TITLE

Labetalol hydrochloride.

SCOPE

Trade Name

TRANDATE ®

Formulation and Strength

Tablets containing 100 mg, 200 mg labetalol hydrochloride.
Film-coated tablets.

Excipients

Lactose Anhydrous
Microcrystalline Cellulose
Magnesium Stearate
Hypromellose 5cP
Opaspray Orange M-1-3499D:
- Industrial Methylated Spirit
- Sodium Benzoate
- Titanium Dioxide
- Sunset Yellow FCF
- Hypromellose 5cP
- Purified Water

CLINICAL INFORMATION

Indications

Treatment of hypertension when rapid control of blood pressure is essential.

Dosage and Administration

Labetalol tablets should be taken with food.

Populations

- **Adults**

Hypertension - Treatment should start with 100 mg twice daily. If necessary, increases in dosage of 100 mg twice daily should be made at intervals (2 - 14 days). Many patients' blood pressure is controlled by 200 mg twice daily and up to 800 mg daily may be given as a twice daily regimen. In severe, refractory hypertension daily doses up to 2400 mg (in 3 or 4 divided doses) have been given.

Hospital in-patients with severe hypertension may have daily increases in dosage.

Additive hypotensive effects may be expected if labetalol tablets are administered together with other antihypertensives, eg. diuretics, methyldopa etc. When transferring patients from such agents, labetalol tablets should be introduced with a dosage of 100mg twice daily and the previous therapy gradually decreased. Abrupt withdrawal of clonidine or beta-blocking agents is undesirable.

For long-term control of hypertension following the use of labetalol Injection, oral therapy with labetalol tablets should start at 100 mg twice daily.

- **Children**

Safety and efficacy in children have not been established.

- **Elderly**

For initiation of anti-hypertensive therapy, the usual starting dose is 100 mg orally twice daily.

Satisfactory blood pressure control may be achieved with lower maintenance doses than those required by younger patients.

- **Hepatic impairment**

In patients with hepatic impairment, lower doses of the oral formulation may be required (see Warnings and Precautions).

Contra-indications

- Labetalol tablets are contraindicated in second or third degree heart block, cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia.

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

- Labetalol is contra-indicated for patients known to have hypersensitivity to the drug.

Warnings and Precautions

There have been very rare reports of severe hepatocellular injury with labetalol therapy. The hepatic injury is usually reversible and has occurred after both short term 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 should be stopped and not re-started.

Particular care should be taken when labetalol is to be used in patients with hepatic impairment as these patients metabolise labetalol more slowly than patients without hepatic impairment. Lower

doses may be required (see Dosage and Administration, Pharmacokinetics Special Patient Populations).

Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may be exacerbated.

If the patient develops symptomatic bradycardia, then the dosage of labetalol should be reduced.

Given the negative effect of beta-adrenoceptor blocking drugs on atrioventricular conduction time, labetalol should be administered with caution to patients with first-degree atrio-ventricular block.

As with other beta-adrenoceptor blocking drugs, labetalol may mask the symptoms of hypoglycemia in diabetic patients and thyrotoxicosis.

Risk of anaphylactic reaction: While taking β 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.

If patients receiving labetalol require adrenaline treatment, a reduced dosage of adrenaline should be used as concomitant administration of labetalol with adrenaline may result in bradycardia and hypertension (see *Interactions*).

There have been reports of skin rashes and/or dry eyes associated with the use of β-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.

The occurrence of Intraoperative Floppy Iris Syndrome (IFIS, a variation of Small Pupil Syndrome) has been observed during cataract surgery in some patients on, or previously treated with, tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation, current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Special care should be taken with patients who suffer from heart failure or poor left ventricular systolic function. Heart failure should be controlled with appropriate therapy before use of labetalol.

Labetalol need not be discontinued prior to anaesthesia but patients should receive i.v. atropine prior to induction. Labetalol may enhance the hypotensive effects of halothane.

In patients with pheochromocytoma, labetalol may be administered only after adequate alpha-blockade is achieved.

Patients, particularly those with ischaemic heart disease, should not interrupt or discontinue abruptly labetalol therapy.
The dosage should be gradually 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 arrhytmias may develop with abrupt discontinuation of labetalol.

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

The elderly should be treated with caution, starting with a lower dosage

Interactions

The hypotensive effect of labetalol may be reduced when used in combination with prostaglandin synthetase inhibitors (eg. NSAIDs). Dosage adjustments may therefore be necessary.

Labetalol fluoresces in alkaline solution at an excitation wavelength of 334nm and a fluorescence wavelength of 412nm and may therefore interfere with the assays of certain fluorescent substances including catecholamines.

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 HCl, a specific method, such as a high performance liquid chromatographic assay with solid phase extraction should be employed in determining levels of catecholamines.

Labetalol has been shown to reduce the uptake of radioisotopes of metaiodobenzylguanidine (MIBG). Care should therefore be taken in interpreting results from MIBG scintigraphy.
Labetalol may enhance digoxin's effect of reducing ventricular rate.

Concomitant administration of labetalol with adrenaline may result in bradycardia and hypertension (*see Warnings and Precautions*).

Care should be taken if labetalol is used concomitantly with either Class I antiarrhythmic agents or calcium antagonists of the verapamil type.

Concomitant use of tricyclic anti-depressants may increase the incidence of tremor.

Cimetidine, may increase the bioavailability of labetalol and care is required in the oral dosing of the latter.

Pregnancy and Lactation

Pregnancy

Although no teratogenic effects have been demonstrated in animals, labetalol should only be used during the first trimester of pregnancy if the potential benefit outweighs the potential risk.

In humans labetalol crosses the placental barrier and the possibility of the consequences of α- and β-adrenoceptor blockade in the fetus and neonate should be borne in mind. Perinatal and neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia) has been rarely reported. Sometimes these symptoms 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. Intra-uterine and neonatal deaths have been reported 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-administation of hydralazine.

Lactation
Labetalol is excreted in breast milk in small amounts (approximately 0.004% of the maternal dose). Adverse events of unknown causality (sudden death syndrome, diarrhoea, hypoglycaemia) have been reported very rarely in breast-fed neonates. Caution should be exercised when labetalol is administered to breast feeding women.

Ability to perform tasks that require judgement, motor or cognitive skills
The use of labetalol is unlikely to result in any impairment of the ability of patients to drive or operate machinery. However, it should be taken into account that occasionally dizziness or fatigue may occur.

Adverse Reactions
For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects.

The following convention has been utilised for the classification of frequency:- Very common ≥1/10, common ≥1/100, <1/10, uncommon ≥1/1000 and <1/100, rare ≥1/10,000 and <1/1000, very rare <1/10,000.

Side-effects indicated by a hash (#) are usually transient and occur during the first few weeks of treatment.

Immune system disorders
Very common: Positive anti-nuclear antibodies unassociated with disease
Common: Hypersensitivity
Hypersensitivity reactions reported include rash (including reversible lichenoid rash), pruritus, dyspnoea and very rarely drug fever or angioedema.

Psychiatric disorders
Uncommon: #Depressed mood

Nervous system disorders
Common: #Dizziness, #headache, #tingling sensation in scalp
Very rare: Tremor in the treatment of hypertension of pregnancy

Eye disorders
Common: Blurred vision
Very rare: Eye irritation
Blurred vision and eye irritation have been reported but were not necessarily related to labetalol.

Cardiac disorders
Common: Congestive heart failure
Rare: Bradycardia
Very rare: Heart block

Vascular disorders
Common: #Postural hypotension
Very rare: Exacerbation of the symptoms of Raynaud's Syndrome
Postural hypotension is more common at very high doses or if the initial dose is too high or doses are increased too rapidly.
Respiratory, thoracic and mediastinal disorders
Common: #Nasal congestion
Uncommon: Bronchospasm

Gastrointestinal disorders
Common: Nausea
Uncommon: Vomiting, epigastric pain

Hepatobiliary disorders
Common: Raised liver function tests
Very rare: Hepatitis, hepatocellular jaundice, cholestatic jaundice hepatic necrosis
The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of the drug.

Skin disorders and subcutaneous tissue disorders
Uncommon: #Sweating

Musculoskeletal and connective tissue disorders
Uncommon: Cramps
Very rare: Toxic myopathy, systemic lupus erythemateous
Cramps have been reported but were not necessarily related to labetalol.

Renal and urinary disorders
Common: Difficulty in micturition
Very rare: Acute retention of urine

Reproductive system and breast disorders
Common: Ejaculatory failure, Erectile dysfunction

General disorders and administration site disorders
Common: #Tiredness, #lethargy
Very rare: #Ankle oedema

Overdosage

Symptoms and Signs
Profound cardiovascular effects are to be expected, eg. excessive, posture-sensitive hypotension and sometimes bradycardia. Oliguric renal failure has been reported after massive overdosage of labetalol orally.

Treatment
Patients should be laid supine with the legs raised.

Use a cardiac glycoside and a diuretic in cardiac failure; for bronchospasm, administer a β_2-agonist per aerosol. Intravenous atropine 0.25 to 3 mg should be given to relieve bradycardia.

Intravenous noradrenaline 5 to 10 μg initially, repeated according to response, may be preferable to isoprenaline to improve the circulation. Alternatively, noradrenaline may be infused at a rate of 5 μg per minute until the response is satisfactory.

In severe overdose, intravenous glucagon may be preferred: an initial bolus dose of 5 to 10 mg in dextrose or saline should be followed by an intravenous infusion of 5 mg/hour or as sufficient to maintain cardiac output. Transvenous pacing may be required.

Oliguric renal failure has been reported after massive overdosage of labetalol orally. In one case, the use of dopamine to increase the blood pressure may have aggravated the renal failure.

Haemodialysis removes less than 1% labetalol HCl from the circulation.

Further management should be as clinically indicated or as recommended by the national poison centre, where available.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Mechanism of Action
Labetalol lowers blood pressure by blocking peripheral arteriolar alpha- adrenoceptors, thus reducing peripheral resistance, and by concurrent β-blockade, protects the heart from reflex sympathetic drive that would otherwise occur.

Pharmacodynamic Effects
Cardiac output is not significantly reduced at rest or after moderate exercise. Increases in systolic blood pressure during exercise are reduced but corresponding changes in diastolic pressure are essentially normal. All these effects would be expected to benefit hypertensive patients.

In patients with angina pectoris coexisting with hypertension, the reduced peripheral resistance decreases myocardial afterload and oxygen demand. All these effects would be expected to benefit hypertensive patients and those with coexisting angina.

Pharmacokinetics

Absorption
Labetalol is rapidly absorbed from the gastro-intestinal tract with peak plasma levels occurring one to two hours after oral administration. There is a significant first-pass metabolism leading to a bioavailability of approximately 25%, but there is considerable variation.

Distribution
About 50% of labetalol in the blood is protein bound. Only negligible amounts of the drug cross the blood brain barrier in animal studies. Labetalol crosses the placental barrier and is secreted in breast milk.

Metabolism
Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolites.

Elimination
The glucuronide metabolites are excreted both in the urine and via the bile, into the faeces.
The plasma half-life of labetalol is about four hours.

Special Patient Populations
- **Renal Impairment**

Labetalol does not adversely affect renal function and is particularly suitable for use in hypertensive patients with renal disease.

- **Hepatic Impairment**

Labetalol undergoes significant but variable first-pass metabolism when given by the oral route. In a study of 10 patients with histologically proven cirrhosis, exposure to oral labetalol was increased approximately three-fold compared with healthy controls. Inter-subject variability in both patients and controls was high (approximately 2.5-fold). Patients with hepatic impairment may require lower oral doses of labetalol (see Dosage and Administration, Warnings and Precautions).

Non-Clinical Information

- **Carcinogenicity, Mutagenicity**

There was no evidence of mutagenic potential from *in vitro* and *in vivo* tests.

Labetalol showed no evidence of carcinogenesis in long-term studies performed in mice and rats.

PHARMACEUTICAL INFORMATION

Incompatibilities

None known.

Shelf Life

Five years when stored below 30^{o}C.

Storage

Below 30^{0}C

Nature and Contents of Container

Labetalol tablets are supplied in polypropylene containers with a tamper-evident snap-on polyethylene closure.

Use and Handling

None.

Manufacturer: Aspen Bad Oldesloe GmbH, Germany

License Holder: Perrigo Israel Agencies Ltd.
29 Lehi St. Bnei-Brak 51200

License Number:

TRANDATE® TABLETS 100mg	20-86-27785
TRANDATE® TABLETS 200mg	20-84-27786

9.1.2012