CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74787

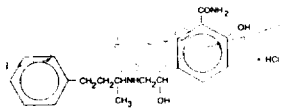
DRAFT FINAL PRINTED LABELING

LABETALOL HYDROCHLORIDE
TABLETS, USP

DESCRIPTION

Labetalol HCl is an adrenergic receptor blocking agent that has both selective alpha$_1$-and non-selective beta-adrenergic receptor blocking actions in a single substance.

Labetalol HCl is a racemate, chemically designated as 5-[1-Hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl] salicylamide monohydrochloride, and has the following structural formula:



$C_{19}H_{24}N_2O_3$ •HCl M.W. 364.87

Labetalol HCl has two asymmetric centers and therefore exists as a molecular complex of two diastereoisomeric pairs. Dilevalol, the R,R' stereoisomer, makes up 25% of racemic labetalol.

Labetalol HCl is a white or off-white crystalline powder, soluble in water.

Each tablet, for oral administration, contains 100 mg, 200 mg, or 300 mg of labetalol hydrochloride, USP. In addition, each tablet contains the following inactive ingredients: corn starch, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate, titanium dioxide and colorants (100 mg: D&C yellow #10 aluminum lake and FD&C yellow #6 aluminum lake, and 300 mg: D&C yellow #10 aluminum lake, FD&C yellow #6 aluminum lake and FD&C blue #1 aluminum lake).

CLINICAL PHARMACOLOGY

Labetalol combines both selective, competitive alpha$_1$-adrenergic blocking and nonselective, competitive beta-adrenergic blocking activity in a single substance. In man, the ratios of alpha-to beta-blockade have been estimated to be approximately 1:3 and 1:7 following oral and intravenous administration, respectively. Beta$_2$-agonist activity has been demonstrated in animals with minimal beta$_1$-agonist (ISA) activity detected. In animals, at doses greater than those required for alpha- or beta-adrenergic blockade, a membrane-stabilizing effect has been demonstrated.

Pharmacodynamics

The capacity of labetalol to block alpha receptors in man has been demonstrated by attenuation of the pressor effect of phenylephrine and by a significant reduction of the pressor response caused by immersing the hand in ice-cold water ("cold-pressor test"). Labetalol's beta$_1$-receptor blockade in man was demonstrated by a small decrease in the resting heart rate, attenuation of tachycardia produced by isoproterenol or exercise, and by attenuation of the reflex tachycardia to the hypotension produced by amyl nitrite. Beta$_2$-receptor blockade was demonstrated by inhibition of the isoproterenol-induced fall in diastolic blood pressure. Both the alpha- and beta-blocking actions of orally administered labetalol HCl contribute to a decrease in blood pressure in hypertensive patients. Labetalol consistently, in dose-related fashion, blunted increases in exercise-induced blood pressure and heart rate, and in their double product. The pulmonary circulation during exercise was not affected by labetalol HCl dosing.

Single oral doses of labetalol HCl administered in patients with coronary artery disease had no significant effect on sinus rate, intraventricular conduction, or QRS duration. The AV conduction time was modestly prolonged in 2 of 7 patients. In another study, intravenous labetalol slightly prolonged AV nodal conduction time and atrial effective refractory period with only small changes in heart rate. The effects on AV nodal refractoriness were inconsistent.

Labetalol produces dose-related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its alpha-blocking and beta-blocking effects. Hemodynamic effects are variable with small nonsignificant changes in cardiac output seen in some studies but not others, and small decreases in total peripheral resistance. Elevated plasma renins are reduced.

Doses of labetalol HCl that controlled hypertension did not affect renal function in mild to severe hypertensive patients with normal renal function.

Due to the alpha$_1$-receptor blocking activity of labetalol, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension (2%), including rare instances of syncope, can occur. Following oral administration, when postural hypotension has occurred, it has been transient and is uncommon when the recommended starting dose and titration increments are closely followed (see **DOSAGE AND ADMINISTRATION**). Symptomatic postural hypotension is most likely to occur 2 to 4 hours after a dose, especially following the use of large initial doses or upon large changes in dose.

The peak effects of single oral doses of labetalol HCl occur within 2 to 4 hours. The duration of effect depends upon dose, lasting at least 8 hours following single oral doses of 100 mg and more than 12 hours following single oral doses of 300 mg. The maximum, steady-state blood pressure response upon oral, twice-a-day dosing occurs within 24 to 72 hours.

The antihypertensive effect of labetalol has a linear correlation with the logarithm of labetalol plasma concentration, and there is also a linear correlation between the reduction in exercise-induced tachycardia occurring at 2 hours after oral administration of labetalol HCl and the logarithm of the plasma concentration.

About 70% of the maximum beta-blocking effect is present for 5 hours after the administration of a single oral dose of 400 mg, with suggestion that about 40% remains at 8 hours.

The anti-anginal efficacy of labetalol has not been studied. In 37 patients with hypertension and coronary artery disease, labetalol did not increase the incidence or severity of angina attacks.

Exacerbation of angina and, in some cases, myocardial infarction and ventricular dysrhythmias have been reported after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with coronary artery disease. Abrupt withdrawal of these agents in patients without coronary artery disease has resulted in transient symptoms, including tremulousness, sweating, palpitation, headache, and malaise. Several mechanisms have been proposed to explain these phenomena, among them increased sensitivity to catecholamines because of increased numbers of beta receptors.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. Beta-adrenergic blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic activity on conduction. Beta$_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

Pharmacokinetics and Metabolism

Labetalol is completely absorbed from the gastrointestinal tract with peak plasma levels occurring 1 to 2 hours after oral administration. The relative bioavailability of labetalol tablets compared to an oral solution is 100%. The absolute bioavailability (fraction of drug reaching systemic circulation) of labetalol when compared to an intravenous infusion is 25%; this is due to extensive "first-pass" metabolism. Despite "first-pass" metabolism there is a linear relationship between oral doses of 100 to 3000 mg and peak plasma levels. The absolute bioavailability of labetalol is increased when administered with food.

The plasma half-life of labetalol following oral administration is about 6 to 8 hours. Steady-state plasma levels of labetalol during repetitive dosing are reached by about the third day of dosing. In patients with decreased hepatic or renal function, the elimination half-life of labetalol is not altered; however, the relative bioavailability in hepatically impaired patients is increased due to decreased "first-pass" metabolism.

The metabolism of labetalol is mainly through conjugation to glucuronide metabolites. These metabolites are present in plasma and are excreted in the urine, and via the bile, into the feces. Approximately 55% to 60% of a dose appears in the urine as conjugates or unchanged labetalol within the first 24 hours of dosing.

Labetalol has been shown to cross the placental barrier in humans. Only negligible amounts of the drug crossed the blood-brain barrier in animal studies. Labetalol is approximately 50% protein bound. Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol from the general circulation (<1%).

INDICATIONS AND USAGE

Labetalol HCl tablets are indicated in the management of hypertension. Labetalol HCl tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.

CONTRAINDICATIONS

Labetalol HCl tablets are contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, severe bradycardia, other conditions associated with severe and prolonged hypotension, and in patients with a history of hypersensitivity to any component of the product (see **WARNINGS**).

WARNINGS

Hepatic Injury

Severe hepatocellular injury, confirmed by rechallenge in at least one case, occurs rarely with labetalol therapy. The hepatic injury is usually reversible, but hepatic necrosis and death have been reported. Injury has occurred after both short- and long-term treatment and may be slowly progressive despite minimal symptomatology. Similar hepatic events have been reported with a related compound, dilevalol HCl, including two deaths. Dilevalol HCl is one of four isomers of labetalol HCl. Thus, for patients taking labetalol, periodic determination of suitable hepatic laboratory tests would be appropriate. Laboratory testing should also be done at the very first symptom or sign of liver dysfunction (e.g., pruritus, dark urine, persistent anorexia, jaundice, right upper quadrant tenderness, or unexplained "flu-like" symptoms). If the patient has jaundice or laboratory evidence of liver injury, labetalol should be stopped and not restarted.

Cardiac Failure

Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure

In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, labetalol therapy should be withdrawn (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal

Angina pectoris has not been reported upon labetalol discontinuation. However, hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after abrupt discontinuation of such therapy. When discontinuing chronically administered labetalol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, labetalol administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue labetalol therapy abruptly even in patients treated only for hypertension.

Nonallergic bronchospasm (e.g., chronic bronchitis and emphysema) patients with bronchospastic disease should, in general, not receive beta-blockers. Labetalol may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if labetalol is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

Pheochromocytoma

Labetalol has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia

Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery

The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol and halothane anesthesia has been shown (see **PRECAUTIONS-Drug Interactions**).

PRECAUTIONS

General

Impaired Hepatic Function

Labetalol should be used with caution in patients with impaired hepatic function since metabolism of the drug may be diminished.

Jaundice or Hepatic Dysfunction

(see **WARNINGS**)

Information for Patients

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol is warranted. This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol, dosing with labetalol HCl tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with labetalol HCl tablets should consult a physician at any signs or symptoms of impending cardiac failure or hepatic dysfunction (see **WARNINGS**). Also, transient scalp tingling may occur, usually when treatment with labetalol HCl tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests

As with any new drug given over prolonged periods, laboratory parameters should be observed over regular intervals. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions

In one survey, 2.3% of patients taking labetalol in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol alone. The contribution of each of the treatments to this adverse reaction is unknown but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol. During controlled hypotensive anesthesia using labetalol in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol.

Labetalol blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Care should be taken if labetalol is used concomitantly with calcium antagonists of the verapamil type.

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.

Drug/Laboratory Test Interactions

The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction (e.g., *J Chromatogr* 385 241,1987) should be employed in determining levels of catecholamines.

Labetalol has also been reported to produce a false-positive test for amphetamine when screening urine for the presence of drugs using the commercially available assay methods Toxi-Lab A® (thin-layer chromatographic assay) and Emit-d.a.u® (radioenzymatic assay). When patients being treated with labetalol have a positive urine test for amphetamine using these techniques, confirmation should be made by using more specific methods, such as a gas chromatographic-mass spectrometer technique.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral dosing studies with labetalol for 18 months in mice and for 2 years in rats showed no evidence

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of carcinogenesis. Studies with labetalol, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C

Teratogenic studies have been performed with labetalol in rats and rabbits at oral doses up to approximately 6 and 4 times the maximum recommended human dose (MRHD), respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the MRHD revealed no evidence of drug-related harm to the fetus. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects

Hypotension, bradycardia, hypoglycemia, and respiratory depression have been reported in infants of mothers who were treated with labetalol for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery

Labetalol given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers

Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when labetalol HCl tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Most adverse effects are mild, transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months duration, discontinuation of labetalol HCl tablets due to one or more adverse effects was required in 7% of all patients. In these same trials, beta-blocker control agents led to discontinuation in 8% to 10% of patients, and a centrally acting alpha-agonist in 30% of patients.

The incidence rates of adverse reactions listed in the following table were derived from multicenter controlled clinical trials, comparing labetalol, placebo, metoprolol and propranolol over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol and placebo is similar, causal relationship is uncertain. The rates are based on adverse reactions considered probably drug related by the investigator. If all reports are considered, the rates are somewhat higher (e.g., dizziness 20%, nausea 14%, fatigue 11%), but the overall conclusions are unchanged.

	Labetalol (N=227) %	Placebo (N=98) %	Propranolol (N=84) %	Metoprolol (N=49) %
Body as a whole				
fatigue	5	0	12	12
asthenia	1	1	1	0
headache	2	1	1	2
Gastrointestinal				
nausea	6	1	1	2
vomiting	<1	0	0	0
dyspepsia	3	1	1	0
abdominal pain	0	0	1	2
diarrhea	<1	0	2	0
taste distortion	1	0	0	0
Central and Peripheral Nervous Systems				
dizziness	11	3	4	4
paresthesias	<1	0	0	0
drowsiness	<1	2	2	2
Autonomic Nervous System				
nasal stuffiness	3	0	0	0
ejaculation failure	2	0	0	0
impotence	1	0	1	3
increased sweating	<1	0	0	0
Cardiovascular				
edema	1	0	0	0
postural hypotension	1	0	0	0
bradycardia	0	0	5	12
Respiratory				
dyspnea	2	0	1	2
Skin				
rash	1	0	0	0
Special Senses				
vision abnormality	1	0	0	0
vertigo	2	1	0	0

The adverse effects were reported spontaneously and are representative of the incidence of adverse effects that may be observed in a properly selected hypertensive patient population, i.e. a group excluding patients with bronchospastic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy.

Clinical trials also included studies utilizing daily doses up to 2400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are clearly or possibly drug related.

Labetalol HCl

Daily Dose (mg)	200	300	400	600	800
Number of Patients	522	181	606	608	503
Dizziness (%)	2	3	3	3	5
Fatigue	2	1	4	4	5
Nausea	<1	0	1	2	4
Vomiting	0	0	<1	<1	<1
Dyspepsia	1	0	2	1	1
Paresthesias	2	0	2	2	1
Nasal Stuffiness	1	1	2	2	2
Ejaculation Failure	0	2	1	2	3
Impotence	1	1	1	1	2
Edema	1	0	1	1	1

Daily Dose (mg)	900	1200	1600	2400
Number of Patients	117	411	242	175
Dizziness (%)	1	9	13	16
Fatigue	3	7	6	10
Nausea	0	7	11	19
Vomiting	0	1	2	3
Dyspepsia	0	2	2	4
Paresthesias	1	2	5	5
Nasal Stuffiness	2	4	5	6
Ejaculation Failure	0	4	3	5
Impotence	4	3	4	3
Edema	0	1	2	2

In addition, a number of other less common adverse events have been reported

Body as a Whole

Fever

Cardiovascular

Hypotension, and rarely, syncope, bradycardia, heart block

Central and Peripheral Nervous Systems

Paresthesias, most frequently described as scalp tingling. In most cases, it was mild, transient and u occurred at the beginning of treatment.

Collagen Disorders

Systemic lupus erythematosus; positive antinuclear factor (ANF)

Eyes

Dry eyes.

Immunological System

Antimitochondrial antibodies.

Liver and Biliary System

Hepatic necrosis; hepatitis; cholestatic jaundice; elevated liver function tests.

Musculoskeletal System

Muscle cramps; toxic myopathy.

Respiratory System

Bronchospasm.

Skin and Appendages

Rashes of various types, such as generalized maculopapular, lichenoid; urticarial; bullous lichen pla psoriaform; facial erythema; Peyronie's disease; reversible alopecia.

Urinary System

Difficulty in micturition, including acute urinary bladder retention.

Hypersensitivity

Rare reports of hypersensitivity (e.g., rash, urticaria, pruritus, angioedema, dyspnea) and anaphylactoid reactio Following approval for marketing in the United Kingdom, a monitored release survey involving approxima 6,800 patients was conducted for further safety and efficacy evaluation of this product. Results of this su indicate that the type, severity, and incidence of adverse effects were comparable to those cited above.

Potential Adverse Effects

In addition, other adverse effects not listed above have been reported with other beta-adrenergic bloc agents.

Central Nervous System

Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disor tation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decrea performance on neuropsychometrics.

Cardiovascular

Intensification of AV block (see **CONTRAINDICATIONS**)

Allergic

Fever combined with aching and sore throat; laryngospasm; respiratory distress.

Hematologic

Agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura.

Gastrointestinal

Mesenteric artery thrombosis, ischemic colitis.

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported w labetalol.

Clinical Laboratory Tests

There have been reversible increases of serum transaminases in 4% of patients treated with labetalol and test and more rarely, reversible increases in blood urea.

OVERDOSAGE

Overdosage with labetalol HCl tablets causes excessive hypotension that is posture sensitive, and sometime excessive bradycardia. Patients should be placed supine and their legs raised if necessary to improve the blo supply to the brain. If overdosage with labetalol follows oral ingestion, gastric lavage or pharmacologica induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion. The followi additional measures should be employed if necessary: *Excessive bradycardia* - administer atropine or epinephrir *Cardiac failure* - administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be usef *Hypotension* - administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephri may be the drug of choice. *Bronchospasm* - administer epinephrine and/or an aerosolized beta$_2$-agonis *Seizures* -administer diazepam.

In severe beta-blocker overdose resulting in hypotension and or bradycardia, glucagon has been shown to b effective when administered in large doses (5 to 10 mg rapidly over 30 seconds, followed by continuous infusio of 5 mg/hr that can be reduced as the patient improves).

Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol from the general circulatio (<1%).

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater tha 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alon or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may b titrated in increments of 100 mg b.i.d. every 2 or 3 days. The usual maintenance dosage of labetalol HCl i between 200 and 400 mg twice daily.

Since the full antihypertensive effect of labetalol is usually seen within the first 1 to 3 hours of the initial dose o dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established i the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits approximately 12 hours after a dose, to determine whether further titration is necessary.

Patients with severe hypertension may require from 1200 mg to 2400 mg per day, with or without thiazid diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered b.i.d., th same total daily dose administered t.i.d. may improve tolerability and facilitate further titration. Titration increment should not exceed 200 mg b.i.d.

When a diuretic is added, an additive antihypertensive effect can be expected. In some cases this may necessitate a labetalol HCl dosage adjustment. As with most antihypertensive drugs, optimal dosages of labetalol HC tablets are usually lower in patients also receiving a diuretic.

When transferring patients from other antihypertensive drugs, labetalol HCl tablets should be introduced as recommended and the dosage of the existing therapy progressively decreased.

HOW SUPPLIED

Labetalol hydrochloride tablets are available as yellow, round, film-coated tablets, debossed with a bisect, "4364" on one side and "100" on the other containing 100 mg of labetalol hydrochloride.

Labetalol hydrochloride tablets are available as white, round, film-coated tablets, debossed with a bisect, "4365" on one side and "200" on the other containing 200 mg of labetalol hydrochloride.

Labetalol hydrochloride tablets are available as green, round, film-coated tablets, debossed with "4366" on one side and "300" on the other containing 300 mg of labetalol hydrochloride.

All strengths are packaged in bottles of 100, 500, and 1000 tablets.

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

MANUFACTURED BY
ZENITH GOLDLINE PHARMACEUTICALS, INC
FT. LAUDERDALE, FL 33309

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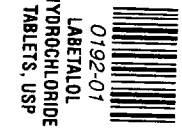
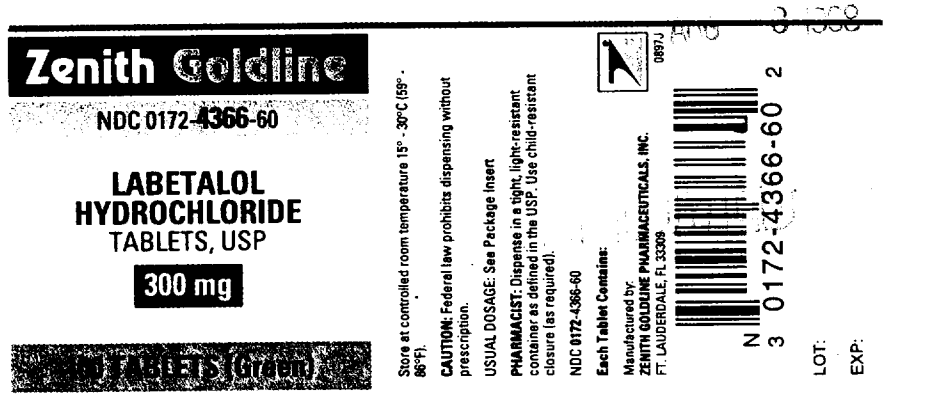
LABETALOL HYDROCHLORIDE TABLETS, USP




Zenith Goldline
NDC 0172-4366-60
LABETALOL HYDROCHLORIDE
TABLETS, USP
300 mg
100 TABLETS (Green)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4366-60
Each Tablet Contains:
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
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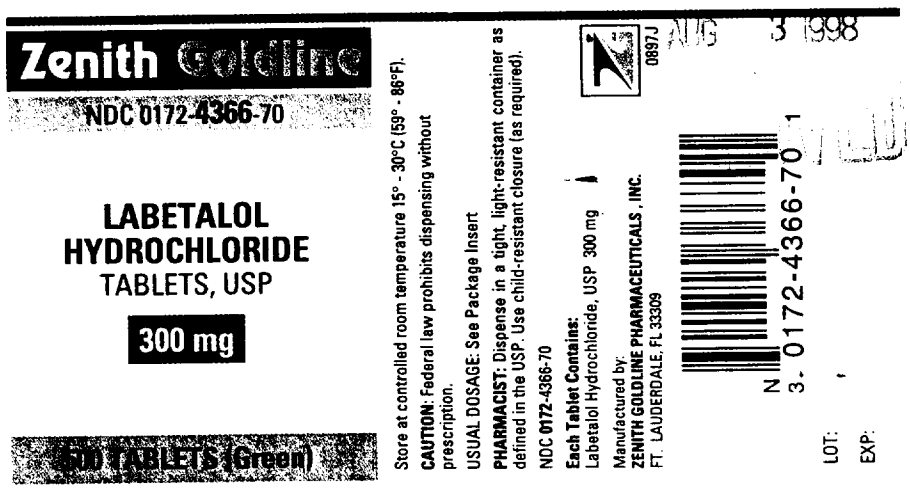
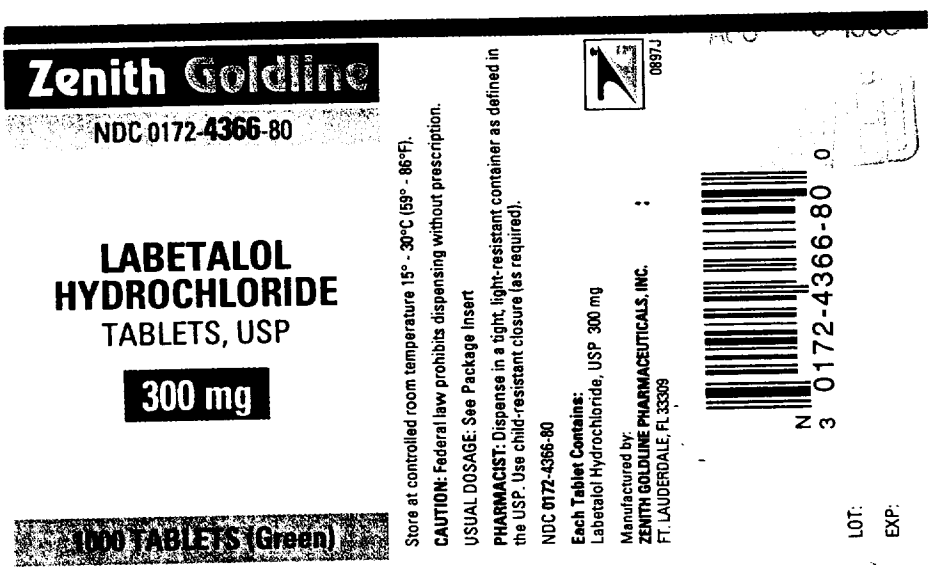

Zenith Goldline
NDC 0172-4366-70
LABETALOL HYDROCHLORIDE
TABLETS, USP
300 mg
500 TABLETS (Green)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4366-70
Each Tablet Contains:
Labetalol Hydrochloride, USP 300 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0897J
N 3 0172-4366-70 1
LOT:
EXP:


Zenith Goldline
NDC 0172-4366-80
LABETALOL HYDROCHLORIDE
TABLETS, USP
300 mg
1000 TABLETS (Green)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4366-80
Each Tablet Contains:
Labetalol Hydrochloride, USP 300 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0897J
N 3 0172-4366-80 0
LOT:
EXP:

Zenith Goldline

NDC 0172-4365-60

LABETALOL HYDROCHLORIDE
TABLETS, USP
200 mg

Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4365-60
Each Tablet Contains:
Labetalol Hydrochloride, USP 200 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0697J

AUG 3 1998

N 3 0172-4365-60 5

LOT:
EXP:

Zenith Goldline

NDC 0172-4365-70

LABETALOL HYDROCHLORIDE
TABLETS, USP
200 mg

Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4365-70
Each Tablet Contains:
Labetalol Hydrochloride, USP 200 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0697J

AUG 3 1998

N 3 0172-4365-70 4

LOT:
EXP:

Zenith Goldline

NDC 0172-4365-80

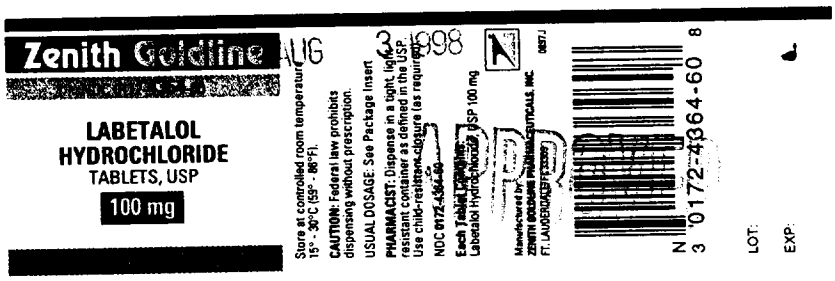
LABETALOL HYDROCHLORIDE
TABLETS, USP
200 mg

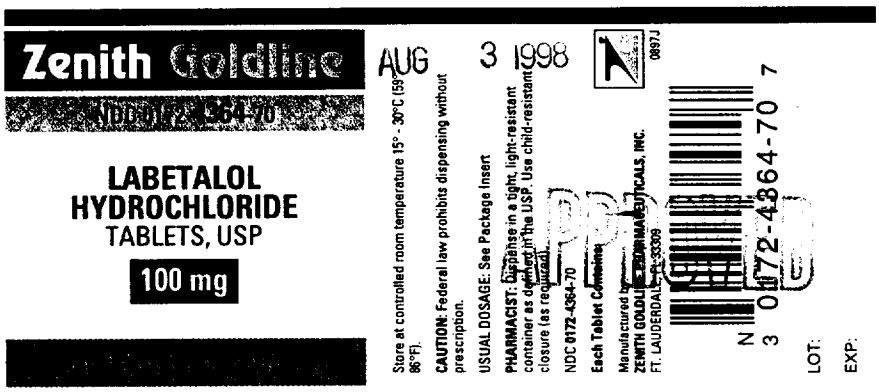
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4365-80
Each Tablet Contains:
Labetalol Hydrochloride, USP 200 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0697J

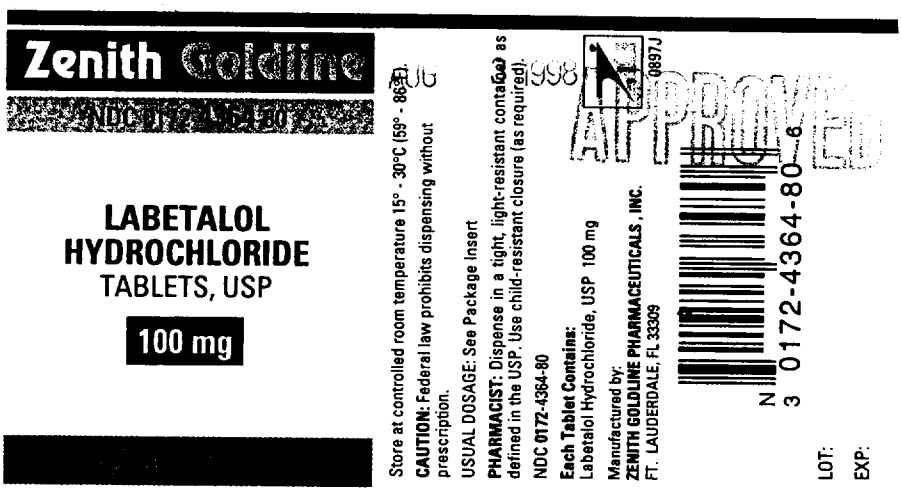
AUG 3 1998

N 3 0172-4365-80 3

LOT:
EXP:


Zenith Goldline
LABETALOL
HYDROCHLORIDE
TABLETS, USP
100 mg
AUG 3 1998
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4364-60
Each Tablet Contains:
Labetalol Hydrochloride, USP 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0897J
N 3 0172-4364-60 8
LOT:
EXP:


Zenith Goldline
LABETALOL
HYDROCHLORIDE
TABLETS, USP
100 mg
AUG 3 1998
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4364-70
Each Tablet Contains:
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0897J
N 3 0172-4364-70 7
LOT:
EXP:


Zenith Goldline
LABETALOL
HYDROCHLORIDE
TABLETS, USP
100 mg
AUG 3 1998
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).
NDC 0172-4364-80
Each Tablet Contains:
Labetalol Hydrochloride, USP 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0897J
N 3 0172-4364-80 6
LOT:
EXP: