# AUSTRALIAN PRODUCT INFORMATION
# LABETALOL SXP (LABETALOL HYDROCHLORIDE)

## 1 NAME OF THE MEDICINE

Labetalol Hydrochloride

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Labetalol hydrochloride solution for injection contains 50 mg of labetalol hydrochloride in 10 mL of solution.

For the full list of excipients, see section 6.1 List of Excipients.
The solution is preservative-free.

## 3 PHARMACEUTICAL FORM

Clear, colourless sterile solution for injection intended for parenteral intravenous administration presented in 10.8 mL clear, type 1 glass ampoules

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

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

### 4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Labetalol hydrochloride solution for injection is intended for 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 labetaloltreatment.
- 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 10-20 minutes after the initial dose. Up to a further 3 x 80 mg slow bolus doses may be given at 10-20 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 2mg (2ml 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 50-200 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°- 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 **Section 4.4 Special warnings and precautions for use**.

Children

Safety and efficacy in children has not been established.

## 4.3 CONTRAINDICATIONS

- Non-selective beta blockers must not be used on patients with a history of asthma or a history of obstructive pulmonary disease.
- Bradycardia (<45-50 bpm).
- Sick sinus syndrome (including sino-atrial block).
- Second or third degree heart block.
- Cardiogenic shock.
- Hypersensitivity to labetalol.
- Symptomatic heart failure.
- Severe peripheral circulatory disturbances.
- Metabolic acidosis.
- Untreated phaeochromocytoma.
- Prinzmetal's angina.
- Where peripheral vasoconstriction suggests low cardiac output, the use of labetalol injection to control hypertensive episodes following acute myocardial infarction is contraindicated.
- Hypotension.
- Right ventricular failure secondary to pulmonary hypertension
- Significant right ventricular hypertrophy

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Effects on Skin and Eyes**

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Gradual discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

**Hepatic Effects**

There have been rare reports of severe hepatocellular injury with labetalol therapy. The hepatic injury is usually reversible and has occurred after both short and long term treatment. Appropriate laboratory testing should be done at the first sign or symptom of liver dysfunction. If there is laboratory evidence of liver injury or the patient is jaundiced, labetalol therapy should be stopped and not re-started.

**Cardiac Effects**

Due to negative inotropic effects, special care should be taken with patients whose cardiac reserve is poor and heart failure should be controlled before starting labetalol therapy.

Patients, particularly those with ischemic heart disease, should not interrupt/discontinue abruptly labetalol therapy. The dosage should gradually be reduced, i.e. over 1-2 weeks, if necessary at the same time initiating replacement therapy, to prevent exacerbation of angina pectoris. In addition, hypertension and arrhythmias may develop.

Beta blockade depresses myocardial contractility and may precipitate cardiac failure in some patients with a history of cardiac failure, chronic myocardial insufficiency or unsuspected cardiomyopathy. In patients with no history of cardiac failure, continuing depression of the myocardium may lead to cardiac failure. If cardiac failure develops, the beta-blocker should be withdrawn

(NOTE: Although congestive heart failure has been considered to be a contraindication to the use of beta-blockers, there is a growing literature on the experimental use of beta-adrenergic blocking drugs in heart failure. As further trials are needed to identify which patients are most likely to respond to which drugs, beta-blockers should not normally be prescribed for heart failure outside of specialist centres.)

**Anaesthetic Agents**

It is not necessary to discontinue labetalol therapy in patients requiring anaesthesia, but the anaesthetist must be informed so consideration may be given to intravenous atropine prior to induction. In addition the anaesthetist must be made aware of the beta-blockade because of the potential for interactions with other drugs, resulting in severe bradyarrhythmias and hypotension, the decreased reflex ability to compensate for blood loss, hypovolaemia and regional sympathetic blockade, and the increased propensity for vagal-induced bradycardia. During anaesthesia 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. Incidents of protracted severe hypotension or difficulty restoring normal cardiac rhythm during anaesthesia have been reported. If beta-blockade is interrupted in preparation for surgery, therapy should be discontinued for at least 24 hours. Anaesthetic agents causing myocardial depression (e.g. cyclopropane, trichloroethylene) should be avoided. Labetalol

may enhance the hypotensive effects of halothane.

Synergistic effects of labetalol and halothane on cardiac output and blood pressure have been reported.

**Peripheral Circulatory Disorders (see also Section 4.3 Contraindications)**
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.

**Bradycardia (see also Section 4.3 Contraindications)**
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.

**Airway Disease (see also Section 4.3 Contraindications)**
Labetalol is contraindicated in patents with asthma or a history of obstructive airways disease as beta-blockade can induce bronchospasm which is refractory to treatment with beta-adrenergic agents

**Heart Block (see also Section 4.3 Contraindications)**
Due to a negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

**Psoriasis**
Patients with a history of psoriasis should take beta-blockers only after careful consideration.

**Anaphylactic Reactions**
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 use to treat allergic reaction.

**Concomitant Therapy with Calcium Antagonists**

The concomitant use of beta-blockers and calcium antagonists with myocardial depressant and sinus node activity, eg verapamil and to a lesser extent diltiazem, may cause hypotension, bradycardia and asystole. Extreme caution is required if these drugs have to be used together.

**Antiarrhythmic Drugs**
Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant beta-blocker therapy with the Class IA agents disopyramide, and less frequently quinidine; Class IB agents, tocainide, mexiletine and lidocaine; Class IC agents, flecainide and propaferone (not available in Australia); the Class III agent, amiodarone; and the Class IV antiarrhythmic agents.

**Use of Catecholamine-Depleting Agents**
Concomitant use of drugs such as reserpine and guanethidine requires careful monitoring since the added effect of a beta-blocker may produce an excessive reduction of the resting sympathetic nervous tone.

**Use in hepatic impairment**
There is evidence that area-under-the-curve of labetalol may be increased by about 25% in patients with hepatic impairment. Patients with hepatic impairment should be closely monitored during treatment.

**Use in renal impairment**

Published studies have shown no significant effects of renal impairment on the pharmacokinetics of labetalol. While dose modification is not generally required in patients with reduced renal function, patients should be carefully monitored, as several cases of severe hyperkalaemia have been reported after administration of labetalol to patients with renal impairment or who have undergone recent kidney transplant.

**Use in the elderly**

The elderly should be treated with caution, starting with a lower dosage but tolerance is usually good.

There is some evidence that elimination of labetalol may be reduced in elderly patients and that they may experience a larger decrease in blood pressure than young patients after receiving the same dose. Elderly patients should be closely monitored during treatment.

**Paediatric use**

Safety and efficacy in children has not been established and there is limited data in the use of labetalol injection in paediatric patients.

**Effects on laboratory tests**

Labetalol fluoresces in alkaline solution at an excitation wavelength of 334 nm and a fluorescence wavelength of 412 nm and may, therefore, interfere with the assays of certain fluorescent substances including catecholamines.

The presence of labetalol metabolites in the urine may result in falsely elevated levels of urinary catecholamines, metanephrine, normetanephrine, and vanillylmandelic acid (VMA) when measured by fluorimetric or photometric methods. In screening patients suspected of having a phaeochromocytoma and being treated with labetalol hydrochloride, a specific method, such as high performance liquid chromatographic assay with solid phase extraction should be employed in determining levels of catecholamines.

Labetalol has been shown to reduce the uptake of radioisotopes of metaiodobenzylguanidine (MIBG), 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 labetalol for several days at least before MIBG scintigraphy, and substituting other beta or alpha-blocking drugs.

Labetalol may produce a false positive result when urine is screened for amphetamines. Care must be taken to corroborate any such result with a more specific method.

## 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

**Concomitant use not recommended:**

- Calcium antagonists such as verapamil and to a lesser extent diltiazem have a negative influence on contractility and atrio-ventricular conduction.
- Digitalis glycosides used in association with beta-blockers may increase atrio-ventricular conduction time.

- 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.
- Monoamine oxidase inhibitors (except MOA-B inhibitors).

**Use with caution:**

- Class I antiarrhythmic agents (e.g. disopyramide, quinidine) and amiodarone may have potentiating effects on atrial conduction time and induce negative inotropiceffect.
- Insulin and oral antidiabetic drugs may intensify the blood sugar lowering effect, especially of non-selective beta-blockers.
- Beta-blockade may prevent the appearance of signs of hypoglycaemia (tachycardia).
- Anaesthetic drugs may cause attenuation of reflex tachycardia and increase the risk of hypotension. Continuation of beta-blockade reduces the risk of arrhythmia during induction and intubation. The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent. Anaesthetic agents causing myocardial depression, such as cyclopropane and trichlorethylene, are best avoided.
- Cimetidine, hydralazine and alcohol may increase the bioavailability of labetalol.
- Several different drugs or drug classes may enhance the hypotensive effects of labetalol: ACE inhibitors; angiotensin-II antagonists; aldesleukin, alprostadil; metoclopramide; anxiolytics; hypnotics; moxisylyte; diuretics; alpha-blockers.
- Several different drugs or drug classes may antagonise the hypotensive effects of labetalol: NSAIDs, corticosteroids; oestrogens; progesterones.

**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 drugs may decrease the hypotensive effect of beta-blockers.
- Sympathicomimetic agents may counteract the effect of beta-adrenergic blockingagents.
- Concomitant use of tricyclic antidepressants, barbiturates, phenothiazines or other antihypertensive agentsmay increase the blood pressure lowering effect of labetalol. Concomitant use of tricyclic antidepressants may increase the incidence oftremor.
- 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 arrhythmia.
- The interaction of labetalol with methyldopa has been examined on blood pressure and heart rate in animals. The results indicate that labetalol, given together with methyldopa or clonidine, should exert an additional hypotensive effect in human beings who are sensitive to both drugs in the combined therapy.

## 4.6 FERTILITY, PREGNANCY ANDLACTATION

### Effects on fertility

No data available.

### Use in pregnancy

Pregnancy Category **C**

Beta-adrenergic blocking agents may cause bradycardia in the foetus and the newborn infant. During the final part of pregnancy and parturition these drugs should therefore only be given after weighing the needs of the mother against the risk to the foetus.

Labetalol is known to cross the placental barrier and has been found to bind to the eyes of foetal animals. Labetalol has been used successfully in the treatment of hypertension arising in the second and third trimester of pregnancy. 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.

Beta-blockers reduce placental perfusion, which may result in intrauterine foetal death, immature and premature deliveries. There is an increased risk of cardiac and pulmonary complications in the neonate in the post-natal period. Perinatal and neonatal distress (bradycardia, hypotension, respiratory depression, hypoglycaemia, hypothermia) has been rarely reported. Sometimes these symptoms developed a day or two after birth. Response to supportive measures (eg intravenous fluids and glucose) is usually prompt but with severe pre-eclampsia, particularly after prolonged intravenous labetalol, recovery may be slower. This may be related to diminished liver metabolism in premature babies. Intra-uterine and neonatal deaths have been reported but other drugs (eg vasodilators, respiratory depressants) and the effects of pre-eclampsia, intrauterine growth retardation and prematurity were implicated. Such clinical experience warns against unduly prolonging high dose labetalol and delaying delivery and against coadministration of hydralazine.

Administration of Labetalol in the first trimester of pregnancy is not recommended. Labetalol does not appear to be teratogenic in rats or rabbits, but it is embryolethal when given in a dose of 50 mg/kg orally.

### Use in lactation

Labetalol is excreted in breast milk. Breast-feeding is therefore not recommended.

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There are no studies on the effect of this medicine on the ability to drive. When driving vehicles or operating machines it should be taken into account that occasionally dizziness or fatigue may occur.

## 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Labetalol Injection is usually well tolerated. Excessive postural hypotension may occur if patients are allowed to assume an upright position within three hours of receiving Labetalol Injection.

Most side-effects are transient and occur during the first few weeks of treatment with labetalol. They include:

**Blood and the lymphatic system disorders:** Rare reports of positive antinuclear antibodies unassociated with disease, hyperkalaemia, particularly in patients who may have impaired renal

excretion of potassium, thrombocytopenia.

**Psychiatric disorders:** Depressed mood and lethargy, hallucinations, psychoses, confusion, sleep disturbances, nightmares.

**Nervous system disorders:** Headache, tiredness, dizziness, tremor has been reported in the treatment of hypertension of pregnancy.

**Eye disorders:** Impaired vision, dry eyes.

**Cardiac disorders:** Bradycardia, tachycardia, palpitations, heart block, heart failure, hypotension.

**Vascular disorders:** Ankle oedema, increase of an existing intermittent claudication, postural hypotension, cold or cyanotic extremities, Raynaud's phenomenon, paraesthesia of the extremities.

**Respiratory, thoracic and mediastinal disorders:** Bronchospasm (in patients with asthma or a history of asthma), nasal congestion, interstitial lung disease.

**Gastrointestinal disorders:** Epigastric pain, nausea, vomiting, diarrhoea.

**Hepato-biliary disorders:** Raised liver function tests, jaundice (both hepatocellular and cholestatic), hepatitis and hepatic necrosis.

**Skin and subcutaneous tissue disorders:** 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:** Cramps, toxic myopathy.

**Renal and urinary disorders:** Acute retention of urine, difficulty in micturition.

**Reproductive system and breast disorders:** Ejaculatory failure.

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

**Reporting Suspected Adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

## 4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

For all overdoses, the mainstay of treatment is supportive and symptomatic care.

Symptoms of overdosage are bradycardia, hypotension, bronchospasm and acute cardiac insufficiency.

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.

Oliguric renal failure has been reported after massive overdosage of labetalol orally. In one case, the

use of dopamine to increase the blood pressure may have aggravated the renal failure.

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

### Mechanism of action

Labetalol lowers the blood pressure primarily by blocking peripheral arteriolar alpha-adrenoceptors thus reducing peripheral resistance and, by concurrent beta-blockade, protects the heart from reflex sympathetic drive that would otherwise occur. 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.

Labetalol antagonises alpha- and beta-adrenoceptors concurrently by competitive inhibition; it has no intrinsic sympathomimetic activity and less pronounced membrane stabilising activity than propranolol. The beta-blockade is non-selective.

The precise relationship between alpha- and beta-blocking effects in contributing to the antihypertensive action is unknown. At therapeutic doses, labetalol is less active at alpha-adrenoceptors than beta-adrenoceptors; the ratio of beta:alpha antagonism is 3:1 after oral and 6.9:1 after intravenous administration. Adequate vasodilatation is achieved with incomplete blockade of the alpha-adrenoceptors in the arterioles.

Reductions in blood pressure and systemic arterial resistance have been found to be linearly related to labetalol plasma concentration, while a quadratic reduction in cardiac output was observed with no reduction in heart rate.

There is evidence from a small trial that, after the same dose, elderly patients exhibited a larger decrease in blood pressure than younger patients.

### Clinical trials

Delgado de Pasquale et al (2014) compared IV labetalol and IV hydralazine for the treatment of severe hypertension of pregnancy in a randomised controlled trial. The study enrolled 261 patients (average age 26 years) with a gestation age of 24 or more weeks and with systolic blood pressure (SBP) > 160 mmHg and/or diastolic blood pressure (DBP) > 110 mmHg.

The hydralazine group received 5 mg as an initial IV bolus in not less than five minutes. After 15 minutes, blood pressure was measured and if SBP persisted above 160 mmHg and/or DBP above 110 mmHg, the procedure was repeated up to a maximum of three hydralazine doses. The labetalol group received 20 mg as the initial IV bolus in not less than 10 minutes. As for the hydralazine group, after 15 minutes the blood pressure was measured and if blood pressure persisted over SBP 160 mmHg or DBP 110 mmHg, a 40 mg dose of labetalol was administered. This could be followed, if necessary, by up to 3 doses of 80 mg labetalol up to a maximum total dose of 300 mg. If the maximum dose was reached without adequate control of blood pressure, a second anti-hypertensive was used.

An average of 1.3 (0.6) doses of labetalol was required to obtain an adequate control of blood pressure and a total of two cases (1.5%) in the labetalol group had persistent hypertension.

A randomised controlled trial by Vigil de Gracia et al (2006) also compared the safety and efficacy of IV labetalol and IV hydralazine in the treatment of severe hypertension of pregnancy in 200 women of at least 24 weeks gestation. Inclusion criteria included a SBP of at least 160 mmHg and/or a DBP of at least 110 mmHg.

Patients in the hydralazine group were treated with an initial 5 mg hydralazine slow IV bolus, which was repeated every 20 minutes until blood pressure dropped below SBP 160 mmHg or DBP 110 mmHg up to a maximum of 5 doses. Patients in the labetalol group were given an initial 20 mg dose, followed 20 minutes later by a 40 mg dose if blood pressure was not adequately controlled. This could be followed, if necessary, by up to 3 doses of 80 mg labetalol up to a maximum total dose of 300 mg.

83% of patients treated with labetalol achieved the target blood pressure with 1 or 2 doses of labetalol and 10% required 3 or 4 doses.

## 5.2 PHARMACOKINETIC PROPERTIES

**Distribution**

After intravenous administration, labetalol is rapidly and extensively distributed into extravascular tissues. About 50% of labetalol in the blood is protein bound. A 100 mg intravenous dose gave an AUC of 675-2470 ng/mL/hr; the area under the curve of an intravenous 0.5 mg/kg dose was reduced by about 17% when administered after a meal but the clinical effect of this is unknown.

**Metabolism**

Labetalol is metabolised mainly through conjugation to inactive glucuronide metabolites, which are excreted both in the urine and via the bile into the faeces.

**Excretion**

Elimination half-lives of 3.5-6.3 hours have been reported.

## 5.3 PRECLINICAL SAFETY DATA

**Genotoxicity**

No data available.

**Carcinogenicity**

No data available.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Hydrochloric Acid
Sodium Hydroxide
Water for Injections

## 6.2 INCOMPATIBILITIES

Labetalol Injection has been shown to be incompatible with sodium bicarbonate injection BP 4.2% w/v.

### 6.3 SHELF LIFE

Store below 25°C.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in the original package. Protect from light.

### 6.5 NATURE AND CONTENTS OF CONTAINER

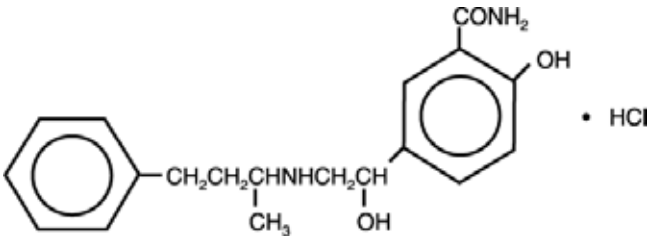
The product is supplied in 10.8 mL Type I amber glass ampoules. Each carton contains 10 ampoules.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

### 6.7 PHYSICOCHEMICAL PROPERTIES

**Chemical structure**




**CAS number**

32780-64-6

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

## 8 SPONSOR

Southern Cross Pharma Pty Ltd
5/118 Church St
Hawthorn Victoria
3122

## 9 DATE OF FIRST APPROVAL

23/8/19

## 10 DATE OF REVISION

TBC

## SUMMARY TABLE OF CHANGES

| Section Changed | Summary of new information |
|---|---|
| **N/A** | First version of this PI |
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| | |