VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

High blood pressure, also known as hypertension, occurs in a large percentage of the adult population. Primary (essential) hypertension is the most common form of hypertension, accounting for 90–95% of all cases.[1] If not treated, it can damage the blood vessels of the brain, heart, and kidneys, and may result in a stroke, heart failure, or kidney failure. High blood pressure increases the risk of heart disease, kidney disease and stroke. As of 2014, approximately one billion adults or ~22% of the population of the world have hypertension.[2] It is slightly more frequent in men.[2] In Europe, hypertension occurs in about 30-45% of people as of 2013, with an increase with age.[3] Treatment options include lifestyle modifications (such as dietary changes, physical exercise, and weight loss) and treatment with antihypertensive medications.[4]

VI.2.2 Summary of treatment benefits

Labetalol has been widely used in the treatment of hypertensive crises for more than 20 years. Labetalol is a beta blocking agent.[5]

Several clinical trials have been carried out to evaluate how safe and effective labetalol is, they showed it to be effective and well-tolerated in patients with all grades of hypertension. It provides good control of blood pressure without serious side effects. Labetalol is effective during pregnancy, in hypertensive emergencies and during surgeries and other medical procedures to rapidly control blood pressure.[6] A systematic review (10 studies; 813 patients), comparing nicardipine vs. labetalol[5] and further clinical studies (136 patients), comparing labetalol to hydrochlorothiazide [7] and esmolol[8], showed the efficacy of labetalol in the treatment of hypertension.

Very little labetalol crosses the placenta, making it useful in the treatment of gestational hypertension.[5] Labetalol is one of the most commonly recommended medications for the management of severe hypertension during pregnancy. Most guidelines recommend labetalol as the go-to treatment in the

[1] Carretero OA, Oparil S. Essential hypertension. Part I: definition and etiology. Circulation 2000. 101 (3): 329–35.

[2] "Raised blood pressure". World Health Organization. Global Health Observatory (GHO) data. http://www.who.int/gho/ncd/risk_factors/blood_pressure_text/en/

[3] Mancia G, Fagard R, Narkiewicz K et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159-219.

[4] "How Is High Blood Pressure Treated?". National Heart, Lung, and Blood Institute. September 10, 2015. 2016. https://www.nhlbi.nih.gov/health/health-topics/topics/hbp/treatment

[5] Peacock WF, Hilleman DE, Levy PD, Rhoney DH, Varon J. A systematic review of nicardipine vs labetalol for the management of hypertensive crises. Am J Emerg Med. 2012;30(6):981-93.

[6] Goa KL, Benfield P, Sorkin EM. Labetalol. A reappraisal of its pharmacology, pharmacokinetics and therapeutic use in hypertension and ischaemic heart disease. Drugs. 1989;37(5):583-627.

[7] MacCarthy EP, Bloomfield SS. Labetalol: a review of its pharmacology, pharmacokinetics, clinical uses and adverse effects. Pharmacotherapy. 1983;3(4):193-219.

[8] Singh SP, Quadir A, Malhotra P. Comparison of esmolol and labetalol, in low doses, for attenuation of sympathomimetic response to laryngoscopy and intubation. Saudi J Anaesth. 2010;4(3):163-8.

emergent treatment of severe hypertension.[9] A recent in depth review and meta-analysis, including 7 trials (363 woman infant pairs) showed that oral nifedipine is as effective and safe as intravenous labetalol for severe hypertension during pregnancy.[10]

VI.2.3 Unknowns relating to treatment benefits

No studies with labetalol have been performed in paediatric patients. Labetalol should not be used in children below 18 years of age. There are no adequate data about the effect of labetalol on fertility.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity reactions)	Allergic reactions, including rash, pruritus, difficulties with breathing, have been reported in patients using labetalol. Frequency of these reactions is common. Drug fever and angioedema (severe swelling of the skin and other tissues most often the lips or the eyes) were very rarely reported. Patients with a history of severe allergic reactions (anaphylactic reaction) are more likely to present such a reaction to beta blockers (the family of medications that labetalol belongs to). Such patients may be unresponsive to the usual doses of epinephrine (medicine used to treat an allergic reaction).	If an allergic reaction occurs, patients should stop using labetalol and talk to their doctor right away. The doctor may prescribe a medicine to treat the allergic reaction and a different medicine for hypertension.
Temporary narrowing of the airways in patients with lung or respiratory system problems (bronchospasm in patients with bronchial asthma or a history of obstructive airway disease)	Temporary narrowing of the airways (bronchospasm) has been reported in patients using labetalol. Frequency of these reactions is uncommon. Labetalol should not be used for patients	Patients should talk to their doctor or pharmacist if they get any side effects. Labetalol is contraindicated in asthma and if there is a history of bronchospasm.

[9] Olson-Chen C, Seligman NS. Hypertensive Emergencies in PregnancyCrit Care Clin. 2016;32(1):29-41.

[10] Shekhar S, Gupta N, Kirubakaran R, Pareek P. Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis. BJOG. 2016;123(1):40-7.

Risk	What is known	Preventability
	with asthma or a similar lung disease. An overreaction of the airways may result in bronchospasm due to the beta-blocking activity of labetalol in the lungs.	
Dizziness due to low blood pressure if patient moves too quickly from a lying to sitting position or from sitting to standing position (postural hypotension).	Postural hypotension has been reported in patients using labetalol. Frequency of these reactions is common. This may occur within three hours after Labetalol injection and is normally temporary and occurs in the first few weeks of treatment.	Patients should talk to their doctor or pharmacist if they get any side effects.
Liver disorders (hepatic disorders)	Liver disorders (including hepatitis, jaundice or laboratory enzyme disorders) have been reported in patients taking labetalol. Liver disorders maybe reversible and have occurred after both short- and long-term treatment. However liver disorders can be very serious such as hepatic necrosis, in some cases fatal outcomes have been reported.	Appropriate laboratory tests 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. Particular care should be taken when labetalol is used in patients with liver impairment as these patients metabolise labetalol more slowly than patients without liver impairment.
Worsening of pre -existing heart failure	Labetalol can exacerbate existing heart failure through its beta-blocking activity.	Before administrating the medicine the patient should inform their doctor of any history of heart disease or if they are taking any medicine for heart disease.
Cardiac conduction disorders (atrioventricular (AV) conduction disturbances)	Labetalol slows down conduction of the electrical impulses in the heart. Slow heart beat is a typical symptom of cardiac conduction disorders.	Physician supervision and care. Labetalol should be administered with caution to patients with pre-existing cardiac conduction abnormalities, such as first-degree atrio-ventricular block. In case of suspected heart problems, specialist advice must be sought before starting treatment to determine if there is any underlying condition for which the medicine is contraindicated.

Risk	What is known	Preventability
Decreased heart rate and low blood pressure (bradycardia and hypotension)	Labetalol is a beta -blocking agent. Its ability to reduce the heart rate and affect heart rhythm is well established. Labetalol also reduces blood pressure through its beta-blocking activity.	Physician supervision and care. Patients should report symptoms of irregular heartbeat to their doctor. Blood pressure should be closely monitored in patients using labetalol.

Important potential risks

Risk	What is known
Poor blood glucose control and masking of low blood sugar (decreased diabetic control and masking of hypoglycaemia)	Labetalol may mask the warning signs of low blood sugar, particularly increased heart rate (tachycardia) and tremor in diabetic patients. The low blood sugar effect of medicines to treat diabetes may be enhanced by beta blockers (the family of medications that labetalol belongs to). Care should be taken in case of uncontrolled or difficult-to-control diabetes mellitus.
Drug interactions (calcium antagonist e.g. verapamil, diltiazem; class I and II antiarrhythmic, anaesthetic agents)	The concomitant use of such drugs (e.g. calcium antagonist e.g. verapamil, diltiazem; class I and II antiarrhythmic) may lead to heart problems like decreased heart rate, low blood pressure and heart failure. There is a potential risk of drug interaction with general anaesthetics, due to an increased risk of hypotension (low blood pressure).

Missing information

Risk	What is known
Patients below18 years of age	Children and adolescents below 18 years should not use this medicine. It is not known if this medicine is safe and effective when used in children and adolescents under 18 years of age.
Fertility	There is no sufficient information on the effects of labetalol on fertility.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

No post authorisation development plan was proposed.

VI.2.7 Summary of changes to the risk management plan over time

Not applicable. This is the initial version of this RMP.