIN-PROPRANOLOL LA 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

General

LUPIN-PROPRANOLOL LA is intended for the maintenance therapy of hypertension and for prophylaxis of angina pectoris. It is not indicated for initial or emergency treatment of these conditions. It should be substituted for conventional propranolol hydrochloride tablets only when the dose requirement is suitable (see **DOSAGE AND ADMINISTRATION**).

The combination of LUPIN-PROPRANOLOL LA with a thiazide-like diuretic and/or peripheral vasodilator produces a greater fall in blood pressure than either drug alone. The same degree of blood pressure control can be achieved by lower than usual dosages of each drug. Therefore, when using such combined therapy, careful monitoring of the dosage is required until the patient is stabilized (see **DRUG INTERACTIONS**).

Cardiovascular

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.

LUPIN-PROPRANOLOL LA acts selectively without completely 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 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 fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, LUPIN-PROPRANOLOL LA should be withdrawn immediately; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and closely followed until the threat of cardiac failure is over.

Peripheral Arterial Circulatory Disturbances: Although contraindicated in severe peripheral arterial circulatory disturbances (see **CONTRAINDICATIONS**), LUPIN-PROPRANOLOL LA, as with other beta-blockers, may also aggravate less severe peripheral arterial circulatory disturbances.

Wolff- Parkinson-White Syndrome: LUPIN-PROPRANOLOL LA 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.

Cardiac Arrhythmias: It has been reported that administration of propranolol hydrochloride tablets to control cardiac arrhythmias in acute myocardial infarction has caused a marked

reduction in cardiac output. Caution should be exercised when administering propranolol hydrochloride tablets 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.

Abrupt Cessation of LUPIN-PROPRANOLOL LA Therapy in Angina Pectoris or Ischaemic Heart Disease: Severe exacerbation of angina and the occurrence of

myocardial infarction have been reported in some patients with angina pectoris following abrupt discontinuation of propranolol hydrochloride therapy. Therefore, when discontinuation of

LUPIN-PROPRANOLOL LA is planned in patients with angina pectoris or ischaemic heart disease, the dosage should be gradually reduced over a period of at least two weeks and the patient should be carefully monitored.

Discontinuation of LUPIN-PROPRANOLOL LA can be achieved by substituting LUPIN-PROPRANOLOL LA 60, 80, 120 and 160 mg by the equivalent dose of conventional propranolol hydrochloride tablets spread throughout the day, and then gradually reducing the dose. In situations of greater urgency, propranolol hydrochloride tablets or LUPIN-PROPRANOLOL LA dosage should be reduced stepwise in four days, under close observation. If angina markedly worsens, or acute coronary insufficiency develops, it is recommended that treatment with conventional propranolol hydrochloride tablets be reinstituted promptly, at least temporarily. In addition, patients with angina pectoris or ischaemic heart disease should be warned against abrupt discontinuation of propranolol hydrochloride.

Respiratory

Patients Prone to Non-allergic Bronchospasm (e.g., chronic bronchitis, emphysema, bronchiectasis): LUPIN-PROPRANOLOL LA capsules should be administered with caution since they may block the bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-adrenergic receptors. Bronchospasm can usually be reversed by beta-2-agonist bronchodilators such as salbutamol. Large doses of the beta-2-agonist bronchodilators may be required to overcome the beta-blockade produced by LUPIN-PROPRANOLOL LA 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.

Central Nervous System

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

Endocrine and Metabolism

Thyrotoxicosis, Hyperthyroidism: Possible deleterious effects from long-term use of propranolol hydrochloride extended-release capsules have not yet been adequately appraised in patients with thyrotoxicosis. Special consideration should be given to the potential of propranolol hydrochloride to aggravate congestive heart failure.

LUPIN-PROPRANOLOL LA may mask the clinical signs of developing or continuing hyperthyroidism or its complications, and give a false impression of improvement. Therefore, abrupt withdrawal of LUPIN-PROPRANOLOL LA may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This may be another instance where

LUPIN-PROPRANOLOL LA should be withdrawn slowly by reducing the 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 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.

Peri-operative Considerations

In patients undergoing elective or emergency surgery: The management of angina patients taking beta-blockers and requiring elective or emergency surgery is controversial because the beta adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.

However, the abrupt discontinuation of propranolol hydrochloride may be followed by severe complications (see **WARNINGS, Abrupt Cessation of LUPIN-PROPRANOLOL LA Therapy in Angina Pectoris or Ischaemic Heart Disease**). Some patients receiving beta adrenergic blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported.

For these reasons, LUPIN-PROPRANOLOL LA should be withdrawn gradually from patients scheduled for elective surgery, following the recommendations provided in **WARNINGS, Abrupt Cessation of Therapy**. According to available evidence, all clinical and physiologic effects of beta blockade are no longer present 48 hours after cessation of medication.

In patients undergoing emergency surgery, the competitive inhibition of beta adrenergic receptor

agonists, by propranolol hydrochloride, may be reversed, if necessary, using sufficient doses of such agonists as isoproterenol or dobutamine.

Anesthesia with agents which maintain cardiac contractility by virtue of their effect on catecholamine release (e.g. ether) should be avoided in patients on propranolol hydrochloride therapy.

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**).

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 the 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 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 extended-release capsules 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, intra- uterine growth retardation and congenital abnormalities have been

reported in neonates when the mother took propranolol during pregnancy. Some infants born to mothers treated with propranolol were reported to have hypoglycaemia, bradycardia and/or respiratory depression. Adequate facilities for monitoring such infants at birth should be available.

LUPIN-PROPRANOLOL LA 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 LUPIN-PROPRANOLOL LA is administered to nursing women.

Diabetics:

Patients with Diabetes and in those Subject to Hypoglycemia: LUPIN-PROPRANOLOL LA, because of its beta-adrenergic blocking activity, may block premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycaemia. This is especially important 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 hypoglycaemia in patients on propranolol hydrochloride.

Pediatrics: LUPIN-PROPRANOLOL LA 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: LUPIN-PROPRANOLOL LA should be administered with caution to patients with impaired renal and hepatic function, including decompensated cirrhosis, since the half-life may be increased in these patients.

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.

Monitoring and Laboratory Tests

Liver and renal function tests should be performed at regular intervals during long-term treatment with LUPIN-PROPRANOLOL LA.

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 system, 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; claudication and cold extremities, Raynaud's phenomenon; dyspnoea; 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 diarrhoea, 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

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 **CONTRAINDICTIONS** 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, thrombocytopenic purpura; pharyngitis; agranulocytosis; 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.

Anti-arrhythmic drugs

- Class I anti-arrhythmic drugs (e.g. disopyramide) and amiodarone may have a potentiating effect on atrial-conduction time and induce negative inotropic effects.
- Other cardiac-depressant anti-arrhythmic drugs: prior administration of other antiarrhythmic drugs, such as procainamide and quinidine may potentiate the cardiac-depressant activity of propranolol hydrochloride. Prior digitalization may be indicated and atropine should be at hand to control bradycardia.

Thiazide-like diuretics and peripheral vasodilators: The combination of LUPIN-PROPRANOLOL LA with a thiazide-like diuretic and/or a peripheral vasodilator produces a greater fall in blood pressure than either drug alone. This occurs regardless of which drug is administered first (see **WARNINGS AND PRECAUTIONS, General**).

Reserpine or guanethidine: Patients receiving catecholamine depleting drugs should be closely observed if administered concomitantly with LUPIN-PROPRANOLOL LA. The added catecholamine blocking action of these drugs may produce an excessive reduction in the resting sympathetic nervous activity.

Rizatriptan: 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.

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.

Fingolimod: Concomitant use of fingolimod with beta blockers may potentiate bradycardic effects and is not recommended. Where such coadministration is considered necessary, appropriate monitoring at treatment initiation, i.e. at least overnight monitoring, is recommended.

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.

Lidocaine: administration of LUPIN-PROPRANOLOL LA during an infusion of lidocaine may increase the plasma concentration of lidocaine by approximately 30%. Patients already receiving propranolol hydrochloride extended-release capsules tend to have higher lidocaine levels than controls. The combination should be avoided.

Cimetidine: Concomitant use of cimetidine will increase plasma levels of propranolol.

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 with beta-blocker therapy, the introduction of the beta-blocker should be delayed for several days after clonidine has been discontinued.

Ergotamine, Dihydroergotamine (and related compounds); Caution must be exercised if ergotamine, dihydroergotamine or related compounds are given in combination with LUPIN-PROPRANOLOL LA, since vasospastic reactions have been reported in a few patients.

Ibuprofen, Indomethacin: Concomitant use of prostaglandin synthetase inhibiting drugs (e.g. ibuprofen and indomethacin) may decrease the hypotensive effects of LUPIN-PROPRANOLOL LA.

Chlorpromazine: The concomitant use of LUPIN-PROPRANOLOL LA and chlorpromazine may

result in an increase in plasma levels of both drugs. This may lead to an enhanced antipsychotic effect of chlorpromazine and an increased antihypertensive effect of LUPIN-PROPRANOLOL LA.

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 and caution should be exercised when using any anaesthetic agents with LUPIN-PROPRANOLOL LA. If anaesthesia is required, the anaesthetist should be informed that the patient has been taking LUPIN-PROPRANOLOL LA and the choice of anaesthetic should be one with as little negative inotropic activity as possible.

Other medications: Pharmacokinetic studies have shown that several drugs may interact with propranolol due to effects on enzyme systems in the liver, which metabolizes propranolol and the following 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 section above on **Nifedipine**).

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

Dosing Considerations

LUPIN-PROPRANOLOL LA Extended-Release Capsules are intended for maintenance therapy in those patients requiring doses within the range of 60 to 320 mg per day. Initiation of treatment and individual titration of dosage should be carried out using conventional propranolol hydrochloride tablets. LUPIN-PROPRANOLOL LA may be preferred for maintenance therapy because of the convenience of once-daily dosage. LUPIN-PROPRANOLOL LA can provide effective beta blockade over 24 hours.

Patients with angina or hypertension, who have been maintained on a regimen of 60 to 320 mg per day of conventional propranolol hydrochloride tablets, in divided daily doses, may be

switched to the appropriate number of LUPIN-PROPRANOLOL LA capsules, taken once daily

in the morning or evening. LUPIN-PROPRANOLOL LA capsules should be swallowed whole and should not be chewed.

LUPIN-PROPRANOLOL LA capsules should not be substituted for conventional tablets on a simple mg-for- mg basis, as blood levels achieved with LUPIN-PROPRANOLOL LA are lower than blood levels achieved with conventional tablets using the same dose two to four times daily. When switching from conventional tablets to LUPIN-PROPRANOLOL LA, it may be necessary to titrate upwards, especially to maintain effectiveness at the end of the dosing interval.

In most clinical settings involving hypertension or angina, there is little correlation between plasma levels and clinical effect and propranolol hydrochloride extended-release capsules has been shown to the therapeutically equivalent to the same mg dose of conventional propranolol hydrochloride tablets, as assessed by 24-hour effects on blood pressure and on 24-hour responses of heart rate, systolic blood pressure and rate pressure product during exercise.

Combinations of LUPIN-PROPRANOLOL LA with Other Antihypertensive Agents

When propranolol hydrochloride is added to another antihypertensive agent, which is already being administered, therapy should be initiated with conventional propranolol hydrochloride tablets, following the usual dosing recommendations. Once adequate blood pressure control has been obtained, LUPIN-PROPRANOLOL LA capsules can be used for maintenance, provided the dose requirement is suitable.

If additional blood pressure control is necessary in the treatment of hypertension, a diuretic and/or peripheral vasodilator can be added to the treatment regimen. Addition of another antihypertensive agent should, however, be gradual, beginning with 50% of the usual recommended starting dose, to avoid excessive reduction in blood pressure.

Elderly Patients: The optimum dose should be individually determined according to clinical response (see **WARNINGS AND PRECAUTIONS, Special Populations**).

Patients with Impaired Renal or Liver Function: LUPIN-PROPRANOLOL LA should be administered with caution to patients with impaired renal and hepatic function, including decompensated cirrhosis, since the half-life may be increased, necessitating lower doses (see **WARNINGS AND PRECAUTIONS, Special Populations**).

OVERDOSAGE

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

Overdosage Overview:

Several reports in the published literature describe cases in which propranolol hydrochloride was used as a suicide agent. In most cases, other agents, such as alcohol, were also involved. One patient who died was thought to have ingested 3600 mg of propranolol hydrochloride. Patients

taking higher single doses have reportedly survived.

Symptoms: The common signs expected in overdosage include bradycardia, hypotension, bronchospasm and acute cardiac failure.

Treatment: If overdosage occurs, discontinue LUPIN-PROPRANOLOL LA and observe the patient closely. The following specific therapeutic measures are suggested.

Bradycardia: Administer atropine incrementally in 0.6 mg doses. If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure: Digitalization and diuretics

Hypotension: Vasopressors (e.g.: epinephrine or levarterenol). There is evidence that epinephrine is the drug of choice.

Bronchospasm: Administer isoproterenol and aminophylline.

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 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 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 bronchodilation (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. When the net effect is beneficial in angina patients, it manifests itself during exercise or stress by delaying the onset of pain and reducing the incidence and severity of angina attacks.

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).

The mechanisms of the anti-migraine anti-tremor effects of propranolol have not been established. The anti-migraine effect may be due to inhibition of vasodilation or arteriolar spasms over the cortex. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain. The anti-tremor effects may be exerted through both peripheral and central sites of action. The mechanism by which propranolol reduces the incidence of cardiovascular mortality in post-myocardial infarct patients is unknown.

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 expiry volume (FEV_1). In asthmatics and patients with other bronchospastic diseases, however, this effect is marked and potentially dangerous.

Injection of propranolol reduced FEV_1 with dyspnea, cough and dizziness in 2 of 11 patients with

chronic obstructive lung disease. When propranolol was given 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

LUPIN-PROPRANOLOL LA is a special formulation of propranolol hydrochloride consisting of capsules filled with spheroids of the active drug that have a sustained-release coating.

Absorption: Propranolol from propranolol hydrochloride extended-release capsules is almost completely absorbed from the gastrointestinal tract. A large part of the absorbed drug is lost from the systemic circulation due to first-pass metabolism in the liver. The first-pass metabolism is saturable.

Peak blood levels following the administration of propranolol hydrochloride extended-release capsules occur at about 6 hours and the apparent plasma half-life has been reported to be between 10 and 12 hours (i.e., 2 to 3 times that of conventional tablets).

Steady state plasma concentrations of propranolol from propranolol hydrochloride extended-release capsules are proportional to the dose over the range of 60 to 160 mg/day, although there is considerable inter-subject variation.

In healthy volunteers, steady state was achieved 2 or 3 days after administration of propranolol hydrochloride extended-release capsules.

When measured at steady state over a 24-hour period, the areas under the propranolol plasma concentration-time curve (AUCs) for propranolol hydrochloride extended-release capsules are approximately

60 to 65% of the AUCs for a comparable divided daily dose of conventional tablets. The lower AUCs for propranolol hydrochloride extended-release capsules are due to more extensive hepatic metabolism of propranolol due to the slower absorption. Over a 24-hour period, blood levels are fairly constant for about 12 hours, then decline exponentially.

Special Populations and Conditions

Hepatic Insufficiency: As LUPIN-PROPRANOLOL LA is metabolized in the liver, it should be administered with caution to patients with impaired hepatic function, including decompensated cirrhosis, since the half-life may be increased in these patients.

STORAGE AND STABILITY

Store at 15°C – 30°C. Keep container tightly closed and protect from heat, light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

60 mg capsules: White cap and light blue body, imprinted with “PRO 60” on cap in blue band and three narrow white bands on body filled with white to off white pellets. Available in bottles of 100 capsules.

80 mg capsules: Light blue cap and light blue body imprinted with "PRO 80" on cap in white band and three narrow white bands on body filled with white to off white pellets. Available in bottles of 100 capsules.

120 mg capsules: Dark blue cap and light blue body imprinted with "PRO 120" on cap in white band and three narrow white bands on body filled with white to off white pellets. Available in bottles of 100 capsules.

160 mg capsules: Dark blue cap and dark blue body imprinted with "PRO 160" on cap in white band and three narrow white bands on body filled with white of off white pellets. Available in bottles of 100 capsules.

Non-medicinal Ingredients

Each 60 mg, 80 mg, 120 mg and 160 mg capsule of LUPIN-PROPRANOLOL LA contains:, D & C Red 28 (not present in 160 mg strength), Ethylcellulose, FD & C Blue 1, Gelatin, Hypromellose, Povidone, Sodium Lauryl sulphate, Sugar spheres, Talc, Tek Prink SW-0012 white ink (shellac, propylene glycol, ammonia solution, potassium hydroxide, titanium dioxide), Tek Print SB-6008 light blue ink (only in 60 mg strength) (shellac, propylene glycol, ammonia solution, titanium dioxide, FD & C#1 Aluminium lake), Titanium dioxide, Triethyl Citrate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

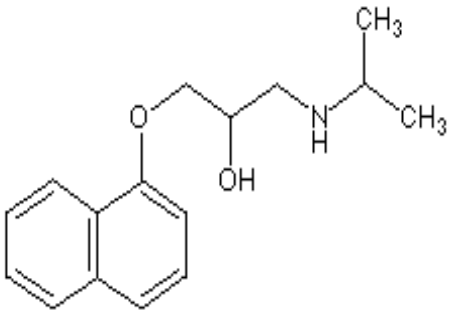
Drug Substance

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:



. HCl

Physicochemical properties:

Propranolol hydrochloride is a stable, colourless, crystalline solid with a melting point of 163 -165^{o}C. It is readily soluble in water and ethanol and insoluble in nonpolar solvents.

CLINCIAL TRIALS

Comparative Bioavailability

A double blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover, adaptive designed oral bioequivalence study comparing LUPIN-PROPRANOLOL LA 160 mg Extended Release Capsules (Lupin Pharma Canada Ltd.) and INDERAL®-LA 160 mg Extended Release Capsules (Pfizer Canada Inc.) was conducted in healthy adult human male subjects under fasting conditions. The data from 81 subjects are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Propranolol (1 x 160 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	94.12% Confidence Interval
AUC_T (hr. ng/mL)	583.29 680.09 (62.94)	542.15 607.72 (54.81)	107.59	97.10 – 119.21
AUC_I (hr. ng/mL)	596.03 690.51 (62.24)	556.68 619.01 (53.81)	107.07	96.86 – 118.36
C_{max} (ng/mL)	39.40 44.0781 (54.92)	33.81 37.21 (49.65)	116.53	106.89 – 127.05
T_{max}§ (h)	7.00 (5.00 – 16.00)	7.00 (5.00-20.00)		
$T_{½}$€ (hr)	5.52 (22.56)	5.54 (26.0)		

* LUPIN-PROPRANOLOL LA 160 mg Extended-Release Capsules (Lupin Pharma Canada Ltd.)

† INDERAL®-LA 160 mg Extended-Release Capsules (Pfizer Canada Inc.) were purchased in Canada

§ Expressed as median (range) only.

€ Expressed as the arithmetic mean (CV%) only.

A double blind, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover oral bioequivalence study comparing LUPIN-PROPRANOLOL LA 160 mg Extended Release Capsules (Lupin Pharma Canada Ltd.) and INDERAL®-LA 160 mg Extended Release Capsules (Pfizer Canada Inc.) was conducted in healthy adult human male subjects under fed conditions. The data from 31 subjects are summarized in the following table.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Propranolol (1 x 160 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (hr. ng/mL)	834.06 894.23 (37.89)	874.67 942.55 (39.21)	95.36	87.66 - 103.73
AUC_I (hr. ng/mL)	845.99 907.01 (38.14)	884.46 953.19 (39.32)	95.36	87.94 - 104.03
C_{max} (ng/mL)	45.47 49.26 (40.88)	50.79 54.58 (40.02)	89.51	81.36 - 98.48
T_{max}§ (h)	10.00 (6.00-16.00)	8.00 (6.00-16.00)		
$T_{½}$€ (hr)	5.72 (20.21)	5.60 (16.24)		

* LUPIN-PROPRANOLOL LA 160 mg Extended-Release Capsules (Lupin Pharma Canada Ltd.)
† INDERAL®-LA 160 mg Extended-Release Capsules (Pfizer Canada Inc.) were purchased in Canada
§ Expressed as median (range) only.
€ Expressed as the arithmetic mean (CV%) only.

DETAILED PHARMACOLOGY

Propranolol hydrochloride is a non-selective competitive antagonist of endogenous and exogenous sympathomimetic amines at beta-adrenergic receptors ($Beta_1$ and $Beta_2$). 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 anaesthetized dogs, propranolol produced a 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 anaesthetized 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 anaesthetic 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[16] 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_{50})

Species	Dose mg/kg I.V.	Dose mg/kg Oral
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

An 18-month toxicity study was conducted in 4 groups of rats (1 control and 3 experimental groups), 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 were observed in both the control and experimental groups.

Dogs

A 1-year toxicity test was conducted in 32 dogs of both sexes. They were divided into 4 groups: controls 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.

Tumorigenic 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 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 the 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 the female rats treated with 150 mg/kg/day of propranolol than in any other group. This was attributed to the markedly decreased bodyweight 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. Propranolol had no adverse effect on fertility, pregnancy, parturition or lactation.

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PART III: CONSUMER INFORMATION

PrLUPIN-PROPRANOLOL LA
Propranolol Hydrochloride
Extended-Release Capsules, USP
60 mg, 80 mg, 120 mg and 160 mg

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

ABOUT THIS MEDICATION

What the medication is used for:
LUPIN-PROPRANOLOL LA contains propranolol hydrochloride, one of a group of substances called beta-adrenergic receptor-blocking agents (beta blockers). It is in an extended release form, used as:

- Maintenance treatment for patients with high blood pressure;
- Preventive treatment of angina pectoris (a condition associated with sharp chest pain and difficulty breathing, often associated with exercise).

What it does:
LUPIN-PROPRANOLOL LA acts to reduce high blood pressure and guard against angina pectoris.

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 LUPIN-PROPRANOLOL LA if you:

- are hypersensitive (allergic) to propranolol hydrochloride or another beta-blocker;
- are hypersensitive to any ingredient in the formulation or component of the container. For a complete listing, see **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 congestive heart failure (a condition where the heart is unable to pump enough blood);
- have pulmonary hypertension (high blood pressure in the arteries 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 phaeochromocytoma (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: LUPIN-PROPRANOLOL LA capsules contains: D & C Red 28, Ethylcellulose, FD & C Blue 1, Gelatin, Hypromellose, Sodium Lauryl sulphate, Sugar spheres, Talc, Titanium dioxide, Triethyl Citrate.

What dosage forms it comes in:
60 mg capsules: White cap and light blue body, imprinted with "PRO 60" on cap in blue band and three narrow white bands on body filled with white to off white pellets.

80 mg capsules: Light blue cap and light blue body imprinted with "PRO 80" on cap in white band and three narrow white bands on body filled with white to off white pellets.

120 mg capsules: Dark blue cap and light blue body imprinted with "PRO120" on cap in white band and three narrow white bands on body filled with white to off white pellets.

160 mg capsules: Dark blue cap and dark blue body imprinted with "PRO 160" on cap in white band and three narrow white bands on body filled with white of off white pellets.

WARNINGS AND PRECAUTIONS

LUPIN-PROPRANOLOL LA should never be stopped abruptly. LUPIN-PROPRANOLOL LA is not intended for use as a starting treatment or for emergency use. It is intended as maintenance therapy only, once your condition has been stabilized. If you have been on a medication that needs to be taken several time daily, your doctor may switch you to LUPIN-PROPRANOLOL LA which is taken just once daily. Your doctor will tell you how to take LUPIN-PROPRANOLOL LA and will monitor your response regularly while you are getting used to LUPIN-PROPRANOLOL LA.

If you have been taking LUPIN-PROPRANOLOL LA for angina pectoris, do not stop treatment or change the dose without directions from your doctor.

Use caution when driving or operating machinery while taking LUPIN-PROPRANOLOL LA, as it may lead to fatigue or dizziness.

Before you use LUPIN-PROPRANOLOL LA, talk to your doctor or pharmacist 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 to undergo surgery;
- are pregnant or intending to become pregnant;
- are nursing;
- are taking any other medications.

LUPIN-PROPRANOLOL LA is not recommended for children.

INTERACTIONS WITH THIS MEDICATION

If taken with some other medicines, the effects of LUPIN-PROPRANOLOL LA 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 LUPIN-PROPRANOLOL LA include:

- Alcoholic beverages
- Diuretics (drugs used to increase urine output, such as hydrochlorothiazide)
- Drugs used to control heart rhythm, e.g., disopyramide, amiodarone, propafenone, quinidine
- Warfarin (to thin the blood)
- Insulin
- Drugs used to reduce high blood pressure, e.g., guanethidine, clonidine, calcium channel blockers (verapamil, diltiazem, nifedipine)
- Rizatriptan (a drug used to treat migraine headaches)
- Digitalis (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)
- Ergotamines (a class of drugs used to treat migraine headaches)
- Chlorpromazine (one of a class of drugs 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
- Fingolimod, a medicine used to treat multiple sclerosis

Please check with your doctor or pharmacist before taking any other medications with LUPIN-PROPRANOLOL LA.

PROPER USE OF THIS MEDICATION

Usual dose:
Take LUPIN-PROPRANOLOL LA capsules exactly as directed by your doctor and your doctor will determine which dose is right for you.

Take LUPIN-PROPRANOLOL LA once daily, either in the morning or the evening. Capsules must be swallowed whole and not chewed.

Overdose:

If you think you have taken too much LUPIN-PROPROPRANOLOL LA, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, talk to your doctor or pharmacist for advice.
However, if it is almost time for your next dose, **do not take the missed dose or take a double dose to make up for the missed capsule. Instead, go back to your regular dosing schedule.**

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, LUPIN-PROPRANOLOL LA 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 common 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 LUPIN-PROPRANOLOL LA are congestive 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 LUPIN-PROPRANOLOL LA. The table does not include a complete list. **Therefore, check with your doctor immediately if you notice or are bothered by any unusual symptoms.**

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Frequency unknown	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, asthma		√	
	Weakness, insomnia, headache, fatigue	√		
	Changes in mood, hallucinations, memory loss	√		
	Dry eyes, visual disturbances	√		
Common	Abdominal pain, nausea, vomiting, diarrhea, loss of appetite	√		
Uncommon	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 LUPIN-PROPRANOLOL LA, contact your doctor or pharmacist.

HOW TO STORE IT

Store at 15°C - 30°C. Keep container tightly closed and protect from heat, light and moisture. Keep out of the reach and sight of children.

Reporting Side Effects

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

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

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

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.lupinpharma.ca or by contacting the sponsor, Lupin Pharma Canada Ltd. at 514.866.3863.

This leaflet was prepared by Lupin Pharma Canada Ltd.

Date prepared: August 28, 2019