Labetalol Hydrochloride

CATEGORIES:

Ingredients: Labetalol Hydrochloride.
Indications: Hypertension, essential.
Off-label Indications: Not clinically relevant: Angina Pectoris, Chronic Stable; Hypertension, Acute (during laryngoscopy); Hypotension, Controlled (to produce, during anesthesia); Pheochromocytoma; Tetanus, Severe.
Pregnancy Category C.
FDA Approved 1984-08-01.
DRUG CLASS: Antiadrenergics, beta blocking.

Brand Names: Abetol (Italy); Albetol (Finland); Amipress (Italy); Biascor (Argentina); Hybloc (New-zealand); Ipolab (Italy); Labelol (Argentina); Labesine (Korea); Lamitol (Slovenia); Liondox (Argentina); Normodyne (US); Presolol (Australia, Taiwan); Pressalolo (Italy); Salmagne (Greece); Trandate (US, Austria, Belgium, Canada, Chile, Czech-republic, Denmark, England, France, Hong-kong, Hungary, Ireland, Italy, Japan, Korea, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, Taiwan, Turkey, Venezuela). (International brand names outside U.S. in italics)

DESCRIPTION:

Labetalol hydrochloride is an adrenergic receptor blocking agent that has both selective alpha\_1-adrenergic and nonselective beta-adrenergic receptor blocking actions in a single substance. Labetalol hydrochloride is a racemate, chemically designated as 2-hydroxy-5-[(1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide monohydrochloride. Labetalol hydrochloride has the empirical formula C\textsubscript{19}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3}·HCl and a molecular weight of 364.9. It has two asymmetric centers and therefore exists as a molecular complex of two diastereoisomeric pairs. Dilevalol, the R,R\textsuperscript{′} stereoisomer, makes up 25\% of racemic labetalol. Labetalol hydrochloride is a white or off-white crystalline powder, soluble in water.

Injection

Labetalol hydrochloride injection is a clear, colorless to light yellow, aqueous, sterile, isotonic solution for intravenous (IV) injection. It has a pH range of 3-4. Each ml contains 5 mg labetalol hydrochloride, 45 mg anhydrous dextrose, 0.1 mg edetate disodium; 0.8 mg methylparaben and 0.1 mg propylparaben as preservatives, citric acid monohydrate and sodium hydroxide, as necessary, to bring the solution into the pH range.

Tablets

Labetalol hydrochloride tablets contain 100, 200 or 300 mg labetalol hydrochloride and are taken orally. The tablets also contain the inactive ingredients corn starch, FD&C yellow no. 6 (100 and 300 mg tablets only), hydroxypropyl methylcellulose, lactose, magnesium stearate, methylparaben, pregelatinized corn starch, propylparaben, sodium benzoate (200 mg tablet only), talc (100 mg tablet only), and titanium dioxide.

CLINICAL PHARMACOLOGY:

Labetalol HCl 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 IV 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 HCl 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 HCl'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. Beta₂-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 HCl 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 to patients with coronary artery disease had no significant effect on sinus rate, intraventricular conduction, or QRS duration. The atrioventricular (AV) conduction time was modestly prolonged in 2 of 7 patients. In another study, IV labetalol HCl 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 HCl produces dose-related falls in blood pressure without reflex tachycardia and without significant reduction in heart rate, presumably through a mixture of its alpha- 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 mildly to severely hypertensive patients with normal renal function.

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. Beta₂-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.

**Injection**

Due to the alpha₁-receptor blocking activity of labetalol HCl, blood pressure is lowered more in the standing than in the supine position, and symptoms of postural hypotension can occur. During dosing with IV labetalol HCl, the contribution of the postural component should be considered when positioning patients for treatment, and patients should not be allowed to move to an erect position unmonitored until their ability to do so is established.

In a clinical pharmacologic study in severe hypertensives, an initial 0.25 mg/kg injection of labetalol HCl, administered to patients in the supine position, decreased blood pressure by an average of 11/7 mm Hg. Additional injections of 0.5 mg/kg at 15 minute intervals up to a total cumulative dose of 1.75 mg/kg of labetalol HCl caused further dose-related decreases in blood pressure. Some patients required cumulative doses of up to 3.25 mg/kg. The maximal effect of each dose level occurred within 5 minutes. Following discontinuation of IV treatment with labetalol HCl, the blood pressure rose gradually and progressively, approaching pretreatment baseline values within an average of 16-18 hours in the majority of patients.

Similar results were obtained in the treatment of patients with severe hypertension requiring urgent blood pressure reduction with an initial dose of 20 mg (which corresponds to 0.25 mg/kg for an 80 kg patient) followed by additional doses of either 40 or 80 mg at 10 minute intervals to achieve the desired effect, or up to a cumulative dose of 300 mg. Labetalol HCl administered as a continuous IV infusion, with a mean dose of 136 mg (27-300 mg) over a period of 2-3 hours (mean of 2 hours and 39 minutes) lowered the blood pressure by an average of 60/35 mmHg.

**Tablets**

Due to the alpha₁-receptor blocking activity of labetalol HCl, 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 more likely to occur 2-4 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 2-4 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 24-72 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 antianginal efficacy of labetalol HCl has not been studied. In 37 patients with hypertension and coronary artery disease, labetalol HCl did not increase the incidence or severity of angina attacks.

Pharmacokinetics and 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 55-60% 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 HCl from the general circulation (<1%).

Injection

Following IV infusion of labetalol, the elimination half-life is about 5.5 hours and the total body clearance is approximately 33 ml/min/kg. The plasma half-life of labetalol following oral administration is about 6-8 hours. 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.

Tablets

Labetalol HCl is completely absorbed from the gastrointestinal tract with peak plasma levels occurring 1-2 hours after oral administration. The relative bioavailability of labetalol HCl tablets compared to an oral solution is 100%. The absolute bioavailability (fraction of drug reaching systemic circulation) of labetalol when compared to an IV infusion is 25%; this is due to extensive "first-pass" metabolism. Despite "first-pass" metabolism there is a linear relationship between oral doses of 100-3000 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 6-8 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.

Elderly Patients

Some pharmacokinetic studies indicate that the elimination of labetalol is reduced in elderly patients. Therefore, although elderly patients may initiate therapy at the currently recommended dosage of 100 mg bid, elderly patients will generally require lower maintenance dosages than nonelderly patients.

INDICATIONS AND USAGE:

Injection

Labetalol HCl injection is indicated for control of blood pressure in severe hypertension.

Tablets

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

Labetalol HCl injection and 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). Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with a history of obstructive airway disease, including asthma.

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 2 deaths. Dilevalol HCl is 1 of the 4 isomers of labetalol HCl. Thus, for patients taking labetalol, periodic determination of suitable hepatic laboratory tests would be appropriate. 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 laboratory evidence of liver injury or jaundice, labetalol HCl 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 HCl 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 HCl 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 HCl therapy should be withdrawn (gradually, if possible).

Pheochromocytoma

Labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required-(Injection). However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl 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 of desirability of withdrawing beta-blocking therapy before a 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 HCl's alpha-adrenergic activity has not been evaluated in this setting.
A synergism between labetalol HCl and halothane anesthesia has been shown (see DRUG INTERACTIONS).

**Injection Ischemic Heart Disease**

Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of labetalol HCl is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, labetalol HCl administration should be reinstated promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

**Nonallergic Bronchospasm (e.g., chronic bronchitis and emphysema)**

Since labetalol HCl injection at the usual IV therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

**Major Surgery**

Several deaths have occurred when labetalol HCl was used during surgery (including when used in cases to control bleeding).

**Rapid Decreases of Blood Pressure**

Caution must be observed when reducing severely elevated blood pressure. A number of adverse reactions, including cerebral infarction, optic nerve infarction, angina, and ischemic changes in the electrocardiogram have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

**Tablets Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal**

Angina pectoris has not been reported upon labetalol HCl 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 HCl tablets, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1-2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, labetalol HCl administration should be reinstated 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 HCl 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 HCl tablets may be used with caution, however, in patients who do not respond to, or cannot tolerate, other antihypertensive agents. It is prudent, if labetalol HCl is used, to use the smallest effective dose, so that inhibition of endogenous or exogenous beta-agonists is minimized.

**PRECAUTIONS:**

**General**

**Impaired Hepatic Function:** Labetalol HCl 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.

Injection Following Coronary Artery Bypass Surgery

In one uncontrolled study, patients with low cardiac indices and elevated systemic vascular resistance following IV labetalol HCl experienced significant declines in cardiac output with little change in systemic vascular resistance. One of these patients developed hypotension following labetalol treatment. Therefore, use of labetalol HCl should be avoided in such patients.

High-Dose Labetalol HCl

Administration of up to 3 g/day as an infusion for up to 2-3 days has been anecdotally reported; several patients experienced hypotension or bradycardia.

Hypotension

Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol HCl injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Information for the Patient

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl 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 HCl, 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).

Injection

The following 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. During and immediately following (for up to 3 hours) labetalol HCl injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on labetalol HCl tablets, following adequate control of blood pressure with labetalol HCl injection, appropriate directions for titration of dosage should be provided (see DOSAGE AND ADMINISTRATION).

Laboratory Tests Injection

Routine laboratory tests are ordinarily not required before or after IV labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Tablets

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/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 when measured by fluorimetric or photometric methods. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, 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** HCl 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 HCl 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, and Impairment of Fertility**

Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl 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 Effects**

Teratogenic studies have been performed with labetalol HCl 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 HCl in rabbits at IV 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** HCl 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 HCl for hypertension during pregnancy. Oral administration of labetalol to rats during late gestation through weaning at doses of 2-4 times the MRHD caused a decrease in neonatal survival.

**Labor and Delivery**

**Labetalol** HCl 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 injection or tablets are administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in children have not been established.

**Geriatric Use Tablets**

As in the general population, some elderly patients (60 years of age and older) have experienced orthostatic hypotension, dizziness, or lightheadedness during treatment with labetalol. Because elderly patients are generally more likely than younger patients to experience orthostatic symptoms, they should be cautioned about the possibility of such side effects during treatment with labetalol.

**INTERACTIONS:**

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor, as compared to 0.7% reported to occur with labetalol HCl 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 HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, 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 HCl. During controlled hypotensive anesthesia using labetalol HCl 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 HCl.

Labetalol HCl 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 HCl 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 reactions 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.

Injection

Since labetalol HCl injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

ADVERSE REACTIONS:

Injection

Labetalol HCl injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence, 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving labetalol HCl injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with labetalol HCl injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.
Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.
Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.
Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.
Psychiatric Disorders: Somnolence/yawning in 3.
Respiratory System: Wheezing in 1.
Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see labetalol HCl tablet information for details).

Tablets

Most adverse effects are mild and transient and occur early in the course of treatment. In controlled clinical trials of 3-4 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, other agents with solely beta-blocking activity used in the control groups led to discontinuation in 8-10% of patients, and a centrally acting alpha-agonist in 30% of patients.
The incidence rates of adverse reactions listed in TABLE 1 were derived from multicenter, controlled clinical trials comparing labetalol HCl, placebo, metoprolol, and propranolol over treatment periods of 3 and 4 months. Where the frequency of adverse effects for labetalol HCl 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.

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<th>Body as a Whole</th>
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<th>Propranolol (n=84)</th>
<th>Metoprolol (n=49)</th>
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<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Impotence</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Increased sweating</td>
<td>&lt;1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Labetalol HCl (n=227)</th>
<th>Placebo (n=98)</th>
<th>Propranolol (n=84)</th>
<th>Metoprolol (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>12%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Labetalol HCl (n=227)</th>
<th>Placebo (n=98)</th>
<th>Propranolol (n=84)</th>
<th>Metoprolol (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>2%</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin</th>
<th>Labetalol HCl (n=227)</th>
<th>Placebo (n=98)</th>
<th>Propranolol (n=84)</th>
<th>Metoprolol (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Special Senses</th>
<th>Labetalol HCl (n=227)</th>
<th>Placebo (n=98)</th>
<th>Propranolol (n=84)</th>
<th>Metoprolol (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision abnormality</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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 TABLE 2 which depicts the entire US therapeutic trials data base for adverse reactions that are clearly or possibly drug related.
TABLE 2
Labetolol HCl Daily Dose (mg)

<table>
<thead>
<tr>
<th>Dizziness</th>
<th>Fatigue</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Dyspepsia</th>
<th>Paresthesia</th>
<th>Nasal stuffiness</th>
<th>Ejaculation failure</th>
<th>Impotence</th>
<th>Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>2%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>3%</td>
<td>1%</td>
<td>0%</td>
<td>&lt;1%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>3%</td>
<td>4%</td>
<td>2%</td>
<td>&lt;1%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>1%</td>
<td>3%</td>
<td>5%</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>2%</td>
<td>1%</td>
<td>3%</td>
<td>0%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>4%</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>4%</td>
<td>2%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>3%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

In addition, a number of the 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:** Paresthesia, most frequently described as scalp tingling. In most cases, it was mild and transient and usually occurred at the beginning of treatment.

**Collagen Disorders:** Systemic lupus erythematosus, positive antinuclear factor.

**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 planus, 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 reactions.

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6800 patients was conducted for further safety and efficacy evaluation of this product. Results of this survey 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 blocking agents.

**Central Nervous System:** Reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly cloudy sensorium, and decreased performance on psychometrics.

**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 with labetalol HCl.

**Clinical Laboratory Tests**
There have been reversible increases of serum transaminases in 4% of patients treated with labetalol HCl and tested, and more rarely, reversible increases in blood urea.

**OVERDOSAGE:**

Overdosage with labetalol HCl injection or tablets causes excessive hypotension that is posture sensitive, and sometimes, excessive bradycardia. Patients should be placed supine and their legs raised if necessary to improve the blood supply to the brain. If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) may be useful for removal of the drug shortly after ingestion. The following additional measures should be employed if necessary: *Excessive bradycardia:* Administer atropine or epinephrine. *Cardiac failure:* Administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. *Hypotension:* Administer vasopressors, e.g., norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. *Bronchospasm:* Administer epinephrine and/or an aerosolized beta₂-agonist. *Seizures:* Administer diazepam.

In severe beta-blocker overdose resulting in hypotension and/or bradycardia, glucagon has been shown to be effective when administered in large doses (5-10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg/h that can be reduced as the patient improves). Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol HCl from the general circulation (<1%). The oral LD₅₀ value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The IV LD₅₀ in these species is 50-60 mg/kg.

**DOSAGE AND ADMINISTRATION:**

**Injection**

Labetalol HCl injection is intended for IV use in hospitalized patients. DOSAGE MUST BE INDIVIDUALIZED depending upon the severity of hypertension and the response of the patient during dosing.

Patients should always be kept in a supine position during the period of IV drug administration. A substantial fall in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position should be established before permitting any ambulation, such as using toilet facilities.

Either of two methods of administration of labetalol HCl injection may be used: a) repeated IV injection, b) slow continuous infusion.

**Repeated Intravenous Injection**

Initially, labetalol HCl injection should be given in a 20 mg dose (which corresponds to 0.25 mg/kg for an 80 kg patient) by slow IV injection over a 2 minute period. Immediately before the injection and at 5 and 10 minutes after injection, supine blood pressure should be measured to evaluate response. Additional injections of 40 or 80 mg can be given at 10 minute intervals until a desired supine blood pressure is achieved or a total of 300 mg labetalol HCl has been injected. The maximum effect usually occurs within 5 minutes of each injection.

**Slow Continuous Infusion**

Labetalol HCl injection is prepared for continuous IV infusion by diluting the vial contents with commonly used IV fluids (see Compatibility With Commonly Used Intravenous Fluids). Examples of methods of preparing the infusion solution are:

Add 40 ml labetalol HCl injection to 160 ml of a commonly used IV fluid such that the resultant 200 ml of solution contains 200 mg of labetalol HCl, 1 mg/ml. The diluted solution should be administered at a rate of 2 ml/min to deliver 2 mg/min.

Alternatively, add 40 ml of labetalol HCl injection to 250 ml of a commonly used IV fluid. The resultant solution will contain 200 mg of labetalol HCl, approximately 2 mg/3 ml. The diluted solution should be administered at a rate of 3 ml/min to deliver approximately 2 mg/min.
The rate of infusion of the diluted solution may be adjusted according to the blood pressure response, at the discretion of the physician. To facilitate a desired rate of infusion, the diluted solution can be infused using a controlled administration mechanism, e.g., graduated burette or mechanically driven infusion pump.

Since the half-life of labetalol is 5-8 hours, steady-state blood levels (in the face of a constant rate of infusion) would not be reached during the usual infusion time period. The infusion should be continued until a satisfactory response is obtained and should then be stopped and oral labetalol HCl started (see Initiation of Dosing With Labetalol HCl Tablets). The effective IV dose is usually in the range of 50-200 mg. A total dose of up to 300 mg may be required in some patients.

**Blood Pressure Monitoring**

The blood pressure should be monitored during and after completion of the infusion or IV injections. Rapid or excessive falls in either systolic or diastolic blood pressure during IV treatment should be avoided. In patients with excessive systolic hypertension, the decrease in systolic pressure should be used as an indicator of effectiveness in addition to the response of the diastolic pressure.

**Initiation of Dosing With Labetalol HCl Tablets**

Subsequent oral dosing with labetalol HCl tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 or 400 mg, depending on the blood pressure response. Thereafter, inpatient titration with labetalol HCl tablets may proceed as shown in TABLE 3.

**TABLE 3 Inpatient Titration Instructions**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Daily Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg bid</td>
<td>400 mg</td>
</tr>
<tr>
<td>400 mg bid</td>
<td>800 mg</td>
</tr>
<tr>
<td>800 mg bid</td>
<td>1600 mg</td>
</tr>
<tr>
<td>1200 mg bid</td>
<td>2400 mg</td>
</tr>
</tbody>
</table>

* If needed, the total daily dose may be given in 3 divided doses.

The dosage of labetalol HCl tablets used in the hospital may be increased at 1 day intervals to achieve the desired blood pressure reduction. For subsequent outpatient titration or maintenance dosing see the labetalol HCl tablets section for additional recommendations.

**Compatibility With Commonly Used Intravenous Fluids**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Labetalol HCl injection was tested for compatibility with commonly used IV fluids at final concentrations of 1.25-3.75 mg labetalol HCl per ml of the mixture. Labetalol HCl injection was found to be compatible with and stable (for 24 hours refrigerated or at room temperature) in mixtures with the following solutions: Ringers injection, lactated Ringers injection, 5% dextrose and Ringers injection, 5% lactated Ringers and 5% dextrose injection, 5% dextrose injection, 0.9% sodium chloride injection, 5% dextrose and 0.2% sodium chloride injection, 2.5% dextrose and 0.45% sodium chloride injection, 5% dextrose and 0.9% sodium chloride injection, 5% dextrose and 0.33% sodium chloride injection.

Labetalol HCl injection was NOT compatible with 5% sodium bicarbonate injection. Care should be taken when administering alkaline drugs, including furosemide, in combination with labetalol. Compatibility should be assured prior to administering these drugs together.

**Tablets**

DOSAGE MUST BE INDIVIDUALIZED. The recommended initial dose is 100 mg twice daily whether used alone or added to a diuretic regimen. After 2 or 3 days, using standing blood pressure as an indicator, dosage may be titrated in increments of 100 mg bid every 2 or 3 days. The usual maintenance dosage of labetalol HCl is between 200 and 400
mg twice daily. Since the full antihypertensive effect of labetalol HCl is usually seen within the first 1-3 hours of the initial dose or dose increment, the assurance of a lack of an exaggerated hypotensive response can be clinically established in the office setting. The antihypertensive effects of continued dosing can be measured at subsequent visits, approximately 12 hours after a dose, to determine whether future titration is necessary.

Patients with severe hypertension may require from 1200-2400 mg per day, with or without thiazide diuretics. Should side effects (principally nausea or dizziness) occur with these doses administered twice daily, the same total daily dose administered 3 times daily may improve tolerability and facilitate further titration. Titration increments should not exceed 200 mg twice daily. 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 HCl 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.

**Elderly Patients**

As in the general patient population, labetalol therapy may be initiated at 100 mg twice daily and titrated upwards in increments of 100 mg bid as required for control of blood pressure. Since some elderly patients eliminate labetalol more slowly, however, adequate control of blood pressure may be achieved at a lower maintenance dosage compared to the general population. The majority of elderly patients will require between 100 and 200 mg bid.

**HOW SUPPLIED:**

**Injection**

Trandate injection, 5 mg/ml, is supplied in 20 ml (100 mg) and 40 ml (200 mg) vials. **Storage:** Store between 2-30°C (36-86°F). Do not freeze. Protect from light.

**Tablets**

Trandate tablets are available in:

- **100 mg:** Light orange, round, scored, film-coated tablets engraved on one side with "TRANDATE 100".
- **200 mg:** White, round, scored, film-coated tablets engraved on one side with "TRANDATE 200".
- **300 mg:** Peach, round, scored, film-coated tablets engraved on one side with "TRANDATE 300".

**Storage:** Store between 2-30°C (36-86°F). Labetalol HCl tablets in the unit-dose boxes should be protected from excessive moisture.