Long-term oral dosing studies with Small amounts of labetalol (approximately 0.004% of the maternal dose) are has been observed during cataract surgery in some

While taking beta-blockers, patients with a history of severe abrupt

Labetalol HCl has been shown to be effective in lowering blood pressure

bioavailability (fraction of drug reaching systemic circulation) of labetalol when compared to an

Labetalol HCl combines both selective, competitive, alpha-adrenergic blocking and nonselective, competitive, beta-adrenergic blocking activity in a single substance. In man, the

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

Labetalol HCl does not abolish the isotropic effect of the pressor response caused by immersing the hand in ice-cold water ("cold-pressor test").

In patients with impaired hepatic function since metabolism of the drug may be diminished.

There does not appear to be a benefit to stopping alpha-l blocker therapy prior to cataract surgery.

Other antihypertensive agents. It is prudent, if labetalol hydrochloride tablets are used, to use the

It is prudent to avoid discontinuing therapy with labetalol HCl tablets abruptly in patients being treated for hypertension.

Labetalol Hydrochloride Tablets, USP are adrenergic receptor blocking agents that have both

If oral administration of labetalol is interrupted or discontinued without a physician’s advice. Patients being treated with labetalol hydrochloride tablets

The plasma half-life of labetalol following oral administration is about 6 to 8 hours. Steady-state plasma levels of labetalol are reached in 4 to 5 days following a single oral dose.

Labetalol HCl does 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 isolated reports of exacerbation of congestive heart failure, palpitations, hypotension, headache, and malaise. Various mechanisms have been proposed to explain these phenomena, among them increased sensitivity to carboxyhemoglobin because of increased numbers of beta receptors.

Labetalol Hydrochloride Tablets, USP are adrenergic receptor blocking agents that have both selective alpha, adrenergic and nonselective beta-adrenergic receptor blocking activities in a single substance.

Labetalol HCl is white or off-white crystalline powder, soluble in water. Labetalol hydrochloride tablets contain 200, 300, or 400 mg of labetalol HCl and are available in delayed release tablets.
The tablets also contain the inactive ingredients lactose monohydrate, corn starch, croscarmellose, magnesium stearate, silicon dioxide, povidone, polyethylene glycol, titanium dioxide and talc.

PHARMACOKINETICS AND METABOLISM:

There are also in a linear correlation between the reduction in exercise-induced labetalol HCl is 37% to 42% at doses of two to four times the MRHD caused a decrease in neonatal survival.

Teratogenic Effects: Pregnancy Category C:

The maximum, steady-state blood pressure response upon oral, twice-a-day dosing occurs within 42 to 72 hours.

The antihypertensive effect of labetalol is of gradual onset, usually becoming apparent by a small decrease in the resting heart rate, alteration of tachycardia produced by propranolol or by exercise, and by attenuation of the reflex increase in BP produced by a cold pressor test.

Labetalol HCl contains approximately 55% to 60% of a dose appears in the urine as conjugates or unchanged labetalol within the first 24 hours of dosing. Labetalol HCl has been shown to have relatively low protein binding in humans. Only negligible amounts of the drug cross the blood-brain barrier in animal studies. Labetalol is approximately 50% protein bound in plasma. Labetalol is readily bound to plasma proteins from the general circulation (<1%).

Labetalol HCl has been shown to cross the placental barrier in humans. Only negligible amounts of labetalol has been shown to cross the placental barrier in humans. Only negligible amounts of labetalol 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 isolated reports of exacerbation of congestive heart failure, palpitations, hypotension, headache, and malaise. Various mechanisms have been proposed to explain these phenomena, among them increased sensitivity to carboxyhemoglobin because of increased numbers of beta receptors.

Although beta-adrenergic receptor blockade is used in the treatment of angina and hypertension, there are also situations in which sympathetic inhibition is desirable. For example, in patients with severely damaged hearts, adequate heart rate control may depend on reducing the chronic beta-stimulation of the heart. Blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic tone on conduction. Aging, adrenergic blockade results in a reduced blood pressure response to stress in anesthetized animals and this is associated with a reduced blood pressure response in patients with echocardiographic evidence of impaired left ventricular function.

Pharmacodynamics:

Although beta-adrenergic receptor blockade is used in the treatment of angina and hypertension, there are also situations in which sympathetic inhibition is desirable. For example, in patients with severely damaged hearts, adequate heart rate control may depend on reducing the chronic beta-stimulation of the heart. Blockade may worsen AV block by preventing the necessary facilitating effects of sympathetic tone on conduction. Aging, adrenergic blockade results in a reduced blood pressure response to stress in anesthetized animals and this is associated with a reduced blood pressure response in patients with echocardiographic evidence of impaired left ventricular function.

Pregnancy Category C:

In juvenile patients with pheochromocytoma. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when using labetalol hydrochloride tablets in patients with pheochromocytoma.

Aguilera and coworkers have also 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 isolated reports of exacerbation of congestive heart failure, palpitations, hypotension, headache, and malaise. Various mechanisms have been proposed to explain these phenomena, among them increased sensitivity to carboxyhemoglobin because of increased numbers of beta receptors.

The maximum, steady-state blood pressure response upon oral, twice-a-day dosing occurs within 42 to 72 hours. The antihypertensive effect of labetalol is of gradual onset, usually becoming apparent by a small decrease in the resting heart rate, alteration of tachycardia produced by propranolol or by exercise, and by attenuation of the reflex increase in BP produced by a cold pressor test.

The oral and intravenous (IV) administration, respectively. Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with a history of obstructive airway disease, including asthma. Labetalol HCl does not increase the incidence or severity of angina attacks.

Almost 70% of the maximum beta-blocking effect is present in 5 hours after the administration of a single oral dose and almost 90% of the maximum beta-blocking effect is present in 48 hours after the administration of a single oral dose. The oral bioavailability of labetalol HCl has not been studied. In patients with hypertension and coronary artery disease, labetalol HCl does not increase the incidence or severity of angina attacks.

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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 breschihombic disease, overt congestive heart failure, or other contraindications to beta-blocker therapy. Clinical trials also included studies utilizing daily doses up to 2,400 mg in more severely hypertensive patients. Certain of the side effects increased with increasing dose, as shown in the following table that depicts the overall U.S. experience base for adverse reactions that are clearly or possibly dose related.

<table>
<thead>
<tr>
<th>Labetalol HCl</th>
<th>Daily Dose (mg)</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>600</th>
<th>800</th>
<th>900</th>
<th>1,200</th>
<th>1,600</th>
<th>2,400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>502</td>
<td>181</td>
<td>606</td>
<td>938</td>
<td>503</td>
<td>117</td>
<td>451</td>
<td>242</td>
<td>179</td>
<td></td>
</tr>
<tr>
<td>Dizziness (%)</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>9</td>
<td>13</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal stuffiness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td>11</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision abnormality</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parosmia</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin rash</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

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 System: Paresthesia, most frequently described as scapulolingual. In most cases, it was mild and transient and usually occurred at the beginning of treatment.

Gastrointestinal: Diarrhea, nausea, vomiting, constipation, flatulence, and anorexia.

Immunological: Rare reports of hypoprothrombinemia (e.g., rash, arthritis, urticaria, angioedema, dyspnea, and anaphylactoid reactions).

Lipi6 and Lipid Systems: Hepatitis, cholestasis, hypercholesterolemia, elevated liver function tests.

Musculoskeletal System: Muscle cramps, tonic myopathy.

Respiratory System:bronchospasm.

Skin and Appendages: Rash of various types, such as generalized maculopapular, lichenoid, urticarial, bullous, urticariform, angioneurotic edema, morbilliform, and erythema multiforme. Pneumonitis, fever, and reversible alopexia.

Urinary System: Difficulty in urination, including acute urinary bladder retention.

Gastrointestinal: Rare reports of hypersensitivity (e.g., rash, arthritis, urticaria, angioedema, dyspnea, and anaphylactoid reactions).

Following approval for marketing in the United Kingdom, a monitored release survey involving approximately 6,000 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 labetalol HCl.

Central Nervous System: Reversal of mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly blurred sensorium, and decreased performance on psychometric tests.

Cardiovascular: Interference of AV block (see CONTRAINDICATIONS).

Allergic: Fever combined with chills and sore throat, laryngospasm, respiratory distress.

Hematologic: Agranulocytosis, thrombocytopenia or nonthrombocytopenic purpura.

Immunologic System:

Ophthalmologic: Rare reports of hypersensitivity (e.g., conjunctivitis, dermatitis, and photophobia).

Eyes:

Evaluation:

DOSAGE AND ADMINISTRATION

OVERDOSAGE

Overdosage with labetalol HCl 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 related 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 ephrine. Cardiac failure—administer a digitalis glycoside and a diuretic. Dopamine or dobutamine may also be useful. Hypotension—administer vasopressors, e.g., norepinephrine. There is pharmacologic evidence that norepinephrine may be the drug of choice. Bronchospasm—administer epinephrine and/or an aerosolized beta-agonist. Seizures—administer dextrose 5% in water. If necessary, a beta-blocker overdose resulting in hypertension and/or bradycardia, glucagon has been shown to be effective when administered in large doses (0.1 to 0.5 mg) orally over 30 seconds, followed by continuous infusion of 5 mg per hour that can be reduced as the patient improves. Further hemodilution non-perfusion dialysis removes a significant amount of labetalol HCl from the general circulation (<1%). The oral LD50 value of labetalol HCl is in the mouse is approximately 600 mg/kg and in the rat is ~2.5 g/kg. The TD50 in these species is 50 to 60 mg/kg.

A 22-lb dog with labetalol HCl.

Client: Par Pharmaceutical HT

Item ID #: 054988412201.01

Proof ID: 23450-3

Barcode Type 1: C128

Date: 06/22/2017

Fold Size: 11.125" x 11.125"

Barcode Type 2: 498841220101

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