PROFESSIONAL INFORMATION

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

ADCO LABETALOL 5 mg/ml, solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 5 mg labetalol hydrochloride.

Excipients with known effect:

Preservatives:

Propylparaben 0,08 % *w/v*

Methylparaben 0,01 % *w/v*

Contains sugar: Glucose anhydrous 45 mg/ml.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO LABETALOL is indicated when rapid control of blood pressure is essential in severely hypertensive patients, including severe hypertension of pregnancy and use in anaesthesia where a hypotensive technique is indicated.

4.2 Posology and method of administration

Posology

Adults:

ADCO LABETALOL is intended for intravenous use in hospitalised patients.

The plasma concentrations achieved after intravenous doses of **ADCO LABETALOL** in severe hypertension are substantially greater than those following oral administration of the medicine.

Patients should therefore always receive **ADCO LABETALOL** whilst in the supine position. Raising the patient into the upright position within three hours of **ADCO LABETALOL** administration should be avoided since excessive postural hypotension may occur.

The heart rate and blood pressure should be monitored after injection and during infusion.

In most patients, there is a 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 respiratory impairment. Labetalol hydrochloride has been administered to patients with uncontrolled hypertension already receiving other hypotensive medicines, including beta-blocking medicines, without adverse effects.

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

Severe hypertension (Adults)

Bolus injection

If it is essential to reduce blood pressure quickly as, for example, in hypertensive encephalopathy, a dose of 50 mg should be given by IV injection (over a period of at least 1 min) and, if necessary, repeated at 5 minute intervals until a satisfactory response occurs. The total dose should not exceed 200 mg. The maximum effect usually occurs within 5 minutes and the duration of action is usually about 6 hours but may be as long as 18 hours.

Intravenous infusion

An intravenous infusion of a solution is made by diluting the contents of one vial (200 mg) to 200 ml with any of the diluents as per section 6.6 below. The resultant infusion solution contains 1 mg/ml of **ADCO LABETALOL**. It should be administered using a volume-controlled infusion pump to facilitate accurate dosage.

Hypertension due to other causes

The rate of infusion of **ADCO LABETALOL** should be about 2 mg (2 ml of infusion solution) per minute until a satisfactory response is obtained; the infusion should then be stopped.

The effective dose is usually in the range of 50 to 200 mg depending on the severity of the hypertension. For most patients, it is unnecessary to administer more than 200 mg but doses up to 300 mg may be required, especially in patients with phaeochromocytoma. The rate of infusion may be adjusted according to the response, at the discretion of the medical practitioner.

Abrupt withdrawal of clonidine or beta-blocking medicines 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.

Severe hypertension of pregnancy

In case of severe hypertension of pregnancy, a slower and increasing rate of infusion should be used. Infusion may be started at a rate of 20 mg/hour, and then may be doubled every 30 minutes until a satisfactory response is obtained or a dosage of 160 mg/hour is reached.

Hypotensive anaesthesia

In hypotensive anaesthesia, induction should be with standard medicines (e.g. sodium thiopentone) and anaesthesia maintained with halogenated inhalation anaesthetics. The recommended starting dose of **ADCO LABETALOL** is 10 to 20 mg intravenously depending on the age and condition of the patient. If satisfactory blood pressure reduction is not achieved after five minutes, increments of 5 to 10 mg should be given until the desired level of blood pressure is attained.

Halogenated inhalation anaesthetics and labetalol act synergistically therefore the concentration of halogenated inhalation anaesthetics should not exceed 1 to 1,5 % as profound drops in blood pressure may be precipitated.

Following **ADCO LABETALOL** the blood pressure can be quickly and easily adjusted by altering the halogenated inhalation anaesthetic concentration and/or adjusting table tilt. The mean duration of hypotension following 20 to 25 mg of **ADCO LABETALOL** is fifty minutes.

Hypotension induced by **ADCO LABETALOL** is readily reversed by atropine 0,6 mg and discontinuation of halogenated inhalation anaesthetics. A non-depolarising muscle relaxant can be used when assisted or controlled ventilation is required. IPPV (intermittent positive pressure ventilation) may further increase the hypotension resulting from **ADCO LABETALOL** and/or halogenated inhalation anaesthetics.

Paediatric population:

Safety and efficacy in children have not been established.

No data are available.

Method of administration

ADCO LABETALOL is intended for intravenous use in hospitalised patients.

Patients should always receive the medicine whilst in the supine position or left lateral position. Raising the patient into the upright position within three hours of **ADCO LABETALOL** administration should be avoided since excessive postural hypotension may occur.

ADCO LABETALOL may be administered via intravenous infusion using a volume-controlled infusion pump to facilitate accurate dosage.

For instructions on dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to labetalol or to any of the excipients listed in section 6.1
- Cardiogenic shock
- Uncontrolled, incipient or digitalis refractory heart failure
- Unstable/uncontrolled heart insufficiency
- Sick sinus syndrome (including sinoatrial block) unless pacemaker *in situ*
- Sick sinus syndrome (including sinus atrial block) unless pacemaker *in situ*
- Second or third degree atrio-ventricular heart block unless pacemaker *in situ*
- Prinzmetal's angina
- Non-selective beta-blockers should not be used in patients with asthma or those with a history of obstructive airway disease.
- Untreated phaeochromocytoma
- Metabolic acidosis
- Conditions associated with severe and prolonged hypotension or severe bradycardia (< 50 bpm) and low cardiac output after myocardial infarction.
- Severe peripheral circulatory disturbances and Raynaud's phenomenon
- Where peripheral vasoconstriction suggests low cardiac output, the use of **ADCO LABETALOL** to control hypertensive episodes following acute myocardial infarction is contraindicated.
- **ADCO LABETALOL** should not be used by women who are breastfeeding their infants (see section 4.6).

4.4 Special warnings and precautions for use

Liver disease

ADCO LABETALOL may cause severe hepatocellular injury, including fatal liver toxicity. The hepatic injury is usually reversible on stopping treatment 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, **ADCO LABETALOL** therapy should be stopped and not re-started. Particular care should be taken when **ADCO LABETALOL** is to be used in patients with hepatic impairment, as these patients metabolise labetalol more slowly than normal patients.

Peripheral vascular disease

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.

Selective alpha-blockers may counter the effect of beta-blockers. Severe peripheral circulatory disorders and Raynaud's syndrome are contraindicated with labetalol. (see section 4.3)

Symptomatic bradycardia

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, or should be stopped.

First degree atrio-ventricular block

Due to a negative effect on conduction time, beta-blockers should only be given with caution to patients with digoxin-resistant heart failure first degree heart block. Labetalol is contraindicated in patients with second or third degree atria-ventricular block (see section 4.3).

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.

Diabetes mellitus

Care should be taken in case of uncontrolled or difficult-to-control diabetes mellitus. **ADCO LABETALOL** may mask the symptoms of hypoglycaemia (tachycardia and tremor) in diabetic patients (see section 4.5). The hypoglycaemic effect of insulin and oral

hypoglycaemic medicines may be enhanced by beta-blockers. **ADCO LABETALOL** should be used with caution in patients with diabetes mellitus. A slight increase in blood sugar levels occurs following the administration of **ADCO LABETALOL** and the possibility of interactions of **ADCO LABETALOL** with insulin and/or anti-diabetic medicines.

Thyrotoxicosis

ADCO LABETALOL may mask the symptoms of thyrotoxicosis, although the thyroid function is unaltered (see section 4.5).

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 (adrenaline) used to treat allergic reactions.

Adrenaline

If patients receiving **ADCO LABETALOL** require epinephrine (adrenaline) treatment, a reduced dosage of epinephrine (adrenaline) should be used, as concomitant administration of **ADCO LABETALOL** with epinephrine (adrenaline) may result in bradycardia and hypertension (see section 4.5).

Skin rashes and/or dry eyes

There have been reports of skin rashes and/or dry eyes associated with the use of **ADCO LABETALOL**. Gradual discontinuance of **ADCO LABETALOL** should be considered if any such reaction is not otherwise explicable.

Inhalation anaesthetics and sudden haemorrhage

It is not necessary to discontinue **ADCO LABETALOL** therapy in patients requiring anaesthesia, but the anaesthetist must be informed, and the patient should be given intravenous atropine prior to induction. During anaesthesia **ADCO LABETALOL** may

mask the compensatory physiological responses to sudden haemorrhage (tachycardia and vasoconstriction). Close attention must therefore be paid to blood loss and the blood volume maintained. If beta-blockade is interrupted in preparation for surgery, therapy should be discontinued for at least 24 hours. Anaesthetic medicine causing myocardial depression (e.g. cyclopropane, trichloroethylene) should be avoided. Labetalol may enhance the hypotensive effects of volatile anaesthetics (e.g. halothane).

Renal impairment

Caution is advised when **ADCO LABETALOL** is used in patients with severe renal impairment (GFR = 15 to 29 ml/min/1,73 m^2).

Intraoperative floppy iris syndrome

The occurrence of intraoperative floppy iris syndrome (IFIS, a variation of Horner's syndrome) has been observed during cataract surgeries in some patients who were being treated with tamsulosin or have been treated with tamsulosin in the past. IFIS has also been reported when other alpha-1-blockers were being used, and the possibility of a class effect cannot be excluded. Since IFIS can lead to a higher chance of complications during cataract surgeries, the ophthalmologist needs to be informed if alpha-1-blockers are currently being used or have been used in the past.

Cardiac diseases

Due to negative inotropic effects, special care should be taken with patients who suffer from heart failure or poor left ventricular systolic function, whose cardiac reserve is poor and heart failure should be controlled before starting **ADCO LABETALOL** therapy.

ADCO LABETALOL is contraindicated in uncontrolled heart failure but may be used with caution in patients who are well managed and free of symptoms (see section 4.3). Heart failure should be controlled with appropriate therapy before use of **ADCO LABETALOL**.

Patients, particularly those with ischaemic heart disease, should not interrupt/discontinue **ADCO LABETALOL** therapy abruptly as it may cause exacerbation of angina pectoris in patients with ischaemic heart disease. 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 the heart failure. Discontinuation of therapy should be gradual, and patients should be advised to limit the extent of their physical activity during the period that the medicine is being discontinued.

If necessary, discontinuation of therapy can occur at the same time of initiating replacement therapy, to prevent exacerbation of angina pectoris, myocardial infarction and ventricular fibrillation. In addition, hypertension and dysrhythmias may develop.

In the peri-operative period, it is generally unwise to reduce the dosage to which the patient is accustomed, as there may be danger of aggravation of angina pectoris or hypertension. A patient's normal tachycardiac response to hypovolaemia or blood loss may be obscured during or after surgery. Particular caution should be taken in this regard.

Metabolic acidosis and phaeochromocytoma

Care should be taken in case of metabolic acidosis and phaeochromocytoma. In patients with phaeochromocytoma, labetalol may be administered only after an adequate alpha-blockade is achieved. **ADCO LABETALOL** is contraindicated in untreated phaeochromocytoma.

Calcium antagonists

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

Bronchospasm

Bronchoconstriction may occur in patients with asthma, bronchitis and other chronic pulmonary diseases. Beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease (see section 4.3). Any resultant bronchospasm may be controlled by an inhaled beta-agonist; the required dose may be greater than the normal anti-asthmatic dose. If further treatment is required, intravenous atropine 1 mg may be given.

Beta-blockers have negative inotropic effect but does not affect the positive inotropic effect of digitalis.

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.

SPECIAL NOTE: digitalisation of patients receiving long-term beta-blocker therapy may be necessary if congestive cardiac failure is likely to develop. This combination can be considered despite the potentiation of the negative chronotropic effect of the two medicines. Careful control of dosages, and of the individual patient's response (and notably pulse rate), is essential in this situation.

Administration to pregnant mothers shortly before giving birth or during labour may result in the new-born infants being born hypotonic, collapsed and hypoglycaemic.

Concurrent use of **ADCO LABETALOL** may result in an increased plasma concentration of the following medicines: hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines. Such interactions can have life-threatening consequences (see section 4.5).

Caution should be taken to prevent occasional exaggerated hypotensive response, particularly in the presence of hypovolaemia.

Contains glucose anhydrous which may have an effect on the glycaemic control of patients with diabetes mellitus.

Paediatric population:

Safety and efficacy in children have not been established.

4.5 Interactions with other medicines and other forms of interaction

Concomitant use not recommended:

- Risk of marked bradycardia and hypotension in combination with calcium antagonists with negative inotropic effect such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and atrio-ventricular conduction. 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.

- Digitalis glycosides (digoxin) used in association with beta-blockers may increase atrio-ventricular conduction time. **ADCO LABETALOL** may enhance digoxin's effect of reducing ventricular rate.
- Cholinesterase inhibitors may increase the risk of bradycardia.
- Clonidine: Beta-blockers increase the risk of rebound hypertension. When clonidine is used in conjunction with nonselective beta-blockers, such as propranolol, treatment with clonidine should be continued for some time after treatment with the beta-blocker has been discontinued. This is to reduce potential rebound hypertension which is a consequence of withdrawal to clonidine. Accordingly, when changing from clonidine to **ADCO LABETALOL** it is important to discontinue clonidine gradually and start treatment several days after clonidine has been withdrawn.
- Monoamine oxidase inhibitors (except MOA-B inhibitors).
- Alpha-stimulating adrenergic medicines may increase the risk of increased blood pressure (e.g. phenylpropanolamine and adrenaline), while concomitant treatment with beta-stimulating adrenergic medicines results in a mutual reduced effect (antidote effect).

Use with caution:

- Class I antidysrhythmic medicines (e.g. disopyramide, quinidine) and class II antidysrhythmic medicine (e.g. amiodarone) may have potentiating effects on atrial conduction time and induce negative inotropic effect.
- Insulin and oral antidiabetic medicines may intensify the blood sugar lowering effect, especially of non-selective beta-blockers. Beta-blockers may increase the risk of hyperglycaemia in diabetic patients secondary to a deterioration in carbohydrate metabolism and peripheral insulin resistance. Beta-blockade may prevent the appearance of signs of hypoglycaemia (tachycardia, blood pressure and tremor), and delay the normalisation of blood sugar after insulin-induced hypoglycaemia. Dose adjustments of oral antidiabetic medicines and insulin may be necessary.
- Anaesthetic medicines may cause attenuation of reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockade reduces the risk of dysrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking medicine.

Anaesthetic medicines causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided. An anaesthetic medicine with as 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 to 2 mg intravenously (withdrawal prior to surgery). **ADCO LABETALOL** may enhance the hypotensive effects of volatile anaesthetics.

- Cimetidine, hydralazine and alcohol may increase the bioavailability of **ADCO LABETALOL**.
- Several different medicines or medicine classes may enhance the hypotensive effects of **ADCO LABETALOL**: ACE inhibitors; angiotensin-II antagonists; aldesleukin, alprostadil; anxiolytics; hypnotics; moxisylyte; diuretics; alpha-blockers.
- Several different medicines or medicine classes may antagonise the hypotensive effects of **ADCO LABETALOL**: NSAIDs, corticosteroids; oestrogens; progesterones. Additive synergism may occur with other antihypertensive medicines.

Take into account:

- Calcium antagonists: dihydropyridine derivates such as nifedipine. The risk of hypotension may be increased. In patients with latent cardiac insufficiency, treatment with beta-blockers may lead to cardiac failure.
- Prostaglandin synthetase inhibiting medicines may decrease the hypotensive effect of beta-blockers.
- Sympathomimetic medicines may counteract the effect of beta-adrenergic blocking medicines.
- Imipramine: **ADCO LABETALOL** has been shown to increase the bioavailability of imipramine by more than 50 % through the inhibition of its 2-hydroxylation. **ADCO LABETALOL** in combination with imipramine may increase the effect of imipramine and concomitant use of tricyclic antidepressants. Concomitant use of tricyclic antidepressants may increase the incidence of tremor.
- **ADCO 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.

- Concomitant use of tricyclic antidepressants, barbiturates, phenothiazines or other antihypertensive medicines may increase the blood pressure lowering effect of **ADCO LABETALOL**. Concomitant use of tricyclic antidepressants may increase the incidence of tremor.
- **ADCO LABETALOL** has been shown to reduce the uptake of radio-isotopes of meta-iodobenzylguanidine (MIBG) and may increase the likelihood of a false negative study. Care should therefore be taken in interpreting results from MIBG scintigraphy. Consideration should be given to withdrawing **ADCO LABETALOL** for several days at least before MIBG scintigraphy and substituting other beta- or alpha-blocking medicines.
- Antimalarials such as mefloquine or quinine may increase the risk of bradycardia.
- Ergot derivatives may increase the risk of peripheral vasoconstriction.
- Tropisetron may increase the risk of ventricular dysrhythmia.
- Labetalol interferes with laboratory tests for catecholamines.
- Simultaneous administration of **ADCO LABETALOL** with epinephrine (adrenaline) may result in bradycardia and hypertension.

The presence of **ADCO 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 **ADCO LABETALOL**, a specific method, such as a high-performance liquid chromatographic assay with solid phase extraction should be used in determining levels of catecholamines.

Concurrent use of **ADCO LABETALOL** may result in an increased plasma concentration of the following medicines: hypoglycaemic medicines, phenothiazines and various antidysrhythmic medicines. Such interactions can have life-threatening consequences (see section 4.4)

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

ADCO LABETALOL is not expected to increase the risk of congenital malformations.

Labetalol crosses the placental barrier and the possibility of the 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) may occur. These symptoms may develop 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 **ADCO LABETALOL** therapy, recovery may be slower. This may be related to diminished liver metabolism in premature babies.

Beta-blockers may reduce uterine blood flow.

Administration to pregnant mothers shortly before giving birth or during labour may result in the new-born infants being born hypotonic, collapsed, and hypoglycaemic.

Breastfeeding

Safety in breastfeeding has not been established. Labetalol is excreted in breast milk in small amounts (approximately 0,004 to 0,07 % of the maternal dose). Adverse events such as sudden death syndrome, diarrhoea and hypoglycaemia may occur in breast-fed neonates. Women should not breastfeed their infants while receiving **ADCO LABETALOL** injection (see section 4.3).

Fertility

No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

ADCO LABETALOL has no or negligible influence on ability to drive and use machines.

When driving a vehicle or operating machines it should be taken into account that dizziness or fatigue may occur after administration of **ADCO LABETALOL**.

Patients should not drive, use machinery or perform any tasks that require concentration until they are certain that **ADCO LABETALOL** does not adversely affect their ability to do so safely.

4.8 Undesirable effects

a. Summary of the safety profile

Excessive postural hypotension may occur if patients are allowed to assume an upright position within three hours of receiving this medicine. Most side effects are transient and occur during the first few weeks of treatment.

b. Tabulated summary of adverse reactions

Side effects have been ranked according to frequency within each System Organ Class. The following side effects have been reported and may occur with **ADCO LABETALOL**:

System Organ Class	Frequency	Adverse Event
Immune system disorders	Frequent	Hypersensitivity (rash, pruritus and dyspnoea)
	Less frequent	Drug fever, angioedema
Cardiac disorders	Frequent	Congestive heart failure
	Less frequent	Bradycardia, heart block
	Frequency unknown	Hypotension
Vascular disorders	Frequent	Postural hypotension (pronounced postural hypotension may occur with confusion and disorientation if patients are allowed to assume the upright position within three hours of receiving **ADCO LABETALOL**)
	Less frequent	Exacerbation of the symptoms of Raynaud's syndrome
	Frequency unknown	Ankle oedema, increase of an existing intermittent claudication, postural hypotension, cold or cyanotic extremities, paraesthesia of the extremities
Respiratory, thoracic and mediastinal disorders	Frequent	Nasal congestion, interstitial lung disease

	Less frequent	Bronchospasm (in patients with asthma or a history of asthma)
Hepatobiliary disorders	Frequent	Raised liver function tests
	Frequency unknown	Jaundice (both hepatocellular and cholestatic), hepatitis and hepatic necrosis
Blood and the lymphatic system disorders	Frequency unknown	Positive antinuclear antibodies not associated with disease, hyperkalaemia, particularly in patients who may have impaired renal excretion of potassium, thrombocytopenia
Psychiatric disorders	Frequency unknown	Depressed mood and lethargy, hallucinations, psychoses, confusion, sleep disturbances, nightmares
Nervous system disorders	Frequency unknown	Tiredness, headache, dizziness, tremor may occur in the treatment of hypertension of pregnancy
Eye disorders	Frequency unknown	Impaired vision, dry eyes
Gastrointestinal disorders	Frequency unknown	Epigastric pain, nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Frequency unknown	Sweating, tingling sensation in the scalp (usually transient, may occur in a few patients early in treatment), reversible lichenoid rash, systemic lupus erythematosus, exacerbation of psoriasis
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Cramps, toxic myopathy
Renal and urinary disorders	Frequency unknown	Acute retention of urine, difficulty in micturition
Reproductive system and breast disorders	Frequent	Erectile dysfunction

General disorders and administration site conditions	Frequency unknown	Hypersensitivity (rash, pruritus, angioedema and dyspnoea), drug fever, masking of the symptoms of thyrotoxicosis or hypoglycaemia, reversible alopecia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

Symptoms

Overdosage with **ADCO LABETALOL** causes excessive hypotension, which is posture dependent, and excessive bradycardia.

Bronchospasm and heart failure may be produced in certain individuals. Cases of mild overdose should be observed for at least four hours, as apnoea and cardiovascular collapse may appear suddenly.

Treatment

After an overdose or in case of hypersensitivity, the patient should be kept under close supervision and be treated in an intensive-care ward. Artificial respiration may be required.

Patients should be laid supine, and their legs raised if necessary to improve the blood supply to the brain.

The use of dopamine to increase the blood pressure may aggravate renal failure.

Atropine 1 to 2 mg may be used to treat severe bradycardia. If the response is inadequate, glucagon may be given intravenously. Alternatively, dobutamine may be required to reverse beta-blockade. Intravenous cardiac pacing may be required for severe bradycardia. Bronchospasm should be treated with IV aminophylline or inhaled beta-agonist, or IV beta-agonist, e.g. salbutamol. Further treatment is symptomatic and supportive.

Massive overdosage with **ADCO LABETALOL** has not been reported, but profound cardiovascular effects are to be expected. If further measures are required to obtain adequate circulatory pressure, vasopressors may be required.

Administration of calcium ions, or the use of a cardiac pacemaker, may also be considered.

Labetalol does have membrane stabilising activity which may have clinical significance in overdosage.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 7.1.3 Vascular medicines, vasodilators, other hypotensives
Pharmacotherapeutic group and ATC code: Alpha– and beta-blocking agents, C07AG01

Mechanism of action

Labetalol lowers the blood pressure primarily by blocking peripheral arteriolar alpha-adrenoceptors thus reducing peripheral resistance. It also exhibits beta-adrenergic blocking activity and is able to inhibit the re-uptake of norepinephrine into nerve terminals. Labetalol possesses no intrinsic sympathomimetic activity. The concurrent beta-blockade protects the heart from reflex sympathetic drive that would otherwise occur. 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.

In patients with angina pectoris co-existing 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.

5.2 Pharmacokinetic properties

Intravenous labetalol hydrochloride reduces blood pressure without producing tachycardia or increasing plasma renin levels.

Distribution

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

Biotransformation

Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolites.

Elimination

The plasma half-life of labetalol is about 4 - 5 hours. These are excreted both in urine and via the bile into the faeces. Only 5 % of labetalol is excreted unchanged in the urine.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose anhydrous, edetate disodium, methylparaben, propylparaben, citric acid monohydrate, sodium hydroxide solution and water for injection.

6.2 Incompatibilities

ADCO LABETALOL has been shown to be incompatible with sodium bicarbonate injection BP 4,2 % *w/v*.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 24 months

Diluted infusion solution

Chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 – 8 °C and at 25 °C when reconstituted with dilution solutions listed in section 6.6.

From a microbiological point of view, the diluted solutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25 °C, unless the dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C in the outer container and protect from light.
Keep in original packaging until required for use.
For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

ADCO LABETALOL (40 ml) is packaged in a 50 ml clear transparent USP Type I moulded glass vial with a 20 mm dark grey bromobutyl rubber stopper sealed with a 20 mm aluminium flip-off seal with coloured button. The immediate container is then placed in a unit carton.

1/5/10 vials may be packed in a carton.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

ADCO LABETALOL (one vial i.e., 200 mg) may be diluted to 200 ml of any of the following solutions to form an intravenous infusion solution. The resultant infusion solution contains 1 mg/ml of **ADCO LABETALOL**.

Diluent solutions:

Ringers injection, Lactated Ringers injection, 5 % dextrose (glucose) and Ringers injection, 5 % dextrose (glucose) and Lactated Ringers injection, 5 % dextrose (glucose) injection, 0,9 % sodium chloride injection, 5 % dextrose (glucose) and 0,2 % sodium chloride injection, 2,5 % dextrose (glucose) and 0,45 % sodium chloride injection, 5 % dextrose (glucose) and 0,9 % sodium chloride injection, 5 % dextrose (glucose) and 0,33 % sodium chloride injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd.
1 Sabax Road,
Aeroton,
Johannesburg,
2013
Tel: +27 11 494 8000

8. REGISTRATION NUMBER(S)

43/7.1.3/0661

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 May 2022

10. DATE OF REVISION OF THE TEXT

10 May 2024

PI 10 May 2024