1. Name of the Medicinal Product

LABETALOL HYDROCHLORIDE TABLETS USP 200 MG

2. Qualitative and Quantitative Composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABLE CLAIM	OVERAGES %	QTY. / TABLET	PURPOSE
ACTIVE INGREDIENTS						
1.	Labetalol hydrochloride	USP	200 mg	0.00%	200.000 mg	API
INACTIVE INGREDIENTS						
2.	Maize starch	BP	-	0.00%	32.000 mg	Diluent
3.	Anhydrous lactose	BP	-	0.00%	25.000 mg	Diluent
4.	Povidone	BP	-	0.00%	2.000 mg	Binder
5.	Demineral water	INHOUSE	-	0.00%	0.040 ml	Vehicle
6.	Maize starch	BP	-	0.00%	4.500 mg	Binder
7.	Magnesium stearate	BP	-	0.00%	2.000 mg	Lubricant
8.	Purified talc	BP	-	0.00%	4.000 mg	Glidant
9.	Colloidal silicon dioxide	USP	-	0.00%	0.500 mg	Glidant

3. Pharmaceutical Form

Oral Tablet

4. Clinical Particulars

4.1 Therapeutic Indications

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

4.2 Posology and Method of Administration

- The recommended initial dosage is 200 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 b.i.d. every 2 or 3 days. The usual maintenance dosage of Labetalol Hydrochloride is between 200 and 400 mg twice daily.
- Since the full antihypertensive effect of Labetalol Hydrochloride is usually seen within the first 1 to 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 further titration is necessary.

- Patients with severe hypertension may require from 1,200 to 2,400 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 three 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 Hydrochloride dosage adjustment. As with most antihypertensive drugs, optimal dosages of Labetalol Hydrochloride Tablets are usually lower in patients also receiving a diuretic.
- When transferring patients from other antihypertensive drugs, Labetalol Hydrochloride 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 b.i.d. 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 b.i.d.

4.3 Contraindications

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

4.4 Special Warnings and Precautions for Use

- There have been reports of skin rashes and/ or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the drug should be considered if any such reaction is not otherwise explicable.
- There have been rare reports of severe hepatocellular injury with labetalol Hydrochloride therapy. The hepatic injury is usually reversible and has occurred after both short and long term treatment. Appropriate laboratory testing should be done at the first sign or symptom of liver dysfunction. If there is laboratory evidence of liver injury or the patient is jaundiced, labetalol therapy should be stopped and not re-started.
- Due to negative inotropic effects, special care should be taken with patients whose cardiac reserve is poor and heart failure should be controlled before starting Labetalol Hydrochloride therapy. Evidence of recrudescence of such conditions should be regarded as a signal to review therapy.
- Patients particularly those with ischemic heart disease, should not interrupt/ discontinue abruptly Labetalol Hydrochloride therapy. The dosage should gradually be reduced, ie. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop.
- It is not necessary to discontinue Labetalol Hydrochloride therapy in patients requiring anaesthesia but the anaesthetist must be informed and the patient should be given intravenous atropine prior to induction. If beta-blockade is interrupted in preparation for surgery, therapy should be discontinued for at least 24 hours. Anaesthetic agents causing myocardial depression (eg. cyclopropane, trichloroethylene) should be avoided. Labetalol Hydrochloride may enhance the hypotensive effects of halothane.

- In patients with peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication), beta-blockers should be used with great caution as aggravation of these disorders may occur.
- Beta-blockers may induce bradycardia. If the pulse rate decreases to less than 50-55 beats per minute at rest and the patient experiences symptoms related to the bradycardia, the dosage should be reduced.
- Beta-blockers, even those with apparent cardio-selectivity, should not be used in patients with asthma or history of obstructive airways disease unless no alternative treatment is available. In such cases, the risk of inducing bronchospasm should be appreciated and appropriate precautions taken. If bronchospasm should occur after the use of Labetalol Hydrochloride, it can be treated with a $beta_2$-agonist by inhalation, e.g. salbutamol (the dose of which may need to be greater than the usual in asthma) and, if necessary, intravenous atropine 1mg. Adequate supervision must be maintained to permit any necessary adjustment of dosage of the bronchodilator employed.
- Due to a negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block. Patients with liver or kidney insufficiency may need a lower dosage, depending on the pharmacokinetic profile of the compound. The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good in the elderly.
- Patients with a history of psoriasis should take beta-blockers only after careful consideration.
- 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.
- The label will state “Do not take Labetalol Hydrochloride if you have a history of wheezing or asthma as it can make your breathing worse.”
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Concomitant use not recommended: Calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and atrio-ventricular conduction.
Digitalis glycosides used in association with beta-blockers may increase atrio-ventricular conduction time.
Clonidine: Beta-blockers increase the risk of rebound hypertension. When clonidine is used in conjunction with non-selective beta-blockers, such as propranolol, treatment with clonidine should be continued for some time after treatment with the beta-blocker has been discontinued.
Monoamineoxidase inhibitors (except MOA-B inhibitors)
Use with caution:
Class I antiarrhythmic agents (eg. disopyramide, quinidine) and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropic effect.
Insulin and oral antidiabetic drugs may intensify the blood sugar lowering effect, especially of non-selective beta-blockers. Beta- blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).
Anaesthetic drugs may cause attenuation of reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided.
Cimetidine, hydralazine and alcohol may increase the bioavailability of labetalol Hydrochloride.
Several different drugs or drug classes may enhance the hypotensive effects of labetalol: ACE inhibitors; angiotensin-II antagonists; aldesleukin, alprostadil; anxiolytics; hypnotics; moxisylyte.

Several different drugs or drug classes may antagonise the hypotensive effects of labetalol: NSAIDs, corticosteroids; oestrogens; progesterones; xamoterol.
Take into account:

4.6 Pregnancy and Lactation

- Although no teratogenic effects have been demonstrated in animals, Labetalol Hydrochloride should only be used during the first trimester of pregnancy if the potential benefit outweighs the potential risk.
- Labetalol Hydrochloride crosses the placental barrier and the possible consequences of alpha- and beta-adrenoceptor blockade in the foetus and neonate should be borne in mind. Perinatal and neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia) has been rarely reported. Sometimes these symptoms have developed a day or two after birth. Response to supportive measures (e.g. intravenous fluids and glucose) is usually prompt but with severe pre-eclampsia, particularly after prolonged intravenous labetalol, recovery may be slower. This may be related to diminished liver metabolism in premature babies.
- Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period. Intra-uterine and neonatal deaths have been reported with Labetalol but other drugs (e.g. vasodilators, respiratory depressants) and the effects of pre-eclampsia, intra-uterine growth retardation and prematurity were implicated. Such clinical experience warns against unduly prolonging high dose labetalol and delaying delivery and against co-administration of hydralazine.
- Labetalol Hydrochloride is excreted in breast milk. Breast-feeding is therefore not recommended.

4.7 Effects on Ability to Drive and Use Machines

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

4.8 Undesirable Effects

Most adverse effects are mild and transient and occur early in the course of treatment. In controlled clinical trials of 3 to 4 months' duration, discontinuation of Labetalol Hydrochloride 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% to 10% of patients, and a centrally acting alpha-agonist led to discontinuation in 30% of patients.
The incidence rates of adverse reactions listed in the following table 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.
Body as a whole: Fatigue, Asthenia, Headache
Gastrointestinal: Nausea, Vomiting, Dyspepsia, Abdominal pain, Diarrhea, Taste distortion
Central and peripheral nervous systems: Dizziness, Paresthesia, Drowsiness
Autonomic nervous system: Nasal stuffiness, Ejaculation failure, Impotence, Increased sweating
Cardiovascular: Edema, Postural hypotension, Bradycardia
Respiratory: Dyspnea
Skin: Rash

Special senses: Vision abnormality, Vertigo
Musculoskeletal System: Muscle cramps, toxic myopathy
Liver and Biliary System: Hepatic necrosis, hepatitis, cholestatic jaundice, elevated liver function tests

4.9 Overdose

Overdosage with labetalol Hydrochloride 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 Hydrochloride 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: Administers 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 pharmacologic 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 to 10 mg rapidly over 30 seconds, followed by continuous infusion of 5 mg per hour that can be reduced as the patient improves).
Neither hemodialysis nor peritoneal dialysis removes a significant amount of labetalol Hydrochloride from the general circulation (<1%).
The oral LD50 value of labetalol Hydrochloride in the mouse is approximately 600 mg/kg and in the rat > than 2 g/kg. The IV LD50 in these species is 50 to 60 mg/kg.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

The capacity of Labetalol Hydrochloride 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 Hydrochloride's beta1-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 Hydrochloride contribute to a decrease in blood pressure in hypertensive patients. Labetalol Hydrochloride 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 Hydrochloride dosing.

5.2 Pharmacokinetic Properties

Labetalol is completely absorbed after oral administration. Bioavailabilty is significantly reduced to first-pass metabolism in the liver, but can be enhanced by concurrent administration of food. Peak effects are seen 2-4 hours after dosing and the plasma half-life is 6-8 hours. Labetalol exhibits moderately high (~50%)

plasma protein binding. It undergoes hepatic biotransformation with inactive metabolites being excreted in the urine (55-60%) and faeces. Less than 5% of an oral dose is excreted unchanged in the urine.

5.3 Preclinical Safety Data

Not applicable since Labetalol Hydrochloride Tablets have been used in clinical practice for many years and its effects in man are well known.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Maize starch
- Anhydrous lactose
- Demineral water
- Povidone
- Colloidal silicon dioxide
- Purified talc
- Magnesium stearate

6.2 Incompatibilities

None stated

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and Contents of Container

3 X 10 Tablets Alu-Alu pack, packed in printed and laminated carton.

6.6 Special Precautions for Disposal and Other Handling

No special requirements.

7. Marketing Authorisation Holder

West Coast Pharmaceutical Works LTD, Ahmedabad

8. Marketing Authorisation Number(S)

No special requirements.

9. Date of First Authorisation/Renewal of the Authorisation

No special requirements.

10. Date of Revision of the Text

March, 2019