INDELOL (Film coated tablets)

Propranolol hydrochloride (10,40,80) mg

Composition: Each film –tablet contains:10or 40 or 80 mg of propranolol hydrochloride.

Excipients:

core:Maize starch,lactose monohydrate,stearic acid,magnesium stearate,HPMC.

Coating:HPMC,poly sorbate 80,titanium dioxide,red iron oxide,yellow iron oxide.

Mechanism of action:

The mechanism of the antihypertensive effect of propranolol has not been established. Factors that may contribute to the antihypertensive action include:

1- decreased cardiac output.

2- inhibition of renin release by the kidneys.

3- diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

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.

Pharmacokinetics:

Absorption:

Propranolol is highly lipophilic and almost completely

absorbed after oral administration. However, it undergoes high first-pass metabolism by the liver, only about 25% of propranolol reaches the systemic circulation. Peak plasma concentrations occur about 1 to 4 hours after an oral dose.

Administration of protein-rich foods increase the bioavailability of propranolol by about 50% with no change in time to peak concentration, plasma binding, half-life, or the amount of unchanged drug in the urine.

Distribution:

Approximately 90% of circulating propranolol is bound to plasma proteins. 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.

The four major metabolites are propranolol glucuronide, naphthyloxylactic acid and glucuronic acid, and sulfate conjugates of 4- hydroxy propranolol.

The plasma half-life of propranolol is from 3 to 6 hours.

Indications:

Hypertension:

INDELOL tablets are indicated in the management of hypertension. They may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic.

INDELOL tablets are not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis:

INDELOL tablets are indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris.

Atrial Fibrillation:

INDELOL tablets are indicated control ventricular rate in patients with atrial fibrillation and a rapid ventricular response.

Myocardial Infarction:

INDELOL tablets are indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.

Migraine:

INDELOL tablets are indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established, and propranolol is not indicated for such use.

Essential Tremor:

INDELOL tablets are indicated in the management of familial or hereditary essential tremor.

Familial or essential tremor consists of involuntary, rhythmic, oscillatory movements, usually limited to the upper limbs. Propranolol hydrochloride tablets, causes a reduction in the tremor amplitude but not in the tremor frequency. Propranolol hydrochloride tablets are not indicated for the treatment of tremor associated with Parkinsonism.

Hypertrophic Subaortic Stenosis:

INDELOL tablets improve New York Heart Association (NYHA) functional class in symptomatic patients with hypertrophic subaortic stenosis.

Pheochromocytoma:

INDELOL tablets are indicated as an adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine secreting tumors.

Contraindications:

Propranolol is contraindicated in:

1- cardiogenic shock.

2- sinus bradycardia and greater than first degree block.

3- bronchial asthma.

4- in patients with known hypersensitivity to propranolol hydrochloride.

Side 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: Lightheadedness, 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, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, 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 psoriasiform rashes.

Genitourinary: Male impotence; Peyronie's disease.

Warnings:

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 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:

anaphylactic/anaphylactoid reactions, have been associated with the Hypersensitivity reactions, including 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 additional therapies, including 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.

Non allergic 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 the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

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.

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 .

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 insufficiency.

Precautions:

General

Propranolol should be used with caution in patients with impaired hepatic or renal function. Propranolol hydrochloride tablets are not indicated for the treatment of hypertensive emergencies.

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

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, coadministration 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.

Substrates or Inhibitors of CYP2D6:

Blood levels and/ or toxicity of propranolol may be increased by coadministration 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 coadministration 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 coadministration 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 coadministration 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:

The AUC of propafenone is increased by more than 200% by coadministration of propranolol.

The metabolism of propranolol is reduced by coadministration of quinidine, leading to a two-three fold increased blood concentration and greater degrees of clinical beta-blockade.

The metabolism of lidocaine is inhibited by coadministration of propranolol, resulting in a 25% increase in Lidocaine concentrations.

Calcium Channel Blockers:

The mean Cmax and AUC of propranolol are increased respectively, by 50% and 30% by coadministration of nisoldipine and by 80% and 47%, by coadministration of nicardipine.

The mean Cmax and AUC of nifedipine are increased by 64% and 79%, respectively, by coadministration 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 or rizatriptan

Theophylline:

Coadministration 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 coadministration of propranolol.

Neuroleptic Drugs:

Coadministration of long-acting propranolol at doses greater than or equal to 160mg/day resulted in increased thioridazine plasma concentrations ranging from 55% to 369% and increased thioridazine metabolite (mesoridazine) concentrations ranging from 33% to 209%.

Lipid Lowering Drugs:

Coadministration of cholestyramine or colestipol with propranolol resulted in up to 50% decrease in propranolol concentrations.

Coadministration 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.

Alcohol:

Concomitant use of alcohol may increase plasma levels of propranolol.

Doses and Administration:

General:

Because of the variable bioavailability of propranolol, the dose should be individualized based on response.

Hypertension:

The usual initial dosage is 40 mg propranolol hydrochloride twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure control is achieved. The usual maintenance dosage is 120 mg to 240 mg per day.

In some instances a dosage of 640 mg a day may be required. The time needed for full antihypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. If control is not adequate, a larger dose, or 3-times-daily therapy may achieve better control.

Angina Pectoris:

Total daily doses of 80 mg to 320 mg propranolol hydrochloride when administered orally, twice a day, three times a day, or four times a day, have been shown to increase exercise tolerance and to reduce ischemic changes in the ECG. If treatment is to be discontinued, reduce dosage gradually over a period of several weeks.

Atrial Fibrillation:

The recommended dose is 10 mg to 30 mg propranolol hydrochloride three or four times daily before meals and at bedtime.

Myocardial Infarction:

The recommended daily dosage is 180 mg to 240 mg propranolol hydrochloride per day in divided doses. The effectiveness and safety of daily dosages greater than 240 mg for prevention of cardiac mortality have not been established.

Migraine:

The initial dose is 80 mg propranolol hydrochloride daily in divided doses. The usual effective dose range is 160 mg to 240 mg per day. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, propranolol hydrochloride therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

Essential Tremor:

The initial dosage is 40 mg propranolol hydrochloride twice daily. Optimum reduction of essential tremor is usually achieved with a dose of 120 mg per day.

Occasionally, it may be necessary to administer 240 mg to 320 mg per day.

Hypertrophic Subaortic Stenosis:

The usual dosage is 20 mg to 40 mg propranolol hydrochloride three or four times daily before meals and at bedtime.

Pheochromocytoma:

The usual dosage is 60 mg propranolol hydrochloride daily in divided doses for three days prior to surgery as adjunctive therapy to alpha-adrenergic blockade. For the management of inoperable tumors, the usual dosage is 30 mg daily in divided doses as adjunctive therapy to alpha-adrenergic blockade.

Use in pregnancy:

There are no adequate and well-controlled studies in pregnant women.

Nursing Mothers:

Propranolol is excreted in human milk. Caution should be exercised when propranolol hydrochloride tablets are administered to a nursing woman.

Pediatric Use:

Safety and effectiveness of propranolol 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 propranolol hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Over dosage:

Propranolol is not significantly dialyzable. In the event of overdosage or exaggerated response, the following measures should b 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: INDELOL(10,40,80) 3 blister in carton box,Each blister contains 10 F.C.T.

Storage conditions: Store at room temperature,between(20-25)°C
Away from light and moisture.
Rxonly.

*** THIS IS A MEDICAMENT ***

- Keep out of reach of children.
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly doctor's prescriptions, the method of use and instructions of the pharmacist who sold the medicament.
- The doctor and pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

(Council of Arab Ministers) **(Union of Arab Pharmacists)**

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