Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Labetalol hydrochloride

Proprietary Product Name: Labetalol SXP/RMB/TLB

Sponsor: Southern Cross Pharma Pty Ltd

March 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the concentration time curve
CABG	Coronary artery bypass graft
DBP	Diastolic blood pressure
EMA	European Medicines Agency (European Union)
EU	European Union
FDA	Food and Drug Administration (United States)
HCPM	Health Canada Product Monograph
IV	Intravenous
LBS	Literature-based submission
MAP	Mean arterial pressure
mmHg	Millimetres of mercury blood pressure
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PL	Product Label (United States)
RMP	Risk management plan
SBP	Systolic blood pressure
SmPC	Summary of Product Characteristics (United Kingdom)
UK	United Kingdom
USA	United States of America

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications and new dosage form
Decision:	Approved
Date of decision:	23 August 2019
Date of entry onto ARTG:	14 November 2019
ARTG numbers:	306952, 306953, 306954
, *Black Triangle Scheme*	No
Active ingredient:	Labetalol hydrochloride
Product names:	Labetalol SXP, Labetalol RMB, Labetalol TLB
Sponsor's name and address:	Southern Cross Pharma Pty Ltd Suite 5/118 Church Street Hawthorn VIC 3122
Dose form:	Solution for injection
Strength:	50 mg/10 mL
Container:	Glass ampoule
Pack size:	10
Approved therapeutic use:	*The emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.*
Route of administration:	Intravenous (IV)
Dosage:	**Adults** *Labetalol hydrochloride solution for injection is intended for intravenous (IV) use in hospitalised patients.* • Dosage must be individualised depending on the severity of hypertension and the response of the patient during dosing. • Blood pressure should be monitored during and after the completion of labetalol treatment. • Patients should always be kept supine during the period of IV drug administration. A substantial drop in blood pressure on standing should be expected in these patients. The patient's ability to tolerate an upright position on standing should be established before permitting any ambulation.

Bolus dosing

Initial treatment should be by slow IV bolus injection over about 2 minutes, commencing with a 20 mg dose. Blood pressure should be closely monitored and, if necessary, an additional 40 mg slow bolus dose should be given 10 to 20 minutes after the initial dose. Up to a further 3 x 80 mg slow bolus doses may be given at 10 to 20 minute intervals if required to adequately control blood pressure. The maximum total dose given should not exceed 300 mg over a 24 hour period.

Intravenous infusion

If bolus treatment is unsuccessful in reducing blood pressure, patients can be commenced on an IV infusion of labetalol. A 1 mg/mL infusion should be prepared by dilution with sodium chloride/dextrose injection BP or 5% dextrose intravenous infusion BP.

In cases of severe hypertension in pregnancy the infusion should commence at 20 mg/hr and increased by 20 mg/hr at 20 minute intervals if necessary for adequate blood pressure control, up to a maximum of 160 mg/hr. The infusion rate should be decreased or stopped if blood pressure decreases too rapidly. As for bolus dosing, the maximum total dose should not exceed 300 mg over a 24 hour period.

In cases of severe hypertension due to other causes the rate of infusion of labetalol hydrochloride 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 larger doses may be required especially in patients with phaeochromocytoma.

To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2° to 8°C for not more than 24 hours or 6 hours at room temperature. The product is for single use in one patient only. Discard any residue.

Dosage and Administration in special patient groups should take into account the information in Product Information Section 4.4 Special warnings and precautions for use.

For further information refer to the Product Information.

Product background

This AusPAR describes the application by Southern Cross Pharma Pty Ltd (the sponsor) to register Labetalol SXP/RMB/TLB (labetalol hydrochloride) 50 mg/10 mL solution for injection for the following proposed indication:

Treatment of severe hypertension, including severe hypertension of pregnancy.

Severe hypertension can present as an emergency in which blood pressure rises rapidly and there is a risk of end-organ damage such as renal failure, hypertensive encephalopathy or cardiac failure. This can require inpatient management with parenteral anti-hypertensives to achieve a rapid reduction in blood pressure.

Dangerous elevation of blood pressure occurs in approximately 3.1% of pregnancies;[1] which poses a risk to mothers and unborn children. Potential outcomes include the kidney, liver and cerebral damage (including eclampsia) in mothers, and fetal distress due to placental impairment for unborn children. Current Australian and New Zealand obstetric guidelines;[2] define hypertension in pregnancy as a systolic blood pressure (SBP) > 140 mmHg and/or a diastolic blood pressure (DBP) > 90 mmHg. Severe hypertension requiring urgent treatment is defined as a SBP of > 170 mmHg and/or a DBP > 110 mmHg.

Severe hypertensive emergencies can also complicate a range of medical conditions and the level of hypertension which is considered 'severe' in these contexts is highly dependent on the nature and severity of the patients' underlying conditions. Rapid and controlled reduction in blood pressure may be required to avoid further complication in such patients.

Labetalol antagonises alpha- and beta-adrenoreceptors by competitive inhibition. Labetalol lowers blood pressure by blocking alpha-adrenoceptors in peripheral arterioles, reducing peripheral resistance. Labetalol concurrently blocks beta-adrenoceptors and a reduction in blood pressure is achieved without cardiac stimulation. The dosage of labetalol is titrated to response and can be administered as a series of slow bolus doses or as an IV infusion of labetalol if bolus treatment is unsuccessful.

There are currently four tablet forms of Labetalol products (100 mg and 200 mg tablets) in the Australian Register of Therapeutic Goods (ARTG), indicated for the treatment of all grades of hypertension (see 'Regulatory Status', below). An intravenous (IV) preparation has not previously been included in the ARTG.

This submission is a literature-based submission (LBS), as agreed with the TGA.

Regulatory status

Labetalol hydrochloride tablets for oral administration have been approved in Australia for more than 30 years for the treatment of hypertension. These registered products are:

- Trandate 100 mg and 200 mg labetalol hydrochloride tablets ARTG R 12521, 12522; and
- Presolol 100 mg and 200 mg labetalol hydrochloride tablets ARTG R 56475, 56476.

Labetalol SXP/RMB/TLB labetalol hydrochloride 50 mg/10 mL solution for injection is considered an extension of indications and new dosage form for Australian regulatory purposes.

Internationally, IV labetalol has been available in several countries for over 30 years. At the time the TGA considered this application, similar applications had been approved in the United States of America (USA), the European Union (EU), Canada and New Zealand (Table 1).

[1] Centre for Epidemiology and Evidence , NSW Mothers and Babies 2015 report, Sydney: NSW Ministry of Health, 2016.
[2] Society of Obstetric Medicine of Australia and New Zealand, Guideline for the Management of Hypertensive Disorders of Pregnancy (2014).

Table 1: International regulatory status of intravenous labetalol hydrochloride as of 7 May 2019

Region	Approval year	Indication
USA	1985	*For control of blood pressure in severe hypertension*
EU	1978	• *Severe hypertension of pregnancy, when rapid control of blood pressure is essential* • *Anaesthesia when a hypotensive technique is indicated* • *Hypertensive episodes following acute myocardial infarction*
Canada	1986	*The emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential*
New Zealand	1977	As for EU

Product Information

The Product Information (PI) documents approved with the submission which is described in this AusPAR can be found as Attachments 1, 2 and 3. For the most recent PIs, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-01753-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	31 July 2018
First round evaluation completed	12 February 2019
Sponsor provides responses on questions raised in first round evaluation	12 March 2019
Second round evaluation completed	18 April 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	7 May 2019
Sponsor's pre-Advisory Committee response	24 May 2019
Advisory Committee meeting	7 June 2019
Registration decision (Outcome)	23 August 2019
Completion of administrative activities and registration on ARTG	14 November 2019

Description	Date
Number of working days from submission dossier acceptance to registration decision*	248

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

Labetalol hydrochloride is a white or almost white powder, sparingly soluble in water. Labetalol hydrochloride solution for injection is a clear colourless solution containing 50 mg of labetalol hydrochloride in 10 mL solution per ampoule. Labetalol hydrochloride 50 mg/10 mL solution for injection has been developed to be similar to the European innovator product.

The sponsor has not provided any biopharmaceutic studies as the drug product is a simple solution for IV administration only, which was considered acceptable given the submission type.

The Delegate considers that all issues raised by the quality evaluator have been adequately addressed by the sponsor.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval of the labetalol solution for injection with changes to the wording of the indication. The sponsor initially proposed the indication:

> *Labetalol injection is indicated for the treatment of severe hypertension, including severe hypertension of pregnancy.*

The evaluator has recommended changing the indication to align with the indication approved in Canada:

> *The emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.*

These changes were proposed to stipulate that IV labetalol is to be used for acute reduction of severe hypertension, rather than severe hypertension to avoid confusion with severe essential hypertension. In addition, the evaluator was concerned that the phrase 'including severe hypertension of pregnancy' could imply that labetalol has a preferential effect in pregnancy beyond the immediate pharmacodynamic outcome of reducing hypertension and there was not sufficient clinical outcomes data to warrant a specific indication in pregnancy beyond that generally possessed by agents which reduce blood pressure.

The clinical dossier included multiple controlled studies (the sponsor considered 11 to provide pivotal efficacy data) and literature reports which provided supportive efficacy or safety data and studies to support pharmacokinetic (PK) and/or pharmacodynamic (PD) analysis.

Pharmacology

Pharmacokinetics

The dossier presented a number of studies which examined the PK parameters of IV labetalol in hypertensive patients and/or volunteers. The sponsor has also referred to secondary sources such as the United Kingdom (UK) Summary of Product Characteristics (SmPC) and USA Product Label (PL) to support the PK analysis.

The proposed formulation is for IV administration and is therefore completely absorbed with 100% bioavailability. Labetalol is rapidly and extensively distributed through vascular and extravascular water compartments of the body. About 50% of labetalol in blood is protein bound. Labetalol is metabolised in the liver by conjugation to inactive glucuronides. The elimination half-life of IV labetalol is about 5.5 hours. Approximately 55 to 60% of a labetalol dose appears in the urine as conjugates or unchanged labetalol within the first 24 hours of dosing.

Rubin et al;[3] examined the PK of labetalol in hypertensive pregnant women and found no difference in clearance, volume of distribution or plasma half-life in pregnant women compared to age matched controls. There were no differences in PK in the general hypertensive populations examined compared to healthy controls.

In patients with impaired hepatic function, the area under the concentration time curve (AUC) of IV labetalol was increased by 25% and the volume of distribution was decreased by 35%, however the elimination half-life was not altered. Renal impairment had no significant effect on the PK of labetalol. The half-life of IV labetalol was increased in the elderly in one study to 8.5 hours.

Pharmacodynamics

The dossier presented two studies relating blood pressure concentrations of labetalol to its PD effects of lowering blood pressure.

The onset of blood pressure reduction was within minutes of the commencement of an infusion of labetalol. The time to offset of the action was not reported, but the half-life of labetalol is noted at about 5.5 hours.

Dose finding

Dose ranging was addressed by referencing the doses used in pivotal efficacy studies and Australian clinical guidelines.

Efficacy

A number of studies were provided as pivotal efficacy data. All except one involved the use of labetalol in obstetric hypertensive emergencies. The evaluator presented four of these studies in detail. The results of the remaining pivotal studies were reported to be consistent with these four studies.

[3] Rubin, P.C. et al. Labetalol Disposition And Concentration-Effect Relationships During Pregnancy, *Br. J. clin. Pharmac*, 1983; 15: 465-470.

De Pasquale et al (2013)[4] compared the effectiveness of IV labetalol and IV hydralazine as treatments for severe hypertension in pregnancy. A total of 275 hypertensive pregnant women were randomised 1:1 to receive either labetalol or hydralazine. Women > 24 weeks of gestation admitted to hospital for hypertensive crisis (SBP > 160 mmHg and/or DBP > 110 mmHg), who were haemodynamically stable, were eligible for study inclusion. Study participants received either escalating doses of labetalol IV bolus over 10 minutes (20 mg, 40 mg, 80 mg, 80 mg, 80 mg to a maximum of 300 mg) or hydralazine 5 mg IV bolus over 5 minutes (up to 15 mg maximum dose) until blood pressure was < 160 mmHg SBP and/or < 110 mmHg DBP. 261 patients were included in the analysis. Patients were well matched for age, parity and initial blood pressure. The primary efficacy endpoint was the number of doses of medication required to achieve resolution of severe hypertension. There was no significant difference in the average number of doses required to achieve control of severe hypertension in patients receiving labetalol or hydralazine (mean (standard deviation) 1.3 (0.6) versus 1.4 (0.6), p = 0.25), nor was there a significant difference in the blood pressure in the two treatment groups after treatment (SBP 144 mmHg(8.2) versus 144 mmHg (8.3), p = 0.86; DBP 92 mmHg (8.3) versus 91 mmHg (8.3), p = 0.48; mean arterial pressure (MAP) 109 mmHg (7.2) versus 109 mmHg (6.8), p = 0.39). The secondary efficacy endpoint was the rate of persistent hypertension which did not resolve on treatment. There was no significant difference in the rate of persistent hypertension post-treatment among the subjects receiving labetalol or hydralazine (2 (1.5) versus 6 (4.6), p = 0.085).

Vigil-de Gracia et al (2007)[5] was a randomised, active-comparator study conducted in 82 women with severe hypertension post-partum who presented to a single tertiary hospital obstetric unit in Panama. Subjects were randomised 1:1 to receive either labetalol or hydralazine. The study included 82 subjects who were admitted with severe hypertensive disorders, and who had severe hypertension post-partum (SBP > 160 mmHg and/or DBP > 110 mmHg) and more than 24 hours after previous anti-hypertensive treatment. Subjects received either escalating doses of labetalol IV bolus over 10 minutes; (as described for De Pasquale et al),[4] or IV hydralazine 5 mg bolus repeated every 20 minutes (to a maximum of 25 mg) until blood pressure was < 160 mmHg SBP and/or < 110 mmHg DBP. The analysis population included 42 subjects who received hydralazine and 40 subjects who received labetalol. The two treatment groups were well matched for age, parity and degree of hypertension. 76.1% of the hydralazine and 80.0% of the labetalol patients had severe antenatal hypertension and in the remainder severe hypertension had developed post-partum. The primary endpoint was the rate of persistent severe hypertension after treatment. There was no significant difference in the rate of persistent severe hypertension between the two treatment groups, with only one case being observed (2.5% versus 0%, p > 0.05).

Vigil-de Gracia et al (2006)[6] was a randomised active comparator study conducted in 200 pregnant women who were admitted to a single tertiary obstetric hospital in Panama between December 2003 and November 2004 for gestational hypertension. Subjects were randomised 1:1 to receive either IV labetalol or IV hydralazine. Eligible patients had a gestational age of > 24 weeks and a SBP > 160 mmHg and/or signs of pre-eclampsia. Study treatments were the same as that described in Vigil-de Gracia et al (2007).[5] The primary endpoint was the rate of persistent hypertension in the two treatment groups. The analysis population included 200 subjects. The rate of effective blood pressure control was

[4] De Pasquale, D. et al. (2014). Hydralazine vs labetalol for the treatment of severe hypertensive disorders of pregnancy. A randomized, controlled trial. *Pregnancy Hypertens*, 2014; 4: 19-22.
[5] Vigil-De Gracia, P. et al. (2007). Management of Severe Hypertension in the Postpartum Period with Intravenous Hydralazine or Labetalol: A Randomized Clinical Trial, *Hypertension in Pregnancy*, 2007, 26: 163–171.
[6] Vigil-De Gracia, P. et al. (2006). Severe hypertension in pregnancy: Hydralazine or labetalol A randomized clinical trial, European Journal of Obstetrics & Gynecology and Reproductive Biology, 2006; 128: 157–162.

not-significantly different between hydralazine (91%) and labetalol (93%) respectively. The same rate of persistent severe hypertension was reported in both treatment arms (5%).

Shi et al (2016)[7] was a randomised active-comparator study conducted in 147 pregnant women admitted to a single hospital in China between February and November 2015 with severe hypertension. Patients were randomised 1:1 to receive either IV labetalol or oral nifedipine. The objective of the study was to compare the time needed to achieve hypertensive control between the two treatments. Enrolled women were admitted to hospital with a blood pressure of > 160 mmHg (SBP)/110 mmHg (DBP) and a gestational age > 30 weeks. Patients with a history of treatment with antihypertensive drugs or heart failure during pregnancy were excluded. Patients were randomised to receive either escalating bolus doses of labetalol 20 mg, 40 mg and 80 mg every 15 minutes or until blood pressure control was achieved (no maximum dose reported) or oral nifedipine 10 mg repeated up to 5 times or until blood pressure control was achieved (no dose interval reported). The study does not appear have been double blinded. The two treatment arms were well balanced for age, gestational age, and blood pressure at enrolment. The primary efficacy endpoint was the time to achieve blood pressure control. There was no statistically significant difference between the two treatments in the time needed to achieve blood pressure control. There was also no statistically significant difference in the number of doses of medication required to achieve blood pressure control.

Three literature articles examined efficacy in paediatric patients including two case series and a retrospective chart review.

Regueiro et al;[8] was a case series of five children aged between 2 months and 15 years who presented to a tertiary paediatric unit with severe hypertension (> 95th percentile for age) due to a number of causes. IV labetalol was administered at 1 mg/kg/hour until blood pressure control was achieved. An average decrease of 21% in SBP and 24% in DBP was reported.

Deal et al;[9] was a case series of 53 children between 1 month and 17 years of age admitted to a tertiary paediatric unit with severe hypertension due to a range of causes. 25 of these patients were treated with labetalol 1 to 3 mg/kg/hour until blood pressure control was achieved. In all these cases there was improvement in hypertensive signs and symptoms.

Thomas et al;[10] was a retrospective chart review of 27 children < 24 months of age admitted with severe hypertension to a tertiary paediatric unit, 15 of whom were treated with IV labetalol. The primary endpoint was the time to achieve a 20% reduction in SBP. The study reported a mean time of 4.5 hours (± 5.5 hours) to achieve the primary endpoint.

Three literature articles examined efficacy in the elderly population including an open randomised study, a retrospective analysis of consecutive patients receiving labetalol and a case series.

Singh et al;[11] was an open randomised study comparing the effectiveness of IV labetalol (n = 11) and IV esmolol (n = 11) in the treatment of post-operative hypertension in elderly

[7] Shi, D.D. et al. (2016). Oral nifedipine vs. intravenous labetalol for treatment of pregnancy-induced severe pre-eclampsia, *Journal of Clinical Pharmacy and Therapeutics*, 2016; 41: 657–661.
[8] Regueiro, J. et al. (1996). Labetalol in the treatment of hypertensive crises, *Act Ped Esp* 1996; 54: 575-578.
[9] Deal, J.E. et al. (1992). Management of hypertensive emergencies, *Archives of Disease in Childhood*, 1992; 67: 1089-1092.
[10] Thomas, C.A. (2011). Safety and efficacy of intravenous labetalol for hypertensive crisis in infants and small children, *Pediatr Crit Care Med*, 2011; 12: 28-32.
[11] Singh, P.P. et al. (1992). A comparison of esmolol and labetalol for the treatment of perioperative hypertension in geriatric ambulatory surgical patients, Can J Anaesth, 1992; 39: 559-562.

patients (average age 76 years) who had undergone cataract surgery. Included patients had SBP > 200 mmHg or DBP > 100 mmHg. Labetalol was administered as 5 mg boluses up to a maximum of 1 mg/kg or until blood pressure control was achieved. Blood pressure control (SBP < 180 mmHg and DBP < 100 mmHg) was achieved in 10 out of 11 patients in each group.

Malesker et al;[12] was a retrospective analysis of consecutive patients receiving IV labetalol (n = 189) or IV nicardipine (n = 193) for the control of hypertension complicating a range of primary illnesses in two USA intensive care units between 2008 and 2010. The average age of patients in the study was 65 years. Included patients had a SBP of > 160 mmHg or a DBP > 90 mmHg at enrolment. The primary endpoint was the proportion of patients achieving a target blood pressure of < 140/90 mmHg and > 90/60 mmHg or the target specified by their treating doctor. Labetalol was administered as either a bolus or a continuous infusion, and the exact protocol was not reported. Significantly fewer patients receiving labetalol achieved their blood pressure target (67%) compared to those receiving nicardipine (83%, p = 0.04).

Orlowski et al;[13] was a case series of 12 intubated/ventilated patients who developed hypertension, defined as a SBP > 200 mmHg and/or a DBP > 100 mmHg after major vascular surgery. The average age of the patients was 72 years. The primary endpoint was the achievement of acceptable blood pressure, defined as a diastolic blood pressure < 90 mmHg. Labetalol was administered in 10 to 20 mg boluses every 10 minutes to a maximum of 300 mg. All 12 patients achieved an acceptable blood pressure after labetalol treatment.

The dossier does not comply with regulatory guidance for the investigation of anti-hypertensives;[14] in that it does not provide long term treatment data, nor sufficient data in the elderly, nor the close attention to treatment discontinuations which trials of chronic therapy require. The patient exposure is less than usually required to assess safety in a novel agent, a cohort of about 500 to 600 patients.[15] The clinical evaluator noted, however, this guidance is not directly applicable to this submission as IV labetalol is used in the submitted studies to immediately reduce blood pressure rather manage long term end organ damage.

In the submitted studies, persistent hypertension occurred in 1.5 to 5% of labetalol treated patients. In each of the pivotal efficacy studies the effectiveness of labetalol was not statistically significantly different from the comparator. The clinical evaluator noted, however, that no margin of non-inferiority was stipulated in these trials and so statistically non-different effects between the comparators at p = 0.05 should not be taken as equivalence or non-inferiority of effect.

Safety

The safety analysis was based on historical experience with labetalol and the adverse events reported in the published reports of the pivotal studies. A total of 565 patients were treated with labetalol in the pivotal trials, the majority of which (n = 362) involved comparison with hydralazine. The most commonly reported maternal adverse events in

[12] Malesker, M.A. et al. (2012). Intravenous labetalol compared with intravenous nicardipine in the management of hypertension in critically Ill patients, *Journal of Critical Care*, 2012; 27: 528.e7–528.e14.
[13] Orlowski, J. P. et al. (1989). The hemodynamic effects of intravenous labetalol for postoperative hypertension, *Cleve Clin J Med*., 1989; 56: 29-34.
[14] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Clinical investigation on medicinal products in the treatment of hypertension, EMA/CHMP/29947/2013/Rev. 4, 8 July 2016.
[15] European Medicines Agency (EMA), Committee for Proprietary Medicinal Products (CPMP), ICH Topic E 1 Population Exposure: The Extent of Population Exposure to Assess Clinical Safety, CPMP/ICH/375/95, June 1995.

labetalol treated patients were headache (10%), palpitations (6%), nausea (5%), flushing (5%) and dizziness (4%). These occurred at rates similar to other treatment arms. It was not clear whether adverse events were related to drug treatment or the patient's underlying condition. No maternal deaths were reported in the pivotal studies. Seven neonatal deaths were reported in each of labetalol and hydralazine treated groups in the pivotal studies.

Multiple meta-analyses were provided which examined severe hypertension in pregnancy were provided to support the safety analysis.

Duley et al;[16] was a meta-analysis of studies conducted under the auspices of the Cochrane Collaboration. It included randomised trials which compared anti-hypertensive drugs for the treatment of severe hypertension in pregnancy, defined as a SBP > 160 mmHg and and/or a DBP > 105 mmHg. The primary outcomes of the review were maternal death, eclampsia, stroke, persistent hypertension and neonatal death. The review included four studies which compared labetalol and hydralazine, and three studies which compared labetalol and calcium channel blockers (nifedipine or nicardipine). No differences in the rates of the assessed outcomes were found between the comparator treatments, but there was insufficient information for a reliable comparison.

Peacock et al;[17] was a systematic review comparing nicardipine and labetalol in the treatment of hypertensive crisis from a range of non-obstetric causes such as stroke and cardiac ischemia. The review found no significant differences in the rates of adverse events reported between labetalol and nicardipine treated patients.

Shekar et al;[18] was a meta-analysis of trials comparing labetalol and nifedipine for the management of severe hypertension in pregnancy, defined as a SBP > 160 mmHg and/or a DBP > 105 mmHg. The study found that nifedipine was more effective at lowering blood pressure than labetalol, but the authors concluded that this result was not robust due to heterogeneity between the trials. The study authors therefore concluded that labetalol was equivalently safe and effective as nifedipine, but highlighted the need for more complete studies.

Bhorat et al;[19] was an open-label randomised trial which examined the rates of arrhythmia reported in 34 patients with severe hypertension in pregnancy treated with labetalol (n = 18) or hydralazine (n = 16). Labetalol was administered as an infusion of 200 mg administered at an escalating rate of 20 mg/hour to 160 mg/hour until blood pressure control was achieved. Hydralazine was administered as 6.25 mg doses over 30 minutes, repeated to a maximum of 3 doses until blood pressure control was achieved. The study reported a significantly lower rate of arrhythmias in the labetalol than the hydralazine treated arm.

The safety analysis was limited by the statistical power of the studies and the reporting of adverse events such as fetal bradycardia or hypotension could have been caused by labetalol or fetal distress secondary to the obstetric emergency being treated. The evaluator states that the submitted studies do not support an analysis of the safety of IV labetalol with sufficient detail.

The safety profile is well described for oral labetalol agent. The evaluator considered that the IV formulation provides a loading dose of labetalol to allow rapid onset of effect and

[16] Duley, L. et al. (2013). Drugs for treatment of very high blood pressure during pregnancy (Review), Cochrane Database of Systematic Reviews.
[17] Peacock, W. F. et al. (2012). A systematic review of nicardipine vs labetalol for the management of hypertensive crises, American Journal of Emergency Medicine, 2012; 30: 981–993.
[18] Shekhar, S. et al. (2015). Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis, BJOG, 2016; 123: 40–47.
[19] Bhorat, I.E. et al. (1993). Malignant ventricular arrhythmias in eclampsia: a comparison of labetalol with dihydralazine. *Am J Obstet Gynecol*, 1993; 168: 1292-1296.

the differences between the IV and oral formulation to be PK. Therefore, the safety profile for IV labetalol is likely to be similar to that of the oral formulation with additional safety issues related to the rapid onset of antihypertensive effect or the specific clinical context such as fetal arrhythmia.

The studies provided allow for comparison of the adverse event profile of labetalol in obstetric hypertensive emergencies with other commonly used agents such as hydralazine. There was no significant difference in the rates of adverse events reported in the studies between the treatment arms, except where this reflects an expected adverse event of the comparator, for example, headache in nifedipine. The evaluator notes that there appears to be little clinical consensus on the ideal product to use in severe hypertension in pregnancy, suggesting IV labetalol is a valid treatment option. This would appear to be supported by the extensive unregistered use of IV labetalol in Australia currently.

Risk management plan

The sponsor has submitted an Australian-specific risk management plan (RMP) version 1.0 (5 July 2018) in support of this application.

The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 3.[20]

[20] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Hypersensitivity reactions	ü	–	ü	–
	Bronchospasm associated with bronchial asthma/obstructive airway disease	ü	–	ü	–
	Hypotension (including postural)	ü	–	ü	–
	Hepatic disorders	ü	–	ü	–
	Exacerbation of underlying cardiac failure	ü	–	ü	–
	Heart Block	ü	–	ü	–
	Bradycardia	ü	–	ü	–
	Raynaud's disease/intermittent claudication	ü	–	ü	–
Important potential risks	Decreased diabetic control associated with hypoglycaemia masking	ü	–	–	–
	Drug interactions	ü	–	–	–
	Use in pregnancy	ü	–	–	–
Missing information	Fertility: no data available.	ü	–	–	–
	Genotoxicity: no data available	ü	–	–	–
	Carcinogenicity: no data available	ü	–	–	–

No additional pharmacovigilance activities have been proposed. Routine pharmacovigilance measures are a regulatory requirement and are considered suitable for monitoring the risks associated with this medicine.

The sponsor has proposed routine risk minimisation activities for all important identified risks. All risks have been adequately addressed in the product information. No additional risk minimisation activities have been proposed. This is considered acceptable.

Suggested wording for conditions of registration have not been provided as version control of data lock date for the latest RMP documents was not submitted at the time of the second round evaluation report.

Risk-benefit analysis

Delegate's considerations

Labetalol is currently registered in the ARTG as an oral tablet formulation. The oral dosage form has an established efficacy and safety profile as a treatment for hypertension. The sponsor has proposed an IV formulation of labetalol that is intended for use under medical supervision in the hospital setting. IV labetalol has been available internationally for over 30 years as a treatment for severe hypertension and in the EU labetalol has a specific indication for severe hypertension in pregnancy. Despite IV labetalol not being a registered product in Australia, several Australian clinical guidelines include recommendations for labetalol dosing and administration. The sponsor estimates that approximately 30,413 ampoules of IV labetalol are used in Australia annually under the provisions of the TGA Special Access Scheme.[21] This suggests there is a clinical need that is not currently met by registered products.

The clinical evaluator provided a favourable recommendation but proposed changes to the indication. The initial proposed indication for the new formulation was:

> *Labetalol injection is indicated for treatment of severe hypertension, including severe hypertension of pregnancy.*

After the first round clinical evaluation, this was revised to:

> *The emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.*

The clinical evaluator recommended this change so as to not imply that labetalol should be used preferentially over other treatments in the setting of hypertension in pregnancy and also to differentiate that IV labetalol is intended for the acute reduction of severe hypertension rather than the treatment of severe essential hypertension. The sponsor has accepted the clinical evaluator's proposed changes. The negotiated indication is the same as the registered indication in Canada.

The sponsor included multiple pivotal studies to support efficacy, the majority of which were conducted in pregnant patients with hypertension. One study was conducted in hypertensive patients who were post-partum and one study was conducted in patients with hypertension post coronary artery bypass graft (CABG). The clinical evaluator notes that the studies demonstrate an absolute effect of labetalol in treated patients but that as no margin of non-inferiority was stipulated in these trials, statistically non-different effects between the comparators at $p = 0.05$ cannot be taken as equivalence or non-inferiority of effect. The proposed indication allows for treatment of all causes of severe hypertension in an emergency setting but the presented data is limited mostly to severe hypertension in pregnancy.

As outlined above, the submitted safety information is not sufficiently detailed to support of the safety of IV labetalol but the safety profile for oral labetalol is well described and the risks of IV labetalol therapy are expected to include the known adverse effects of oral therapy plus additional safety issues related to the rapid onset of antihypertensive effect or the specific clinical context. IV labetalol has been registered in comparable jurisdictions for many years and is currently accessed in Australia through the TGA Special Access Scheme. IV labetalol is intended for use under medical supervision in the hospital setting for the treatment for life threatening hypertensive emergencies.

[21] The **Special Access Scheme** (**SAS**) allows certain health practitioners to access therapeutic goods (such as medicines, medical devices or biologicals) that are not included in the Australian Register of Therapeutic Goods (ARTG), for a single patient. Therapeutic goods that are not included in the ARTG (and are not otherwise exempt from being in the ARTG) are described by the TGA as 'unapproved'.

The dosage instructions vary across trials, guidelines and international PI documents. The pivotal trials evaluated in the clinical evaluation examined bolus dosing but the PI dosing instructions recommend IV bolus dosing followed by an IV infusion if bolus dosing is unsuccessful in reducing blood pressure. Several of the submitted Australian clinical guidelines recommend the use of IV labetalol infusion if bolus dosing is unsuccessful but none describe the dosing regimen listed in the PI. The proposed dosage instructions do not match those listed in the UK SmPC, the US PL and the Health Canada Product Monograph (HCPM) or the New Zealand Data Sheet. In addition, the UK SmPC lists 200 mg as the maximum recommended dose for bolus dosing. The HCPM does not include instructions to convert to IV infusion after unsuccessful bolus dosing but does list a 300 mg maximum recommended dose for both bolus and IV infusion. The dosing regimen was a concern noted in the RMP. The sponsor has been asked to justify the proposed dosing regimen given that the presented trials are mostly limited to bolus dosing. In addition, clarification has been sought regarding the maximum recommended dosage and how this would be applied in practice.

The outstanding issues are the extrapolation of efficacy and safety from the oral dosage form, the limited efficacy and safety data presented in the submission and the evidence to support the proposed dosage recommendations. The Advisory Committee on Medicines (ACM) is requested to provide advice on these matters.

Questions for the sponsor[22]

1. What evidence is there to support the IV infusion dosing recommendations? The four pivotal efficacy studies considered by the evaluator all appear to use bolus dosing.
2. Please justify the maximum dosage recommendations for the bolus and IV infusion dosing. Over what timeframe does the 300 mg maximum dose apply? It is noted that the Royal Women's Hospital (Melbourne) guideline recommends a maximum 24 hour dose of 300 mg.
3. Why has the contraindication relating to heart failure been removed? Why is a history of obstructive airways disease not included as a contraindication?

Summary of issues

1. Labetalol is currently registered as an oral formulation, approved for the treatment of all grades of hypertension. The submission relies on the extrapolation of efficacy from the approved oral formulation to the IV formulation. In addition, the sponsor has submitted literature studies to support the efficacy of the IV formulation. The majority of studies examined the indication for severe hypertension in pregnancy and whilst a reduction in blood pressure was demonstrated non-inferiority to comparator products was not established due to the nature of the study designs.
2. The safety profile of IV labetalol is not well characterised in the submitted studies but there is extensive international and local experience with the both the IV and oral labetalol formulations.
3. Both IV bolus and IV infusion dosing regimens have been included in the proposed Australian PI but there is variation in dosing recommendations and maximum dosages across trials, Australian clinical guidelines and international product information documents.

Proposed action

The Delegate is not in a position to say, at this time, that the application for Labetalol SXP/RMB/TLB should be approved for registration.

[22] The sponsor's response to these questions is beyond the scope of this AusPAR.

Request for Advisory Committee On Medicines advice

The committee is requested to provide advice on the following specific issues:

1. Please comment on the evidence provided to support the efficacy of the proposed IV formulation and the extrapolation of efficacy from the oral the labetalol dosage form.
2. Please comment on the evidence provided to support the safety of the proposed IV formulation and the extrapolation of safety of oral the labetalol dosage form.
3. What are Advisory Committee on Medicines' (ACM's) views on the extrapolation of the safety profiles for the oral dosage form to the IV dosage form given the limited available information from published studies but extensive worldwide experience with the IV formulations?
4. What are ACM's views on the wording of the proposed indication? Should the indication be limited to hypertension in pregnancy?
5. What are ACM's views on the proposed dosage instructions in the PI, in particular the IV infusion dosing instructions and the maximum recommended dosages?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory Committee Considerations[23]

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM considered the referral for advice from the TGA Delegate in relation to the submission to register Labetalol SXP/RMB/TLB solution for IV injection, containing 5 mg/mL of labetalol.

The ACM agreed that this product had an overall positive risk benefit profile for the proposed indication:

> *The emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.*

Specific advice

The ACM advised the following in response to the Delegate's specific request for advice:

1. Please comment on the evidence provided to support the efficacy of the proposed IV formulation and the extrapolation of efficacy from the oral labetalol dosage form.

The ACM agreed that the IV dosage form of labetalol has a long history of use in overseas jurisdictions. While there is a comparatively small body of evidence for IV labetalol compared to the oral dosage form, its efficacy has been studied and demonstrated for use in both severe hypertension in pregnancy and in other conditions.

[23] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

2. Please comment on the evidence provided to support the safety of the proposed IV formulation and the extrapolation of safety from the oral labetalol dosage form.

The ACM agreed that, similar to the consideration for efficacy, despite the relatively small body of evidence for IV labetalol, it has been in long use in overseas jurisdictions and its safety has been well characterised in studies.

3. What are ACM's views on the extrapolation of the safety profiles for the oral dosage form to the IV dosage form given the limited available information from published studies but extensive worldwide experience with the IV formulations?

The ACM was of the view that extrapolation of safety profiles for the oral dosage form to the IV dosage form was adequate, although they considered that such extrapolation was not strictly necessary, as the efficacy and safety of IV labetalol has been demonstrated in its own right, and the intended use of the IV product is short term emergency use only, compared to the expected longer term use for oral formulations.

4. What are ACM's views on the wording of the proposed indication? Should the indication be limited to hypertension in pregnancy?

The ACM was of the view that the wording of the indication should not be limited to the treatment of hypertension in pregnancy, as it has application in the acute treatment of severe hypertension in other conditions as well.

5. What are ACM's views on the proposed dosage instructions in the PI, in particular the IV infusion dosing instructions and the maximum recommended dosages?

The ACM was of the view that the proposed dosage instructions in the PI were appropriate and that the maximum recommended dosage was well within acceptable safety margins. The ACM agreed that the wording in the PI was appropriately aligned with the US Food and Drug Administration (FDA) and Health Canada approved PIs.

6. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Nil further advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration Labetalol SXP/RMB/TLB (labetalol hydrochloride) 50 mg/10 mL solution for injection, indicated for:

> *The emergency treatment of severe hypertension when prompt and urgent reduction of blood pressure is essential.*

Specific conditions of registration applying to these goods

- The labetalol Australian risk management plan (RMP) (version 1.2, dated 30 April 2019, data lock point 30 April 2019), included with submission PM-2018-01753-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- For all injectable products the PI must be included with the product as a package insert.

Attachments 1, 2 and 3. Product Information

The PIs for Labetalol SXP/RMB/TLB approved with the submission which is described in this AusPAR is at Attachments 1, 2 and 3. For the most recent PIs, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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