CIPLAR-LA Tablets (Propranolol hydrochloride)

Composition

CIPLAR-LA 40 Tablets
Each long acting tablet contains
Propranolol Hydrochloride IP.................40 mg

CIPLAR-LA 80 Tablets
Each long acting tablet contains
Propranolol Hydrochloride IP.................80 mg

Dosage Form

Tablets

Pharmacology

Pharmacodynamics

Propranolol is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately. At dosages greater than required for beta-blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action, which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

Propranolol long acting should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to propranolol sustained-release from conventional propranolol, a possible need for retitration upwards should be considered, especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, propranolol sustained-release has been therapeutically equivalent to the same mg dose of conventional propranolol as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product.

Mechanism of Action

The mechanism of the antihypertensive effect of propranolol has not been established. Among the factors that may be involved in contributing to the antihypertensive action 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. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable.
In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade, and this appears to be its principal antiarrhythmic mechanism of action. In dosages greater than required for beta-blockade, propranolol also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the anti-migraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Pharmacokinetics

Absorption
Propranolol is highly lipophilic and is almost completely absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver and on average, only about 25% of propranolol reaches the systemic circulation. CIPLAR-LA tablets release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with long acting propranolol occur at about 6 hours. The effect of food on sustained release propranolol bioavailability has not been investigated.

Distribution
Approximately 90% of circulating propranolol is bound to plasma proteins (albumin and alpha-1-acid glycoprotein). The binding is enantiomer-selective. The S(-)-enantiomer is preferentially bound to alpha-1-glycoprotein and the R(+) -enantiomer preferentially bound to albumin. The volume of distribution of propranolol is approximately 4 liters/kg.

Propranolol crosses the blood-brain barrier and the placenta, and is distributed into breast milk.

Metabolism and Elimination
Propranolol is extensively metabolized with most metabolites appearing in the urine. Propranolol is metabolized through three primary routes: aromatic hydroxylation (mainly 4-hydroxylation), N-dealkylation followed by further side-chain oxidation, and direct conjugation. It has been estimated that the percentage contributions of these routes to total metabolism are 42%, 41%, and 17%, respectively, but with considerable variability between individuals. The four major metabolites are propranolol glucuronide, naphthyloxylactic acid, and glucuronic acid and sulfate conjugates of 4-hydroxy propranolol.

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

Propranolol is also a substrate for CYP2C19 and a substrate for the intestinal efflux transporter, p-glycoprotein (p-gp). Studies suggest however that p-gp is not dose-limiting for intestinal absorption of propranolol in the usual therapeutic dose range.

In healthy subjects, no difference was observed between CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs) with respect to oral clearance or elimination half-life. Partial clearance to 4-hydroxy propranolol was significantly higher and to naphthyloxylactic acid was significantly lower in EMs than PMs.

When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the sustained-release propranolol are approximately 60% to 65% of the AUCs for a comparable divided daily dose of conventional propranolol. The lower AUCs for the sustained-release propranolol was due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four hour period,
blood levels are fairly constant for about twelve hours, then decline exponentially. The apparent plasma half-life is about 10 hours.

Enantiomers
Propranolol is a racemic mixture of two enantiomers, R(+) and S(-). The S(-)-enantiomer is approximately 100 times as potent as the R(+)-enantiomer in blocking beta-adrenergic receptors. In normal subjects receiving oral doses of racemic propranolol, S(-)-enantiomer concentrations exceeded those of the R(+)-enantiomer by 40-90% as a result of stereoselective hepatic metabolism. Clearance of the pharmacologically active S(-)-propranolol is lower than R(+)propranolol after intravenous and oral doses.

Special Populations

Geriatric: The pharmacokinetics of sustained-release propranolol has not been investigated in patients over 65 years of age. In a study of 12 elderly (62-79 years old) and 12 young (25-33 years old) healthy subjects, the clearance of the S-enantiomer of propranolol was decreased in the elderly. Additionally, the half-life of both R- and S-propranolol were prolonged in the elderly compared with the young (11 hours versus 5 hours).

Clearance of propranolol is reduced with aging due to decline in oxidation capacity (ring oxidation and side chain oxidation). Conjugation capacity remains unchanged. In a study of 32 patients age 30 to 84 years given a single 20-mg dose of propranolol, an inverse correlation was found between age and the partial metabolic clearances to 4-hydroxypropranolol (40HP ring oxidation) and to naphthoxyacetic acid (NLA-side chain oxidation). No correlation was found between age and the partial metabolic clearance to propranolol glucuronide (PPLG conjugation).

Gender: In a study of 9 healthy women and 12 healthy men, neither the administration of testosterone nor the regular course of the menstrual cycle affected the plasma binding of the propranolol enantiomers. In contrast, there was a significant, although non-enantioselective diminution of the binding of propranolol after treatment with ethinyl estradiol. These findings are inconsistent with another study, in which administration of testosterone cypionate confirmed the stimulatory role of this hormone on propranolol metabolism and concluded that the clearance of propranolol in men is dependent on circulating concentrations of testosterone. In women, none of the metabolic clearances for propranolol showed any significant association with either estradiol or testosterone.

Renal Impairment: The pharmacokinetics of sustained release propranolol has not been evaluated in patients with renal impairment. In a study conducted in 5 patients with chronic renal failure, 6 patients on regular dialysis, and 5 healthy subjects, who received a single oral dose of 40 mg of propranolol, the peak plasma concentrations (C_max) of propranolol in the chronic renal failure group were 2 to 3-fold higher (161±41 ng/mL) than those observed in the dialysis patients (47±9 ng/mL) and in the healthy subjects (26±1 ng/mL). Propranolol plasma clearance was also reduced in the patients with chronic renal failure. Studies have reported a delayed absorption rate and a reduced half-life of propranolol in patients with renal failure of varying severity. Despite this shorter plasma half-life, propranolol peak plasma levels were 3-4 times higher and total plasma levels of metabolites were up to 3 times higher in these patients than in subjects with normal renal function. Chronic renal failure has been associated with a decrease in drug metabolism via down regulation of hepatic cytochrome P450 activity resulting in a lower "first-pass" clearance. Propranolol is not significantly dialyzable.

Hepatic Impairment: The pharmacokinetics of sustained release propranolol have not been evaluated in patients with hepatic impairment. Propranolol is extensively metabolized by the liver. In a study conducted in 6 patients with cirrhosis and 7 healthy subjects receiving 160 mg of a long-acting preparation of propranolol once a day for 7 days, the steady-state propranolol concentration in patients with cirrhosis was increased 2.5-fold in comparison to controls. In the patients with cirrhosis, the half-life obtained after a single intravenous dose of 10 mg propranolol increased to 7.2 hours compared to 2.9 hours in control.

Race: A study conducted in 12 Caucasian and 13 Africa-American male subjects taking propranolol, showed that at steady state, the clearance of R(+)- and S(-)-propranolol were about 76% and 53% higher in Africa-Americans than in
Caucasians, respectively. Chinese subjects had a greater proportion (18% to 45% higher) of unbound propranolol in plasma compared to Caucasians, which was associated with a lower plasma concentration of alpha-1-glycoprotein.

### Indications

- Hypertension
- Angina pectoris due to coronary atherosclerosis
- Migraine prophylaxis
- Management of essential tremor
- Relief of situational anxiety and generalised anxiety, particularly those of somatic type
- Adjunctive management of thyrotoxicosis
- Prophylaxis of upper gastro-intestinal bleeding in patients with portal hypertension and esophageal varices
- Hypertrophic subaortic stenosis

### Dosage And Administration

#### General

CIPLAR-LA provides propranolol hydrochloride in a sustained-release tablet for administration once daily. If patients are switched from CIPLAR tablets to CIPLAR-LA tablets, care should be taken to assure that the desired therapeutic effect is maintained. CIPLAR-LA should not be considered a simple mg-for-mg substitute for CIPLAR. CIPLAR-LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

#### Hypertension

The usual initial dosage is 80 mg CIPLAR-LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

#### Angina Pectoris

Starting with 80 mg CIPLAR LA once daily, dosage should be gradually increased at three-to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established. If treatment is to be discontinued, reduce dosage gradually over a period of few weeks.

#### Migraine

The initial oral dose is 80 mg CIPLAR-LA once daily. The usual effective dose range is 160 to 240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, CIPLAR-LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks depending on the patient's age, comorbidity, and dose of CIPLAR-LA.

#### Essential Tremor and Thyrotoxicosis

Dose of 80 mg CIPLAR-LA once daily, taken either morning or evening, may be sufficient to provide adequate control in many patients. If necessary, the dose may be increased to 160 mg once daily and also may be increased to 240 mg.
**Situational and Generalised Anxiety**

CIPLAR-LA 80 mg taken daily should be sufficient to provide short-term relief of acute situational anxiety. Generalised anxiety, requiring longer term therapy, usually responds adequately at the same dosage. In individual cases, the dosage may be increased to 160 mg/day. Treatment should be continued according to response. Patients should be reviewed after 6 to 12 months of treatment.

**Hypertrophic Subaortic Stenosis**

The usual dose is 80 to 160 mg CIPLAR-LA once daily

**Contraindications**

- Cardiogenic shock
- Sinus bradycardia, sick sinus syndrome, and greater than first-degree block
- Bronchial asthma or bronchospasm
- Patients with known hypersensitivity to propranolol hydrochloride

**Warnings And Precautions**

**Drug Interactions**

All drug interaction studies were conducted with propranolol. There are no data on drug interactions with long acting propranolol tablets.

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

Substrates or Inhibitors of CYP2D6: Blood levels and/or toxicity of propranolol may be increased by co-administration of long-acting propranolol with substrates or inhibitors of CYP2D6 (eg. amiodarone, cimetidine, delavudin, fluoxetine, paroxetine, quinidine, and ritonavir). No interactions were observed with either ranitidine or lansoprazole.

Substrates or Inhibitors of CYP1A2: Blood levels and/or toxicity of propranolol may be increased by co-administration with substrates or inhibitors of CYP1A2, such as imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, zileuton, zolmitriptan, and rizatriptan.

Substrates or Inhibitors of CYP2C19: Blood levels and/or toxicity of propranolol may be increased by co-administration with substrates or inhibitors of CYP2C19, such as fluconazole, cimetidine, fluoxetine, fluvoxamine, tenioposide, and tolbutamide. No interaction was observed with omeprazole.

Inducers of Hepatic Drug Metabolism: Blood levels of propranolol may be decreased by co-administration with inducers such as rifampin, ethanol, phenytoin, and phenobarbital. Cigarette smoking also induces hepatic metabolism and has been shown to increase up to 77% the clearance of propranolol, resulting in decreased plasma concentrations.

**Cardiovascular Drugs**

**Antiarrhythmics**

Propafenone has negative inotropic and beta-blocking properties that can be additive to those of propranolol. The AUC of propafenone is increased by more than 200% by co-administration of propranolol. Quinidine increases the concentration of propranolol and produces greater degrees of clinical beta-blockade and may cause postural hypotension. The metabolism of propranolol is reduced by co-administration of quinidine, leading to a two- to three-fold increased blood concentration and greater degrees of clinical beta-blockade. The metabolism of lidocaine is inhibited by co-
administration of propranolol, resulting in a 25% increase in lidocaine concentrations. Lidocaine toxicity has been reported following co-administration with propranolol. Caution should be exercised when administering long-acting propranolol with drugs that slow A-V nodal conduction, e.g., lidocaine and calcium channel blockers. Amiodarone is an antiarrhythmic agent with negative chronotropic properties that may be additive to those seen with beta-blockers such as propranolol.

**Digitalis Glycosides**
Both digitalis glycosides and beta-blockers slow atrioventricular conduction and decrease heart rate. Concomitant use can increase the risk of bradycardia.

**Calcium Channel Blockers**
Caution should be exercised when patients receiving a beta-blocker are administered a calcium channel-blocking drug with negative inotropic and/or chronotropic effects. Both agents may depress myocardial contractility or atrioventricular conduction. The mean $C_{\text{max}}$ and AUC of propranolol are increased respectively, by 50% and 30% by co-administration of nisoldipine and by 80% and 47%, by co-administration of nicardipine. The mean $C_{\text{max}}$ and AUC of nifedipine are increased by 64% and 79%, respectively, by co-administration of propranolol. Propranolol does not affect the pharmacokinetics of verapamil and norverapamil. Verapamil does not affect the pharmacokinetics of propranolol. There have been reports of significant bradycardia, heart failure, and cardiovascular collapse with concurrent use of verapamil and beta-blockers. Co-administration of propranolol and diltiazem in patients with cardiac disease has been associated with bradycardia, hypotension, high degree heart block, and heart failure.

**Angiotensin-Converting Enzyme (ACE) Inhibitors**
When combined with beta-blockers, ACE inhibitors can cause hypotension, particularly in the setting of acute myocardial infarction. The antihypertensive effects of clonidine may be antagonized by beta-blockers. Long acting propranolol should be administered cautiously to patients withdrawing from clonidine.

**Alpha-Blockers**
Prazosin has been associated with prolongation of first dose hypotension in the presence of beta-blockers. Postural hypotension has been reported in patients taking both beta-blockers and terazosin or doxazosin.

**Reserpine**
Patients receiving catecholamine-depleting drugs, such as reserpine should be closely observed for excessive reduction of resting sympathetic nervous activity, which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

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

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

**Non-Cardiovascular Drugs**

**Alcohol**
Concomitant use of alcohol may increase plasma levels of propranolol.

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

Administration of indomethacin with propranolol may reduce the efficacy of propranolol in reducing blood pressure and
Migraine Drugs

Administration of zolmitriptan or rizatriptan with propranolol resulted in increased concentrations of zolmitriptan (AUC increased by 56% and $C_{\text{max}}$ by 37%) or rizatriptan (the AUC and $C_{\text{max}}$ were increased by 67% and 75%, respectively).

Theophylline

Co-administration of theophylline with propranolol decreases theophylline oral clearance by 30% to 52%.

Benzodiazepines

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

Neuroleptic Drugs

Co-administration of long-acting propranolol at doses greater than or equal to 160 mg/day resulted in increased thioridazine plasma concentrations ranging from 55% to 369% and increased thioridazine metabolite (mesoridazine) concentrations ranging from 33% to 209%. Co-administration of chlorpromazine with propranolol resulted in a 70% increase in propranolol plasma level.

Anti-Ulcer Drugs

Co-administration of propranolol with cimetidine, a non-specific CYP450 inhibitor, increased propranolol AUC and $C_{\text{max}}$ by 46% and 35%, respectively. Co-administration with aluminum hydroxide gel (1200 mg) may result in a decrease in propranolol concentrations. Co-administration of metoclopramide with the long-acting propranolol did not have a significant effect on propranolol's pharmacokinetics.

Lipid Lowering Drugs

Co-administration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations. Co-administration of propranolol with lovastatin or pravastatin, decreased 18% to 23% the AUC of both, but did not alter their pharmacodynamics. Propranolol did not have an effect on the pharmacokinetics of fluvastatin.

Warfarin

Concomitant administration of propranolol and warfarin has been shown to increase warfarin bioavailability and increase prothrombin time.

Antidepressants

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

Anesthetic Agents

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

Neuroleptic Drugs

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

Thyroxine

Thyroxine may result in a lower than expected $T_3$ concentration when used concomitantly with propranolol.

Angina Pectoris

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

### Hypersensitivity and Skin Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of propranolol. Cutaneous reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis, exfoliative dermatitis, erythema multiforme, and urticaria, have been reported with use of propranolol.

### Cardiac Failure

Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, some have been shown to be highly beneficial when used with close follow-up in patients with a history of failure who are well compensated and are receiving diuretics as needed. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. In patients without a history of heart failure, continued use of beta-blockers can, in some cases, lead to cardiac failure.

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

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

### Major Surgery

Chronically administered beta-blocking therapy should not be routinely withdrawn prior to major surgery, however the impaired ability of heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

### Diabetes and Hypoglycemia

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

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

### Thyrotoxicosis

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

### Wolff-Parkinson-White Syndrome

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

### Glaucoma Screening Test

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that CIPLAR-LA may
interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

### Risk of Anaphylactic Reaction

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

### Hypertensive Emergencies

Propranolol long acting is not indicated for the treatment of hypertensive emergencies.

### Clinical Laboratory Tests

In patients with hypertension, use of propranolol has been associated with elevated levels of serum potassium, serum transaminases, and alkaline phosphatase. In severe heart failure, the use of propranolol has been associated with increases in Blood Urea Nitrogen.

### Renal Impairment

CIPLAR-LA should be used with caution in patients with renal impairment.

### Hepatic Impairment

CIPLAR-LA should be used with caution in patients with hepatic impairment.

### Pregnancy

Category C

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

### Lactation

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

### Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Bronchospasm and congestive heart failure have been reported coincident with the administration of propranolol therapy in pediatric patients.

### Geriatric Use

Clinical studies of CIPLAR-LA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of the decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

### Undesirable Effects

The following adverse events were observed and have been reported in patients using propranolol.

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

- Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate release formulations, fatigue, lethargy, and vivid dreams appear dose related.
- Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.
- Allergic: Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions; pharyngitis and agranulocytosis; erythematous rash; fever combined with aching and sore throat; laryngospasm; respiratory distress.
- Respiratory: Bronchospasm.
- Hematologic: Agranulocytosis, nonthrombocytopenic purpura, and thrombocytopenic purpura.
- Autoimmune: Systemic lupus erythematosus (SLE).
- Skin and mucous membranes: Stevens-Johnson Syndrome, toxic epidermal necrolysis, dry eyes, exfoliative dermatitis, erythema multiforme, urticaria, alopecia, SLE-like reactions, and psoriasisiform rashes. Oculomucocutaneous syndrome involving the skin, serous membranes, and conjunctivae reported for a beta-blocker (practolol) have not been associated with propranolol.
- Genitourinary: Male impotence; Peyronie's disease.

### Overdosage

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

#### General

If ingestion is or may have been recent, evacuate gastric contents, taking care to prevent pulmonary aspiration.

#### Supportive Therapy

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

### Packaging Information

CIPLAR-LA 40: Blister pack of 10 tablets
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*Last updated: October 2013*
*Last reviewed: October 2013*

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