CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-438

Approved Labeling

GLUE PANEL

InnoPran XL®
(propranolol hydrochloride)
Extended Release Capsules

225F000 2253000

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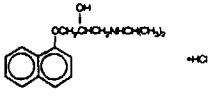
DESCRIPTION

InnoPran XL (propranolol hydrochloride) is a nonselective, beta-adrenergic receptor-blocking agent for oral administration, available as an extended release product. The capsules contain sustained-release beads. Each of the beads contains propranolol hydrochloride and is coated with dual membranes. These membranes are designed to retard release of propranolol hydrochloride for several hours after ingestion followed by the sustained release of propranolol.

The active ingredient in InnoPran XL is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride. Its structural formula is:



Propranolol hydrochloride is a stable, white, crystalline solid, which is readily soluble in water and ethanol. Its molecular weight is 295.81. InnoPran XL is available as 60 mg and 120 mg capsules. Each capsule for oral administration contains sugar spheres, ethylcellulose, povidone, hypromellose phthalate, diethyl phthalate, hypromellose, polyethylene glycol, gelatin, titanium dioxide and black iron oxide. In addition, InnoPran XL 120-mg capsules contain yellow iron oxide.

CLINICAL PHARMACOLOGY

General

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, 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.

Mechanism of Action

The mechanism of the antihypertensive effect of propranolol has not been established. Among factors that contribute 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 of propranolol. Effects of propranolol on plasma volume appear to be minor and somewhat variable.

PHARMACOKINETICS AND DRUG METABOLISM

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.

A single-dose, food-effect study in 36 healthy subjects showed that a high fat meal administered with InnoPran XL at 10 PM, increased the lag time from 3 to 5 hours and the time to reach the maximum concentration from 11.5 to 15.4 hours, under fed conditions, with no effect on the AUC. (See DOSAGE AND ADMINISTRATION).

Following multiple-dose administration of InnoPran XL at 10 PM under fasting conditions, the steady-state lag time was between 4-5 hours and propranolol peak plasma concentrations were reached approximately 12-14 hours after dosing. Propranolol trough levels were achieved 24-27 hours after dosing, and persisted for 3-5 hours after the next dose. The elimination half-life of propranolol was approximately 8 hours.

The plasma levels of propranolol showed dose proportional increases after single and multiple administration of 80, 120, and 160 mg of InnoPran XL.

At steady state, the bioavailability of 160-mg dose of InnoPran XL and propranolol hydrochloride long acting capsules did not differ significantly.

Distribution

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

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 glucuronidation. 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, naphthoxylactic 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 naphthoxylactic acid was significantly lower in EMs than PMs.

Enantiomers

Of the two enantiomers of propranolol the S-enantiomer blocks beta-adrenergic receptors. In normal subjects receiving oral doses of racemic propranolol, S-enantiomer concentrations exceeded those of the R-enantiomer by 40-60% as a result of stereoselective hepatic metabolism.

Special Populations

Pediatric

The pharmacokinetics of InnoPran XL have not been investigated in patients under 18 years of age.

Geriatric

The pharmacokinetics of InnoPran XL have not been investigated in patients over 65 years of age. In a study of 12 elderly (62-78 years old) and 12 young (25-33 years old) healthy subjects, the clearance of S-enantiomer of propranolol was decreased in the elderly. Additionally, the half-life of both the R- and S-propranolol were prolonged in the elderly compared with the young (11 hours vs. 5 hours).

Gender

In a dose-proportionality study, the pharmacokinetics of InnoPran XL were evaluated in 22 male and 14 female healthy volunteers. Following single doses under fasting conditions, the mean AUC and C_{max} were about 49% and 16% higher for females across the dosage range. The mean elimination half-life was longer in females than in males (11 hours vs. 7.5 hours).

Race

A study conducted in 12 Caucasian and 13 African-American male subjects taking propranolol, showed that at steady state, the clearance of R- and S-propranolol were about 76% and 53% higher in African-Americans than in Caucasians, respectively.

Renal Insufficiency

The pharmacokinetics of InnoPran XL have not been evaluated in patients with renal insufficiency. 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.

Chronic renal failure has been associated with a decrease in drug metabolism via down regulation of hepatic cytochrome P450 activity.

Hepatic Insufficiency

The pharmacokinetics of InnoPran XL have not been evaluated in patients with hepatic impairment. However, propranolol is extensively metabolized by the liver. In a study conducted in 7 patients with cirrhosis and 9 healthy subjects receiving 80-mg oral propranolol every 8 hours for 7 doses, the steady-state unbound propranolol concentration in patients with cirrhosis was increased 3-fold in comparison to controls. In cirrhosis, the half-life increased to 11 hours compared to 4 hours (see PRECAUTIONS).

Drug Interactions

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), administration of InnoPran XL with drugs that are metabolized by, or effect the activity (induction or inhibition) of one or more of these pathways may lead to clinically relevant drug interactions (see DRUG INTERACTIONS under PRECAUTIONS).

Substrates or Inhibitors of CYP2D6

Blood levels and/or toxicity of propranolol may be increased by administration of InnoPran XL with substrates or inhibitors of CYP2D6, such as 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 administration of InnoPran XL with substrates or inhibitors of CYP1A2, such as imipramine, cimetidine, ciprofloxacin, fluvoxamine, isoniazid, ritonavir, theophylline, ticlutan, zolmitriptan, and rizatriptan.

Substrates or Inhibitors of CYP2C19

Blood levels and/or toxicity of propranolol may be increased by administration of InnoPran XL with substrates or inhibitors of CYP2C19, such as fluconazole, cimetidine, fluoxetine, fluvoxamine, teniposide, and teltuxtamide. No interaction was observed with omeprazole.

Inducers of Hepatic Drug Metabolism

Blood levels of propranolol may be decreased by administration of InnoPran XL with inducers such as rifampin and ethanol. Cigarette smoking also induces hepatic metabolism and has been shown to increase up to 100% the clearance of propranolol, resulting in decreased plasma concentrations.

Cardiovascular Drugs

Antiarrhythmics

The AUC of propafenone is increased by more than 200% by co-administration of propranolol.

The metabolism of propranolol is reduced by co-administration of quinidine, leading to a two-three fold increase in blood concentrations 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.

Calcium channel blockers

The mean C_{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_{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.

Non-Cardiovascular Drugs

Migraine Drugs

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

Theophylline

Co-administration of theophylline with propranolol decreases theophylline oral clearance by 33% to 52%.

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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 propranolol at doses greater than or equal to 160 mg/day resulted in increased thioridazine plasma concentrations ranging from 50% to 370% and increased thioridazine metabolites concentrations ranging from 33% to 210%.

Co-administration of chlorpromazine with propranolol resulted in increased plasma levels of both drugs (70% increase in propranolol concentrations).

Anti-Ulcer Drugs

Co-administration of propranolol with cimetidine, a non-specific CYP450 inhibitor, increased propranolol concentrations by about 40%. Co-administration with aluminum hydroxide gel (1200 mg) resulted in a 50% 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 20% to 25% 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.

PHARMACODYNAMICS AND CLINICAL EFFECTS

Hypertension

In a double-blind, parallel, dose-response study in patients with mild-to-moderate hypertension (n=434), doses of InnoPran XL from 80 to 640 mg were taken once daily taken at approximately 10 PM. InnoPran XL significantly lowered sitting systolic and diastolic blood pressure when measurements were taken approximately 16 hours later. The placebo-subtracted diastolic blood pressure effect for the 80 and 120 mg doses were -3.0 and -4.0 mm Hg, respectively. Higher doses of InnoPran XL (160, 640 mg) had no additional blood pressure lowering effect when compared with 120 mg. The antihypertensive effects of InnoPran XL were seen in the elderly (greater than or equal to 65 years old) and men and women. There were too few non-white patients to assess the efficacy of InnoPran XL in these patients.

INDICATIONS AND USAGE

Hypertension

InnoPran XL is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents.

CONTRAINDICATIONS

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

WARNINGS

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

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

Nonallergic Bronchospasm (e.g., Chronic Bronchitis, Emphysema): In general, patients with bronchospastic lung disease should not receive beta-blockers. Propranolol should be administered with caution in this setting since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta-receptors.

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

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

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

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

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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 T_4 and reversing T_3, and decreasing T_3.

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

PRECAUTIONS

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

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

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

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

Cardiovascular Drugs

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

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

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

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

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

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

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

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

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

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

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

The antihypertensive effects of clonidine may be antagonized by beta-blockers. InnoPran XL 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 and InnoPran XL, 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. Administration of reserpine with propranolol may also potentiate depression.

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

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.

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Non-Cardiovascular Drugs

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

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

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

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

Warfarin
Propranolol when administered with warfarin increases the concentration of warfarin. Prothrombin time, therefore, should be monitored.

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

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

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

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

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

Nursing Mothers
Propranolol is excreted in human milk. Caution should be exercised when InnoPran XL is administered to a nursing mother.

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

Geriatric Use
Clinical studies of InnoPran XL did not include sufficient numbers of subjects ages 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 decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS
Adverse events occurring at a rate of ≥3%, excluding those reported more commonly in placebo encountered in the InnoPran XL placebo-controlled hypertension trials and are plausibly related to treatment, are shown in Table 1.

Table 1. Treatment Emergent Adverse Events Reported in ≥ 3% of Subjects

		InnoPran XL	
	Placebo	80 mg	120 mg
Body System	(N=88)	(N=88)	(N=85)
Fatigue	3 (3.0%)	4 (5.0%)	6 (7.0%)
Dizziness (except vertigo)	2 (2.0%)	6 (7.0%)	3 (4.0%)
Constipation	0	3 (3.0%)	1 (1.0%)

The following adverse events were observed and have been reported with use of formulations of sustained- or immediate-release 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; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate-release formulations, fatigue, lethargy, and vivid dreams appear dose related.

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

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

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

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

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

DOSAGE AND ADMINISTRATION
InnoPran XL should be administered once daily at bedtime (approximately 10 PM) and should be taken consistently either on an empty stomach or with food. The starting dose is 80 mg but dosage should be individualized and titration may be needed to a dose of 120 mg. In the clinical trial, doses of InnoPran XL above 120 mg had no additional effects on blood pressure (See PHARMACODYNAMICS AND CLINICAL EFFECTS). The time needed for full antihypertensive response is variable, but is usually achieved within 2-3 weeks.

OVERDOSAGE
Most overdoses of propranolol are mild and respond to supportive care.

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

Decontamination: Gastric lavage

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.

HOW SUPPLIED
InnoPran XL (propranolol hydrochloride) Extended Release Capsules

Each gray/white capsule, imprinted with "80", 2 segmented bands, "RD201", and Reliant logo contains 80 mg of propranolol hydrochloride in bottles of 30 (NDC 65726-250-10), bottles of 100 (NDC 65726-250-25), bottles of 500 (NDC 65726-250-35), and a Unit Dose package of 100 (NDC 65726-250-90).

Each gray/off-white capsule, imprinted with "120", 3 segmented bands, "RD201", and Reliant logo contains 120 mg of propranolol hydrochloride in bottles of 30 (NDC 65726-251-10), bottles of 100 (NDC 65726-251-25), bottles of 500 (NDC 65726-251-35), and a Unit Dose package of 100 (NDC 65726-251-90).

Store at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature] in a tightly closed container. The unit dose packaging should be stored in the carton.

Rx only
April 2003

Reliant PHARMACEUTICALS

Manufactured for:
Reliant Pharmaceuticals, LLC
Liberty Corner, NJ 07938

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Vandalia, OH 45377

Address Medical Inquiries to:
Reliant Pharmaceuticals, LLC
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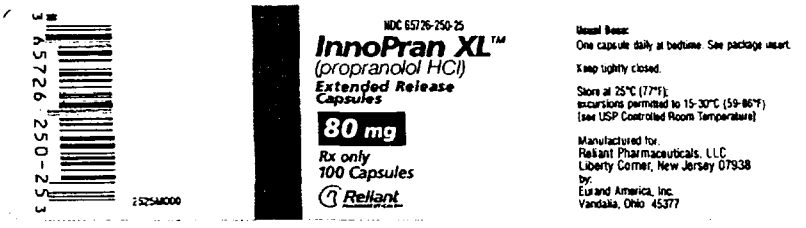
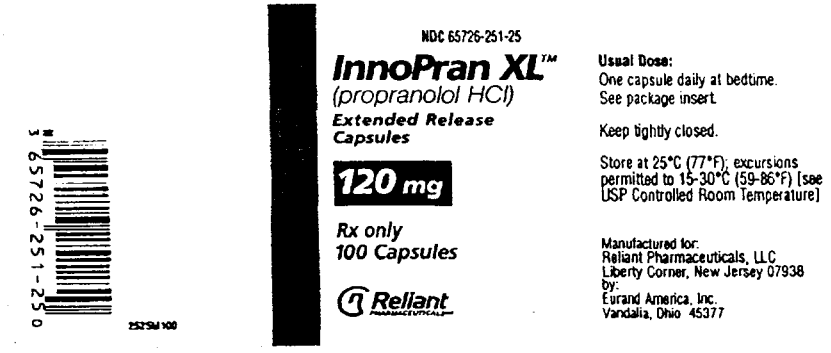
RELIANT PHARM. 90cc BOTTLE

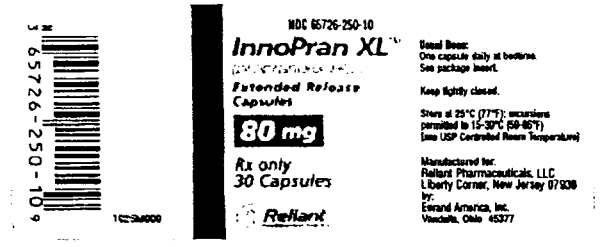
DRAFT

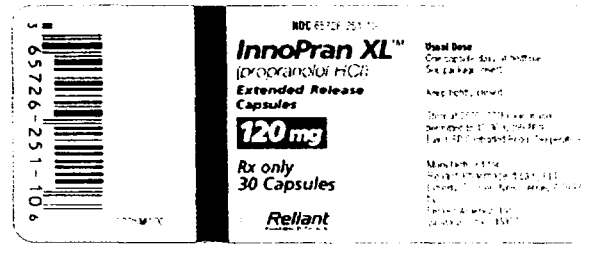


RELIANT PHARM. 120cc BOTTLE



RELIANT PHARM. 45cc BOTTLE





RELIANT PHARM. 400cc BOTTLE

NDC 65726-250-35

InnoPran XL™

(propranolol HCl)

Extended Release Capsules

80 mg

Rx only
500 Capsules

Reliant PHARMACEUTICALS

Usual Dose:
One capsule daily at bedtime.
See package insert.

Dispense in a tight, light-resistant container.

Keep tightly closed.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Manufactured for:
Reliant Pharmaceuticals, LLC
Liberty Corner, New Jersey 07938
by:
Eurand America, Inc.
Vandalia, Ohio 45377

RELIANT PHARM. 500cc BOTTLE

NDC 65726-251-35

InnoPran XL™

(propranolol HCl)

Extended Release Capsules

120 mg

Rx only
500 Capsules

Reliant PHARMACEUTICALS

Usual Dose:
One capsule daily at bedtime.
See package insert.

Dispense in a tight, light-resistant container.

Keep tightly closed.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]

Manufactured for:
Reliant Pharmaceuticals, LLC
Liberty Corner, New Jersey 07938
by:
Eurand America, Inc.
Vandalia, Ohio 45377

DRAFT

DRAFT

RELIANT PHARM. 45cc BOTTLE