SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Trandate tablets 100 mg
Trandate tablets 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains 100 mg or 200 mg respectively of labetalol hydrochloride.

Excipient with known effect:
100 mg: Each film-coated tablet contains 14.6 mg anhydrous lactose, 1.15 microgram sodium benzoate and 17.2 microgram sunset yellow (E110).

200mg: Each film-coated tablet contains 29.3 mg anhydrous lactose, 2.3 microgram sodium benzoate and 34.4 microgram sunset yellow (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

100 mg: Orange, round, biconvex, engraved TT01 on one face.
200 mg: Orange, round, biconvex, engraved TT02 on one face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of all grades of hypertension (mild, moderate and severe) when oral antihypertensive therapy is desirable.

4.2 Posology and method of administration

Posology

Populations

- **Adults:**

Mild, moderate or severe hypertension - Treatment should be initiated with 100 mg twice daily. If required, the dose can be increased by 100 mg twice daily at an interval of 2-14 days. Many patients achieve blood pressure control with a dose of 200 mg twice daily; up to 800 mg daily can be given as two divided doses. In case of severe refractory hypertension, daily doses of up to 2400 mg have been given as three or four divided doses.

The dose administered to patients hospitalised with severe hypertension can be increased on a daily basis.

Further blood pressure lowering effects should be expected if labetalol tablets are administered concomitantly with other blood pressure lowering drugs such as diuretics, methyldopa etc. When patients switch from drugs such as these, labetalol tablets should be introduced with a dosage of 100mg twice daily and the previous therapy should be phased out gradually. Abrupt withdrawal of clonidine or beta-blocking agents is undesirable.

For long-term control of hypertension following the use of labetalol injections, oral treatment with labetalol tablets should be initiated with 100 mg twice daily.

- **Paediatric population:**

The safety and efficacy of labetalol in children aged 0 to 18 years has not been determined. There is no data available.

- **Elderly:**

When initiating blood pressure lowering therapy, the most common start dose is 100 mg orally twice daily.

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

- **Hepatic impairment**

For patients with impaired hepatic function, lower doses of the oral preparation may be required (see section 4.4 Special warnings and precautions for use).

Method of administration

Labetalol tablets should be taken with food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Nonselective beta blockers must not be used in patients with asthma or a history of obstructive airway disease.
- Labetalol injections and tablets are contraindicated in second or third degree heart block (unless a pacemaker is present), cardiogenic shock and other conditions associated with severe and prolonged hypotension or severe bradycardia
- Uncompensated heart failure
- Unstable/uncontrolled cardiac insufficiency
- Sick sinus syndrome (including sino-atrial block) unless a pacemaker is present
- Prinzmetal angina
- Sinus node dysfunction

4.4 Special warnings and precautions for use

Hepatic disease

Caution must be observed in the presence of 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-term and long-term treatment. However, hepatic necrosis has been reported and in some cases been fatal. Laboratory testing should be done at the first sign or symptom of hepatic

dysfunction. If laboratory results show hepatic injury or the patient is jaundiced, labetalol therapy should be discontinued and not resumed.
Particular caution must be observed when labetalol is used in patients with hepatic impairment, as these patients metabolise labetalol slower than patients without hepatic impairment. Lower doses may be required (see section 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties - Specific patient populations).

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

Peripheral vascular disease
Labetalol should be used with caution in patients with peripheral vascular disease as their symptoms may deteriorate. Caution should be observed for patients with peripheral arterial disease (Raynaud syndrome, intermittent claudication), as labetalol may aggravate symptoms. Alpha blockers can counteract the unwanted effect of beta blockers.

Symptomatic bradycardia
The labetalol dose should be decreased if the patient develops symptomatic bradycardia.

First degree atrioventricular block
Due to the negative effect of beta blockers on atrioventricular conduction time, labetalol should be administered with caution to patients with first degree atrioventricular block.

Diabetes mellitus
Caution must be observed in the presence of uncontrolled or difficult-to-control diabetes. As with other beta blockers, labetalol can mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients. The hypoglycaemic effect of insulin and oral hypoglycaemic agents may be amplified by beta blockers.

Thyrotoxicosis
Beta blockers can mask the symptoms of *thyrotoxicosis*, however thyroid function is not affected.

Hypersensitivity to beta blockers
Risk of anaphylactic reaction: While taking beta blockers, patients with a history of severe anaphylactic reaction to various allergens may become more reactive to repeated challenges, regardless of whether these are accidental, diagnostic or therapeutic. Such patients might not respond to the usual doses of adrenaline used to treat allergic reactions.

Adrenaline
A reduced adrenaline dose should be used if patients receiving labetalol require treatment with adrenaline, as concurrent administration of labetalol and adrenaline may result in bradycardia and hypertension (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Labetalol can cause a paradoxical rise in blood pressure if there is a significantly elevated level of adrenaline in the blood, such as in phaeochromocytoma.

Skin rash and/or dry eyes
Skin rash and/or dry eyes have been reported in connection with the use of beta blockers. The reported incidence is small and in most cases the symptoms subsided once the treatment was

discontinued. Gradual discontinuation of the drug should be considered if a reaction of this type cannot otherwise be explained.

Intraoperative Floppy Iris Syndrome
The development of intraoperative floppy iris syndrome (IFIS, a type of small pupil syndrome) has been observed in connection with cataract surgery in some patients who were treated with, or previously treated with, tamsulosin. Isolated reports have also been received concerning other alpha-1 blockers; the risk of a drug class effect cannot be excluded. Since IFIS can involve an increase in complications in connection with cataract surgery, the eye surgeon must be informed prior to the procedure of current or previous use of alpha-1 blockers.

Heart failure or impaired left ventricular function
Particular caution must be observed in patients with heart failure or impaired systolic left ventricular function. Labetalol is contraindicated in uncontrolled heart failure, but may be used with caution in symptom-free patients whose condition is well controlled. Heart failure is to be controlled with adequate treatment before using labetalol.

The use of beta blockers indicates a risk of the development or deterioration of heart failure or obstructive lung disease. In the case of heart failure, the heart muscle's contraction capacity must be maintained, and the failure must be compensated. Patients with reduced contraction capacity, especially the elderly, must be monitored regularly with regard to the development of heart failure.

It is strongly recommended that Trandate therapy should not be discontinued abruptly, especially in patients with heart failure or angina pectoris (risk of aggravated angina, myocardial infarction and ventricular fibrillation).

Inhaled anaesthetics
Caution should be observed in cases of concurrent treatment with inhaled anaesthetics (see section 4.5 Interaction with other medicinal products and other forms of interaction). It is not necessary to discontinue labetalol therapy prior to anaesthesia however the patient should receive intravenous atropine prior to the administration of the anaesthetic. Labetalol can amplify the hypotensive effects of volatile anaesthetics.

Metabolic acidosis and pheochromocytoma
Caution should be observed in cases of metabolic acidosis and pheochromocytoma. Labetalol should only be administered to patients with pheochromocytoma once adequate alpha blockade has been achieved.

Calcium antagonists
Caution should be observed if labetalol is used concurrently with calcium antagonists, especially calcium channel antagonists, which negatively affect contraction capacity and AV conduction.

Caution should be observed in cases of concurrent administration of adrenaline, verapamil or class I antiarrhythmics (see section 4.5 Interaction with other medicinal products and other forms of interaction).

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

Ischemic heart disease
Patients -particularly those with ischemic heart disease- should not interrupt or abruptly discontinue labetalol therapy. For patients with ischemic heart disease, the treatment should be phased out gradually over 7-10 days if possible.

Warnings regarding excipients:
Lactose:
Patients with any of the following rare hereditary conditions should not take this medicinal product: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Sunset yellow (E110):
The medicinal product contains the colouring agent sunset yellow, which can cause hypersensitivity reactions.

Sodium benzoate: This medicinal product contains benzoate.

4.5 Interaction with other medicinal products and other forms of interaction

The hypotensive effect of labetalol can be reduced when used in combination with inhibitors of prostaglandin synthesis (NSAIDs). Dosage adjustments may therefore be required. Further interactions may occur with other blood pressure lowering agents.

Labetalol fluoresces in alkaline solutions with an excitation wavelength of 334 nm and a fluorescence wavelength of 412 nm, and can therefore interact with the analysis of certain fluorescent substances including catecholamines.

The presence of labetalol metabolites in the urine may indicate falsely elevated levels of urinary catecholamines, metadrenaline, normetadrenaline and vanillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. When patients with suspected pheochromocytoma who are treated with labetalol hydrochloride are screened, a specific method such as high-performance liquid chromatography with solid phase extraction should be used to determine catecholamine levels.

Labetalol has been shown to reduce the absorption of radioisotopes of metaiodobenzylguanidine (MIBG). Care should therefore be taken when interpreting the results of MIBG scintigraphy.

Concurrent administration of labetalol and adrenaline may result in bradycardia and hypertension (see section 4.4 Special warnings and precautions for use).

Caution should be observed if labetalol is used concurrently with class I antiarrhythmics 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 II antiarrhythmic).

Risk of pronounced bradycardia and hypotension in combination with calcium antagonists with a negative inotropic effect (e.g. verapamil, diltiazem). Particularly for patients with impaired ventricular function and/or conduction disturbances. When making the transition from a calcium antagonist to a beta blocker (or vice versa), new intravenous therapy must not be initiated until at least 48 hours have elapsed from the discontinuation of the previous therapy.
Concurrent treatment with dihydropyridine-derived calcium antagonists (e.g. nifedipine) can increase the risk of hypotension and cause heart failure in patients with latent cardiac insufficiency. The

atrioventricular conduction time may be prolonged by the concurrent use of digitalis glycosides and beta blockers. Labetalol can amplify the effect of digoxin in regards to the reduction of ventricular frequency.

Beta blockers, especially nonselective beta blockers, can increase the risk of hypoglycaemia in diabetic patients, mask the symptoms of hypoglycaemia (e.g. tachycardia and tremor) and delay the normalisation of blood sugar following insulin-induced hypoglycaemia. Dose adjustments of oral antidiabetics and insulin may be required.

Caution must be observed in connection with general anaesthesia in patients using beta blockers. Beta blockers reduce the risk of arrhythmias during anaesthesia but can cause a reduction in reflex tachycardia and increase the risk of hypotension during anaesthesia. The negative inotropic effect of the anaesthetic agent should be as small as possible. Cardiac function must be monitored closely; bradycardia due to vagal dominance should be corrected with the intravenous administration of 1-2 mg atropine.

When beta blockers and clonidine are discontinued in patients taking both agents, a gradual withdrawal of the beta blocker must be made several days prior to the withdrawal of clonidine. The purpose of this measure is to reduce the potential recurring hypertensive crisis resulting from the withdrawal of clonidine. Thus, when changing from clonidine to a beta blocker it is important to gradually withdraw clonidine and initiate beta blocker therapy several days after the withdrawal of clonidine.

Concurrent use of acetylcholinesterase inhibitors may increase the risk of bradycardia.

Concurrent treatment with alpha adrenergic agonists (e.g. phenylpropanolamine and adrenaline) can increase the risk of elevated blood pressure, while concurrent treatment with beta adrenergic agonists results in a mutual reduction of effect (antidote effect).

Concurrent use of ergotamine derivatives can increase the risk of vasospastic reactions in some patients.

Labetalol has been shown to increase the bioavailability of imipramine by over 50 %, due to the inhibition of its 2-hydroxylation. Concurrent treatment with labetalol and imipramine can increase the effect of imipramine. Concurrent use of tricyclic antidepressants can increase the incidence of tremor.

Caution must be observed when prescribing oral labetalol as cimetidine can increase its bioavailability. Improved blood pressure lowering may be achieved with concurrent use of e.g. nitrates, antipsychotics (phenothiazine derivatives such as chlorpromazine) and other antipsychotics and antidepressants.

4.6 Fertility, pregnancy and lactation

Fertility

There is no information on the effect of labetalol on fertility.

Pregnancy

Based on experience of pregnancy in humans, labetalol is not expected to increase the risk of birth defects. Animal studies do not indicate teratogenicity. However, toxic effects on foetal development have been noted (see section 5.3). Depending on the pharmacological mechanism of action of alpha

and beta-adrenoceptor blockade, and when these are used in late pregnancy, undesirable effects to the foetus and the neonate should be taken into consideration (bradycardia, hypotension, respiratory depression, hypoglycaemia), as labetalol crosses the placenta. Beta blockers can reduce the blood flow in the uterus.

Labetalol should be only used in pregnancy when the benefits to the mother outweigh the risks for the foetus.

Breast-feeding
Labetalol is excreted in small quantities in human milk (around 0.004-0.07 % of the mother's dose). Nipple pain and Raynaud's phenomenon of the nipple have been reported (see section 4.8). Caution must be observed when labetalol is administered to lactating women.

4.7 Effects on ability to drive and use machines

The use of labetalol probably has no influence on the patient's ability to drive or use machines. However, it must be remembered that transient dizziness or fatigue may occur.

4.8 Undesirable effects

Summary of the safety profile
Among the most common adverse reactions observed with labetalol tablets and gathered from post-marketing reports are: heart failure, postural hypotension, hypersensitivity, lichenoid eruptions, drug fever, elevated liver function tests, difficulty in micturition, dizziness, headache, tickling sensation on the scalp, blurred vision, nasal congestion, nausea, erectile dysfunction and ejaculatory failure.

Tabulated list of adverse reactions

The following convention has been used to classify the frequency:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000
Not known (cannot be estimated from the available data)

The adverse reactions marked with # are usually transient and occur during the first few weeks of treatment.

Organ system		Adverse reactions
Immune system disorders	Very common	Positive antinuclear antibodies not associated with disease
	Common	Hypersensitivity, lichenoid eruption, drug fever
Psychiatric disorders	Uncommon	#Depressed mood
Central and peripheral nervous system disorders	Common	#Dizziness, #headache, #tickling sensation on the scalp
	Very rare	Tremor on treatment of pregnancy related hypertension
Eye disorders	Common	Blurred vision
	Very rare	Eye irritation
Cardiac disorders	Common	Heart failure
	Rare	Bradycardia
	Very rare	Heart block
Vascular disorders	Common	#Postural hypotension
	Very rare	Aggravated symptoms of Raynaud syndrome
Respiratory, thoracic and mediastinal disorders	Common	# Nasal congestion
	Uncommon	Bronchospasm
Gastrointestinal disorders	Common	Nausea
	Uncommon	Vomiting, epigastric pain
Hepatobiliary disorders	Common	Elevated liver function tests
	Very rare	Hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis
Skin and subcutaneous tissue disorders	Uncommon	#Sweats
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 urine retention
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	#Fatigue, #lethargy
	Very rare	# Foot oedema

Description of selected adverse reactions:

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

Vascular disorders
Postural hypotension is more common with very high doses or if the starting dose is too high, or the dose is increased too rapidly.

Hepatobiliary disorders
Signs and symptoms of hepatic and biliary passage disturbances are usually reversible on discontinuation of the drug.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il
Additionally, you can also report to Padagis via the following address: Padagis.co.il

4.9 Overdose

Symptoms and signs:
Significant cardiovascular effects can be expected, e.g. excessive postural hypotension and occasional bradycardia. Renal failure with oliguria has been reported following massive overdose of oral labetalol.
In one case, the use of dopamine to increase blood pressure may have aggravated the renal failure.

Treatment:
The patient should be recumbent, with the legs in an elevated position.

Parenteral adrenergic/anticholinergic treatment should be administered as required, to improve circulation.

Haemodialysis removes less than 1 % of labetalol hydrochloride from the blood circulation.
Continued management is to proceed according to the clinical indications or as recommended by the Poisons Information Centre, if available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Alpha and beta blocking agents, ATC code: C07AG01

Mechanism of action
Labetalol lowers the blood pressure by blocking alpha adrenoceptors on peripheral arterioles, thus reducing the peripheral resistance; the concurrent beta blockade protects the heart from the reflex sympathetic drive that would otherwise occur.

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

In patients with angina pectoris co-existing with hypertension, the reduced peripheral resistance decreases myocardial afterload and oxygen requirements. All these effects would be expected to benefit hypertensive patients as well as those with co-existing angina.

5.2 Pharmacokinetic properties

Pharmacokinetics

Absorption
Chemically, labetalol consists of four stereoisomers with different pharmacodynamic effects. Labetalol is rapidly absorbed from the gastrointestinal tract and the maximum plasma levels occur 1-2 hours after oral administration. There is significant first pass metabolism which yields bioavailability of 25%, but there are significant variations. The bioavailability of labetalol increases in the elderly.

Distribution
Labetalol is around 50 % protein bound in the blood. In animal studies, only negligible amounts of labetalol have passed the blood-brain barrier. Labetalol passes the placental barrier and is excreted in human milk.

Biotransformation
Labetalol is metabolised primarily through conjugation to inactive glucuronide metabolites.

Elimination
The glucuronide metabolites are excreted both in urine and via the bile into the faeces. Less than 5% of the labetalol dose is excreted unmodified in the urine and bile. The half-life of labetalol in plasma is approximately 4 hours.

Specific patient populations

- **Hepatic failure**

Labetalol undergoes significant but varied first pass metabolism when administered orally. In a study of 10 patients with histologically confirmed cirrhosis, the exposure for oral labetalol increased approximately threefold compared with the healthy control group. Individual variations in both patients and the control group were large (approximately 2.5 times). Patients with hepatic failure may require lower oral doses of labetalol (see section 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use).

5.3 Preclinical safety data

Carcinogenic, mutagenic and teratogenic effects
No signs of mutagenic potential were seen in *in vitro* and *in vivo* examinations.

Labetalol showed no signs of carcinogenicity in long-term studies of mice and rats.
No teratogenicity was observed in rats and rabbits at oral doses of 6 and 4 times the maximum recommended human dose. Increased foetal resorptions were seen in both species at doses approaching the maximum recommended human dose. A teratology study performed with labetalol in rabbits with intravenous doses up to 1.7 times the maximum recommended human dose gave no evidence of drug-related foetal injury.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Microcrystalline cellulose
Lactose anhydrous
Magnesium stearate

Tablet coating:
Opadry Orange 02A230001 (colourant, containing: Hypromellose 5cP, titanium dioxide, sunset yellow FCF (E110)), sodium benzoate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

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

100 mg: plastic bottle containing 50 tablets
200 mg: plastic bottle containing 50 tablets

6.6 Special precautions for disposal and other handling
No special requirements.

7 MANUFACTURER

Aspen Bad Oldesloe GmbH,
Industriestrasse 32 -36,
D - 23843 Bad Oldesloe
Germany

8 REGISTRATION HOLDER

Padagis Israel Agencies Ltd.
1 Rakefet St., Shoham, Israel.

9 REGISTRATION NUMBER

Trandate Tablets 100 mg	02086-27785
Trandate Tablets 200 mg	02084-27786

Revised in May 2023 according to MOH guidelines.

30.5.23