TRANDATE
Labetalol Hydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

TRANDATE Injection is a clear, colourless solution, practically free from visible particles, containing 5mg of Labetalol Hydrochloride per ml and supplied in 5ml ampoule.

TRANDATE Tablets are orange, round, biconvex film-coated tablets, engraved TT01 on one face. Each tablet contains 100mg of Labetalol Hydrochloride.

PHARMACEUTICAL FORM

Solution for injection.
Film-coated tablets.

CLINICAL DATA

Therapeutic Indications

Injection is indicated for:

- Severe hypertension, including severe hypertension of pregnancy, when rapid control of blood pressure is essential.
- May be used to achieve controlled hypotension during anaesthesia.

Tablet is indicated for:

- Mild, moderate or severe hypertension.
- Hypertensions in pregnancy.
- Angina pectoris with coexisting hypertension.

Dosage and Method of Administration

Injection:

Posology

Labetalol injection is intended for i.v. use in hospitalised patients.

Populations

- **Adults**

Indication	Dose
Severe Hypertension	Bolus Injection: If it is essential to reduce the blood pressure quickly a dose of 50 mg should be given by I.V. injection (over a period of at least 1 min) and, if necessary, repeated at 5 min intervals until a satisfactory response occurs. The total dose should not exceed 200 mg.

	The maximum effect usually occurs within 5 min and the duration of action is usually about 6 h but may be as long as 18 h.
	Intravenous Infusion: A 1 mg/ml solution of labetalol should be used, i.e. the contents of eight 5 ml ampoules (200 mg) diluted to 200 ml with Sodium Chloride and Dextrose Injection BP or 5% Dextrose Intravenous Infusion BP. The infusion rate should normally be about 160 mg/h but may be adjusted according to the response at the discretion of the physician. The effective dose is usually 50 to 200 mg but infusion should be continued until a satisfactory response is obtained and larger doses may be needed, especially in patients with phaeochromocytoma. In case of severe hypertension of pregnancy, a slower and increasing rate of infusion should be used. Infusion rate should be started at 20 mg/h, then doubled every 30 min until a satisfactory response is obtained or a dosage of 160 mg/h is reached.
Achieving Controlled Hypotension During Anaesthesia	To achieve controlled hypotension during anaesthesia, the recommended starting dose of labetalol injection is 10 to 20 mg intravenously depending on the age and condition of the patient. If satisfactory hypotension is not achieved after 5 min, increments of 5 to 10 mg should be given until the desired level of blood pressure is attained. The mean duration of hypotension following 20 to 25 mg of labetalol is 50 min.
Hypertension Due To Other Causes	Infuse at a rate of 120-160 mg/h until a satisfactory response is obtained, then stop infusion. The effective dose is usually 50 to 200 mg but larger doses may be needed, especially in patients with phaeochromocytoma.

- **Paediatric population:**

The safety and efficacy of labetalol in paediatric patients aged 0 to 18 years have not been established. No data are available.

Method of Administration

Precautions to be taken before handling or administering the medicinal product:

Patients should always receive the drug whilst in the supine or left lateral position.

Raising the patient into the upright position within 3 h of i.v. labetalol administration should be avoided since excessive postural hypotension may occur**.**

It is desirable to monitor the blood pressure and heart rate after injection and during infusion. In most patients, there is a small decrease in the heart rate; severe bradycardia is unusual but may be controlled by injecting atropine 1 to 2 mg intravenously.

Respiratory function should be observed particularly in patients with any known impairment.

Once the blood pressure has been adequately reduced by bolus injection or infusion, maintenance therapy with labetalol tablets should be substituted with a starting dose of 100 mg twice daily.

Labetalol injection has been administered to patients with uncontrolled hypertension already receiving other hypotensive agents, including beta-blocking drugs, without adverse effects.

Tablet:

Posology

Labetalol tablets should be taken with food.

Populations

- **Adults**

Indication	**Dose**
Mild, Moderate Or Severe 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 to 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 hypotensives, e.g. diuretics, methyldopa etc. When transferring patients from such agents, the previous therapy should be gradually decreased.

	For long-term control of hypertension following the use of labetalol injection, oral therapy with labetalol tablets should start at 100 mg twice daily.
Hypertensions In Pregnancy	The initial dosage of 100 mg twice daily may be increased, if necessary, at weekly intervals, by 100 mg twice daily. The severity of the hypertension may require a three times daily regimen. A total daily dose of 2400 mg should not be exceeded.
Angina Pectoris With Co-existing Hypertension	The dose of labetalol is that required to control the hypertension.

- **Paediatric population**

Safety and efficacy in paediatric patients aged 0 to 18 years has not been established. No data are available.

- **Older people:**

In markets where a 50 mg tablet is available:

For initiation of anti-hypertensive therapy, the usual starting dose is 100 mg orally twice daily. However, an initial dosage of 50 mg twice daily may be given.

In markets where a 50 mg tablet is not available:

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.

- **Patients with hepatic impairment:**

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

Contraindications

- Non- selective beta-blockers should not be used in patients with asthma or a history of obstructive airway disease

- Labetalol injection and tablets are contraindicated in second or third degree heart block (unless pacemaker is in situ), cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia

- Uncompensated heart failure

- Unstable / uncontrolled heart insufficiency

- Sick sinus syndrome (including sinus atrial block) unless pacemaker in situ

- Prinzmetal angina

- Sinus node dysfunction

- Labetalol injection and tablets are contraindicated for patients known to have hypersensitivity to the active substance or to any of the excipients listed

Warnings and Precautions

Liver disease
Care should be taken in liver disease. 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 and long term treatment. However, hepatic necrosis, in some cases with fatal outcome, has been reported. 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.

Tablet:
Particular care should be taken when labetalol is 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 Method of Administration, Pharmacokinetic Properties Special Patient Populations.*)

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

Renal impairment
Caution is advised when labetalol is used in patients with severe renal impairment (GFR = 15-29 ml/min/1.73m^2).

Peripheral vascular disease
Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may be exacerbated. Caution is advised in patients with peripheral arterial disease (Raynaud's syndrome, intermittent claudication) as labetalol may exacerbate their symptoms. Alpha-block may counter the unfortunate effect of beta-blockers.

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

First-degree atrio ventricular block
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.

Diabetes mellitus
Care should be taken in case of uncontrolled or difficult-to-control diabetes mellitus. As with other beta-adrenoceptor blocking medicinal products, labetalol may mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients. The hypoglycaemic effect of insulin and oral hypoglycaemic agents may be enhanced by beta blockers.

Thyrotoxicosis
Beta blockers may mask the symptoms of thyrotoxicosis, but the thyroid function is not altered.

Hypersensitivity to beta blockers
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.

Adrenaline
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 with Other Medicinal Products and Other Interactions*).
Upon severe influence of adrenaline as in pheochromocytoma, labetalol may cause a paradoxical blood pressure elevation.

Skin rashes and/or dry eyes
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.

Intraoperative Floppy Iris Syndrome
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.

Heart failure or poor left ventricular function
Special care should be taken with patients who suffer from heart failure or poor left ventricular systolic function. Labetalol is contraindicated in uncontrolled heart failure, but may be used with caution in patients who are well managed and free of symptoms. Heart failure should be controlled with appropriate therapy before use of labetalol.

Use of beta blockers implies a risk of inducing or exacerbating heart failure or obstructive lung disease. In case of heart failure, the myocardial contractility should be maintained and the failure should be compensated. Patients with reduced contractility, particularly the elderly, should be monitored regularly for development of heart failure.

It is strongly recommended not to stop treatment with labetalol abruptly especially in patients with heart failure and patients with angina pectoris (risk of exacerbation of angina, myocardial infarction and ventricular fibrillation).

Inhalation anaesthetics
Care should be taken with concomitant treatment with inhalation anaesthetics *(see Interactions with Other Medicinal Products and Other Interactions)*. 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 volatile anaesthetics.

Metabolic acidosis and pheochromocytoma
Care should be taken in cases of metabolic acidosis and pheochromocytoma. In patients with pheochromocytoma, labetalol may be administered only after adequate alpha-blockade is achieved.

Calcium antagonists
Care should be taken if labetalol is used concomitantly with calcium antagonists, particularly the "calcium entry blockers", which influence contractility and AV conduction negatively.

Care should be taken with concomitant administration of adrenaline, verapamil or Class-1 antiarrhythmics.

Beta blockers have negative inotropic effect, but do not affect the positive inotropic effect of digitalis.

Injection:
Sudden haemorrhage
During anaesthesia, labetalol injection may mask the compensatory physiological responses of sudden haemorrhage (tachycardia and vasoconstriction). Close attention must therefore be paid to blood loss and the blood volume maintained.

Tablet:

Patients, particularly those with ischaemic heart disease, should not interrupt/discontinue abruptly labetalol therapy. Discontinuation in patients with ischemic heart disease should be done gradually during a period of 7–10 days, if possible.

Excipient warnings:

Lactose:

Patients with any of the following rare hereditary conditions should not take this medicine: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Interactions with Other Medicinal Products and Other Interactions

The hypotensive effect of labetalol may be reduced when used in combination with prostaglandin synthetase inhibitors (NSAIDs). Dosage adjustments may therefore be necessary. Additive synergism may occur with other antihypertensive agents.

Labetalol fluoresces in alkaline solution at an excitation wavelength of 334 nanometres and a fluorescence wavelength of 412 nanometres 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 or 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 hydrochloride, 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.

Concomitant treatment with calcium antagonists which are dihydropyridine derivates (e.g. nifedipine) may increase the risk of hypotension and may lead to heart failure in patients with latent cardiac insufficiency. Digitalis glycosides in combination with beta blockers may increase the atrioventricular conduction time. 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.

Increased risk of myocardial depression in combination with Class I antiarrhythmics (e.g. disopyramide and quinidine) and amiodarone (Class III antiarrhythmics).

Risk of marked bradycardia and hypotension in combination with calcium antagonists with negative inotropic effect (e.g. verapamil, diltiazem). Especially in patients with impaired ventricular function and/or conduction disorders. In case of change from a calcium antagonist

to a beta blocker or reverse, new intravenous therapy must not be initiated before at least 48 hours after withdrawal of the former treatment.

Beta blockers, especially non-selective beta blockers, may increase the risk of hypoglycaemia in diabetic patients and mask the symptoms of hypoglycaemia such as tachycardia and tremor, and delay the normalisation of blood sugar after insulin-induced hypoglycaemia, especially non-selective beta blockers. Dose adjustments of oral antidiabetics and insulin may be necessary.

Care should be taken at general anaesthesia of patients using beta blockers. Beta blockers reduce the risk of arrhythmias during anaesthesia, but may lead to reduction of the reflectoric tachycardia and increase the risk of hypotension during anaesthesia. An anaesthetic agent with a low as possible degree of negative inotropic effect should be used. Heart function must be closely monitored and bradycardia due to vagal dominance should be corrected with intravenous administration of atropine, 1-2 mg intravenously (withdrawal prior to surgery, *see Dosage and Method of Administration*).

For withdrawal in patients using both beta blockers and clonidine, gradual discontinuation of the beta blocker must be done several days before discontinuation of clonidine. This is to reduce the potential rebound hypertensive crisis which is a consequence of withdrawal of clonidine. Accordingly, when changing from clonidine to a beta blocker it is important to discontinue clonidine gradually, and start treatment with the beta blocker several days after clonidine has been withdrawn.

Concomitant administration of labetalol with cholinesterase inhibitors may increase the risk of bradycardia.

Concomitant treatment with alpha stimulating adrenergics may increase the risk of increased blood pressure (e.g. phenylpropanolamine and adrenaline), while concomitant treatment with beta stimulating adrenergics results in a mutual reduced effect (antidote effect).

Concomitant use of ergotamine derivates may increase the risk of vasospastic reactions in some patients.

Labetalol has been shown to increase the bioavailability of imipramine by more than 50% through the inhibition of its 2- hydroxylation. Labetalol in combination with imipramine may increase the effect of imipramine and concomitant use of tricyclic antidepressants.

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

Injection:
Labetalol may enhance the hypotensive effects of volatile anaesthetics.

Tablet:
Cimetidine may increase the bioavailability of labetalol and care is required in the oral dosing of the latter. Enhanced blood pressure reduction may occur in case of concomitant use of e.g. nitrates, antipsychotics (fentiazine derivates such as chlorpromazine) and other antipsychotics, antidepressants.

Fertility, Pregnancy and Lactation

Fertility

There are no data on the effects of labetalol on fertility.

Pregnancy

Based on experience during human pregnancy, labetalol is not expected to increase the risk of congenital malformations. Animal studies do not indicate teratogenicity. However toxicity on embryo-foetal development has been noted (*see Non-Clinical Information*).

Due to the pharmacological action of alpha- and beta-adrenoceptor blockade, adverse effects on the foetus and neonate when used in the later stages of pregnancy (bradycardia, hypotension, respiratory depression, hypoglycaemia) should be borne in mind, as labetalol crosses the placental barrier. Close monitoring 24-48 hours after birth is required. Beta-blockers may reduce uterine blood flow.

Labetalol should only be used during pregnancy if the benefits to the mother outweigh the potential risk for the foetus.

Lactation

Labetalol is excreted in breast milk in small amounts (approximately 0.004-0.07% of the maternal dose). Nipple pain and Raynaud's phenomenon of the nipple have been reported (*see Side Effects*). Caution should be exercised when labetalol is administered to breast feeding women.

Effects on The Ability to Drive and Use Machines

Injection:

No common information.

Tablet:

The use of labetalol tablets is unlikely to result in an 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.

Side Effects

Among the most common undesirable effects observed with labetalol tablets and collected from post-marketing reports include: congestive heart failure, postural hypotension, hypersensitivity, lichenoid rash, drug fever, raised liver function tests, difficulty in micturition, dizziness, headache, tingling sensation in scalp, blurred vision, nasal congestion, nausea, erectile dysfunction and ejaculatory failure.

The most common undesirable effects observed with labetalol injection and collected from post-marketing reports include: congestive heart failure, postural hypotension, hypersensitivity, drug fever, raised liver function tests, nasal congestion and erectile dysfunction.

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, not known (cannot be estimated from the available data).

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

Injection:

Body System	**Frequency**	**Side Effects**
Immune System Disorders	Common	Hypersensitivity, drug fever
Metabolism and Nutrition Disorders	Not known	Hyperkalaemia*
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
Respiratory, Thoracic and Mediastinal disorders	Common	#Nasal congestion
	Uncommon	Bronchospasm
Hepatobiliary Disorders	Common	Raised liver function tests
	Very rare	Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis
Reproductive System and Breast Disorders	Common	Erectile dysfunction
	Not known	Nipple pain, Raynaud's phenomenon of the nipple

* Particularly in patients who may have impaired renal excretion of potassium

Description of selected side effects:

Immune system disorders
Hypersensitivity reactions reported include rash, pruritus, dyspnoea and very rarely, drug fever or angioedema.

Vascular disorders
Pronounced postural hypotension may occur if patients are allowed to assume the upright position within 3 h of receiving labetalol injection.

Hepatobiliary disorders
The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of the medicinal product.

Tablets:

Body System	Frequency	Side Effects
Immune System Disorders	Very common	Positive anti-nuclear antibodies unassociated with disease
	Common	Hypersensitivity, lichenoid rash, drug fever
Metabolism and Nutrition Disorders	Not known	Hyperkalaemia*
Psychiatric Disorders	Uncommon	#Depressed mood
Nervous System Disorders	Common	#Dizziness, #headache, #tingling sensation on scalp
	Very rare	Tremor in the treatment of hypertension of pregnancy
Eye Disorders	Common	Blurred vision
	Very rare	Eye irritation
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
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

Skin and Subcutaneous Tissue Disorders	Uncommon	#Sweating
Musculoskeletal and Connective Tissue Disorders	Uncommon	Cramps
	Very rare	Toxic myopathy, systemic lupus erythematosus
Renal and Urinary Disorders	Common	Difficulty in micturition
	Very rare	Acute retention of urine
Reproductive System and Breast Disorders	Common	Erectile dysfunction, ejaculatory failure
	Not known	Nipple pain, Raynaud's phenomenon of the nipple
General Disorders and Administration Site Conditions	Common	#Tiredness, #lethargy
	Very rare	#Ankle oedema

* Particularly in patients who may have impaired renal excretion of potassium

Description of selected side effects:

Immune system disorders
Hypersensitivity reactions reported include rash (including reversible lichenoid rash), pruritus, dyspnoea and very rarely drug fever or angioedema.

Vascular disorders
Postural hypotension is more common at very high doses or if the initial dose is too high or doses are increased too rapidly.

Hepatobiliary disorders
The signs and symptoms of hepatobiliary disorders are usually reversible on withdrawal of the medicinal product.

Overdosage

Symptoms and Signs

Profound cardiovascular effects are to be expected, e.g. excessive, posture-sensitive hypotension and sometimes bradycardia. 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.

Treatment

Patients should be laid supine with the legs raised.

Parenteral adrenergic/anticholinergic therapy should be administered as needed to improve circulation.

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

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Alpha and beta receptor blocking agents

ATC Code

C07AG01

Mechanism of Action

Labetalol lowers blood pressure by blocking peripheral arteriolar alpha-adrenoceptors, thus reducing peripheral resistance, and by concurrent beta-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.

Tablet:

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.

Pharmacokinetic properties

Absorption

Tablet:

Labetalol chemically consists of four stereoisomers with different pharmacodynamics effect. Labetalol is rapidly absorbed from the gastrointestinal tract with peak plasma levels occurring 1 to 2 h after oral administration. There is a significant first-pass metabolism leading to a bioavailability of approximately 25%, but there is considerable variation. The bioavailability of labetalol is increased in elderly subjects.

Distribution

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

Biotransformation

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. Less than 5% of the labetalol dose is excreted unchanged in urine and bile. The plasma half-life of labetalol is about 4 h.

Special Patient Populations

- **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 Method of Administration, Warnings and Precautions*).

Preclinical Safety Data
Carcinogenesis, mutagenesis and teratogenesis

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

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

No teratogenicity was observed in rats and rabbits at oral doses 6 and 4 times the maximum recommended human dose, respectively. Increased foetal resorptions were seen in both species at doses approximating the maximum recommended human dose. A teratology study performed with labetalol in rabbits at intravenous doses up to 1.7 times the maximum recommended human dose revealed no evidence of drug-related harm to the foetus.

PHARMACEUTICAL PARTICULARS
List of Excipients
Injection:
Dilute hydrochloric acid or sodium hydroxide
Water for injection

Tablet:

Tablet core:	Film coat:
Lactose anhydrous Magnesium stearate Cellulose Microcrystalline	Opadry Orange

Shelf Life
The expiry date is indicated on the packaging.

Unused labetalol injection solution should be discarded 24 hours after preparation.

Storage Conditions
Labetalol Injection: Store below 30ºC. Protect from light.

Labetalol Tablets: Store below 30ºC.

Nature and Contents of Container
Labetalol injection is supplied in clear Type I glass ampoules, 5mL capacity.

Labetalol tablets are supplied in polypropylene containers with a tamper-evident snap on polyethylene closure, or in aluminium double foil blister packs.

Labetalol tablets 100mg: Securitainer of 50 tablets.

Not all presentations are available in all countries.

Incompatibilities
Injection:
Labetalol injection has been shown to be incompatible with Sodium Bicarbonate injection BP 4.2% W/V.

Tablet:
None known.

Instructions for Use and Handling
Injection:

Labetalol injection is compatible with the following i.v. infusion fluids:

5% Dextrose BP
0.18% Sodium Chloride and 4% Dextrose BP
0.3% Potassium Chloride and 5% Dextrose BP
Compound Sodium Lactate BP.

Tablet:

There are no special handling instructions for labetalol tablets.

Version number of package insert: CCDS00031/02/0526
Date of revision of package insert: 01 May 2026

NAME AND ADDRESS OF MANUFACTURER
Tablets:
Aspen Bad Oldesloe GmbH
Bad Oldesloe, Germany

Injection:
Hsinchu Plant of UBI Pharma Inc., Taiwan
for Aspen Global Inc., Mauritius