▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

RAPIBLYK® (landiolol hydrochloride)
POWDER FOR INJECTION

1 NAME OF THE MEDICINE

landiolol hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 300 mg landiolol hydrochloride, equivalent to 280 mg landiolol.

After reconstitution (see section 4.2 Dose and Method of Administration), each mL contains 6 mg landiolol hydrochloride.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Powder for injection for intravenous infusion.

Landiolol hydrochloride is a white to almost white powder.

The reconstituted solution is a clear and colourless liquid practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rapiblyk is indicated in adults for:

- supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable.
- non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention.

Rapiblyk is not intended for use in chronic settings.

4.2 DOSE AND METHOD OF ADMINISTRATION

Note 1: Parenteral drug products should be inspected visually prior to administration. Any solutions which contain visible particulate matter or are hazy or discoloured should not be used. Product is for single use in one patient only. Discard any residue.

Note 2**:** The dosing is based on the salt, landiolol hydrochloride, not the free base.

Dosage

Rapiblyk is intended for intravenous use in a monitored setting. Only an appropriately qualified healthcare professional should administer Rapiblyk. The dosage of Rapiblyk should be titrated individually.

The infusion is usually started with an infusion rate of 10 - 40 micrograms/kg/min, which will establish the heart rate lowering effect within 10 - 20 minutes.

If rapid onset of the heart rate lowering effect is desired (within 2 to 4 minutes), an optional loading dose of 100 micrograms/kg/min for 1 minute can be considered, followed by continuous intravenous infusion of 10 - 40 micrograms/kg/min.

Lower starting doses should be used for patients with cardiac dysfunction. Dosing instructions are provided under “Special populations” and in the integrated dosing scheme.

Maximum dose: The maintenance dose may be increased up to 80 micrograms/kg/min for a limited time period (see section 5.2 Pharmacokinetic Properties) if the cardiovascular status of the patient requires and allows such an increase of the dose and the maximum daily dose is not exceeded.

The maximum recommended daily dose of landiolol hydrochloride is 57.6 mg/kg/day (e.g. infusion of 40 micrograms/kg/min for 24 hours). There is limited experience with Rapiblyk infusion durations beyond 24 hours for doses >10 micrograms/kg/min.

Conversion formula for continuous intravenous infusion: micrograms/kg/min to mL/h

(Rapiblyk (landiolol) 300 mg/50 mL = 6 mg/mL):

Target dose (micrograms/kg/min) x body weight (kg)/100 = infusion rate (mL/h)

Table 1. Conversion table (example):

kg body weight	1 µg/kg/min	2 µg/kg/min	5 µg/kg/min	10 µg/kg/min	20 µg/kg/min	30 µg/kg/min	40 µg/kg/min	
40	0.4	0.8	2	4	8	12	16	mL/h
50	0.5	1	2.5	5	10	15	20	mL/h
60	0.6	1.2	3	6	12	18	24	mL/h
70	0.7	1.4	3.5	7	14	21	28	mL/h
80	0.8	1.6	4	8	16	24	32	mL/h
90	0.9	1.8	4.5	9	18	27	36	mL/h
100	1	2	5	10	20	30	40	mL/h

Optional bolus administration for haemodynamically stable patients:

Conversion formula from 100 micrograms/kg/min bolus dose to mL/h

(Rapiblyk (landiolol) 300 mg/50 mL = 6 mg/mL):

Loading dose infusion rate (mL/h) for 1 minute = body weight (kg)

(Example: 70 mL/h loading dose infusion rate for 1 minute for a 70 kg patient)

In case of an adverse reaction (see section 4.8 Adverse Effects), the dose of Rapiblyk should be reduced or the infusion discontinued, and patients should receive appropriate medical management if needed. In the event of hypotension or bradycardia, administration of Rapiblyk

can be restarted at a lower dose after the blood pressure or heart rate has returned to an acceptable level. In patients with a low systolic blood pressure extra caution is needed when adjusting the dosage and during the maintenance infusion.

Transition to an alternative drug: After achieving adequate control of the heart rate and a stable clinical status, transition to alternative medicinal products (such as oral antiarrhythmics) may be accomplished.

When Rapiblyk is replaced by alternative medicinal products, the physician should carefully consider the labelling and dosage of the alternative drug. If switched to an alternative medicinal product the dosage of Rapiblyk can be reduced as follows:

- Within the first hour after the first dose of the alternative medicinal product has been administered, the infusion rate of Rapiblyk can be reduced by one-half (50%).
- After administration of the second dose of the alternative medicinal product, the patient's response should be supervised and if satisfactory control is maintained for at least one hour, the Rapiblyk infusion can be discontinued.

Dose adjustments in:

Elderly population (≥ 65 years): no dose adjustment is necessary.

Renal impairment: no dose adjustment is necessary (see sections 4.4 Special Warnings and Precautions for Use and 5.2 Pharmacokinetic Properties).

Hepatic impairment: data regarding the treatment in patients with hepatic impairment is limited (see section 5.2 Pharmacokinetic Properties). Careful dosing starting with the lowest dose is recommended in patients with all degrees of hepatic impairment.

Cardiac dysfunction: in patients with impaired left ventricular function (LVEF <40%, CI <2.5 L/min/m^2, NYHA 3-4) e.g. after cardiac surgery, during ischemia or in septic states, lower doses starting from 1 microgram/kg/min and increased in a stepwise fashion under close blood pressure monitoring up to 10 micrograms/kg/min have been used to achieve heart rate control. Further dose increases may be considered under close haemodynamic monitoring if required and tolerated by the patient´s cardiovascular status.

Method of Administration

Rapiblyk must be reconstituted before administration and used immediately after opening.

Rapiblyk must not be mixed with other medicinal products except those listed below.

Reconstitute 1 vial with 50 mL of one of the following solutions:

- 0.9% sodium chloride solution
- 5% glucose solution
- Ringer's solution
- Ringer's lactate solution

The white to almost white powder dissolves completely after reconstitution. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually examined for visible particles and discoloration. Only clear and colourless solutions should be used. However, in order

to reduce microbial contamination hazards, infusion should be commenced as soon as practicable after preparation of the admixture. If storage is necessary:

- hold at 2-8°C for not more than 24 hours, or at room temperature (25°C) for not more than 6 hours, when using the diluents 0.9% sodium chloride solution or Ringer's lactate solution, or,
- hold at 2-8°C or at room temperature (25°C) for not more than 24 hours for 5% glucose solution and Ringer's solution only

The resulting solution should be used within the relevant holding period and any residue discarded. Do not freeze.

Rapiblyk should be administered intravenously via a central line or a peripheral line and should not be administered through the same intravenous line as other medicinal products.

Contrary to other beta-blockers, Rapiblyk did not show withdrawal tachycardia in response to abrupt termination after 24 hours continuous infusion. Nevertheless, patients should be closely monitored when administration of Rapiblyk is to be discontinued.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.
- Severe bradycardia (less than 50 beats per minute)
- Sick sinus syndrome without pacemaker
- Severe atrioventricular (AV) nodal conductance disorders (without pacemaker): 2nd or 3rd degree AV block
- Cardiogenic shock
- Severe hypotension
- Decompensated heart failure when considered not related to the arrhythmia
- Pulmonary hypertension
- Non-treated phaeochromocytoma
- Acute asthmatic attack
- Severe, uncorrectable metabolic acidosis

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Rapiblyk must be reconstituted before administration and used immediately after opening.

Monitoring

It is advised to continuously monitor the blood pressure and the ECG in all patients treated with Rapiblyk.

Hypotension

The most frequently observed side effect is hypotension which is rapidly reversible with fluid administration and/or dosage reduction or discontinuation.

Heart failure and haemodynamically compromised patients

The use of Rapiblyk for the control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution in patients with (pre-existing) heart failure or when the patient is compromised haemodynamically or is taking other drugs that decrease any or all of

the following: peripheral resistance, myocardial filling, myocardial contractility, or electrical impulse propagation in the myocardium. The benefits of potential rate control should be balanced against the risk of further depressing myocardial contractility. At the first sign or symptom of further worsening, dose should not be increased and, if considered necessary, Rapiblyk should be discontinued and patients should receive appropriate medical management.

Pre-excitation syndrome

Beta-blockers should be avoided in patients with Pre-excitation syndrome in combination with atrial fibrillation. In these patients, beta-blockade of the atrioventricular node may increase the conduction through the accessory pathway and may precipitate ventricular fibrillation.

First degree heart block

Due to its negative effect on atrioventricular conduction time, beta-blockers should only be given with caution to patients with first degree heart block (see section 4.3 Contraindications).

Prinzmetal's angina

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal's angina (vasospastic angina) due to unopposed alpha-receptor mediated coronary artery vasoconstriction. Non-selective beta-blockers should not be used for these patients and beta-1 selective blockers only with the utmost care.

Peripheral circulatory disorders

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.

Anaphylactic reaction

Beta-blockers may increase both the sensitivity toward allergens and the seriousness of anaphylactic reactions. Patients using beta-blockers may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions (see section 4.5 Interactions with Other Medicines and Other forms of Interactions).

Concomitant administration

Concomitant administration of Rapiblyk with verapamil or diltiazem is not recommended in patients with atrioventricular conduction abnormalities (see Section 4.5 Interactions with Other Medicines and Other forms of Interactions).

Diabetes mellitus and hypoglycaemia

Rapiblyk should be used with caution in diabetic patients or in case of hypoglycaemia. Hypoglycaemia is more severe with less cardio-selective beta-blockers. Beta-blockers can mask the prodromal symptoms of hypoglycaemia such as tachycardia. Dizziness and sweating, however, may not be affected.

Phaeochromocytoma

Rapiblyk should be used with caution and only after pre-treatment with alpha-receptor blockers in patients with phaeochromocytoma (see also Section 4.3 Contraindications).

Bronchospastic disease

Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of the high relative beta-1 selectivity and titratability, Rapiblyk can be used with caution in such patients. Rapiblyk should be carefully titrated to obtain the lowest possible effective dose. In the event of bronchospasm, the infusion should be terminated immediately and a beta-2 agonist should be administered, if necessary. If the patient already uses a beta-2 receptor-stimulating agent, it might be necessary to re-evaluate the dose of this agent.

Use in hepatic impairment

See Section 4.2 Dose and Method of Administration.

Use in renal impairment

The main metabolite of Rapiblyk (M1) is excreted through the kidneys and is likely to accumulate in patients with renal impairment. Although this metabolite has no beta-blocking activity even at doses 200 times higher than the parent drug, Rapiblyk should be used with caution in patients with insufficient renal function.

Use in the elderly

See Section 4.8 Adverse Effects.

Paediatric Use

The safety and efficacy of Rapiblyk in children aged 0 to 18 years have not yet been established.

Effects on Laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Calcium antagonists

Calcium antagonists such as dihydropyridine derivatives (e.g. nifedipine) may increase the risk of hypotension. In patients with cardiac insufficiency, concomitant treatment with beta-blocking agents may lead to cardiac failure. Careful titration of Rapiblyk and appropriate haemodynamic monitoring is recommended.

Antiarrhythmic drugs

Administration of Rapiblyk should be titrated with caution when concomitantly used with verapamil, diltiazem, class I antiarrhythmic agents, or amiodarone or digitalis preparations since co-administration can result in excessive suppression of cardiac function and/or atrioventricular conduction abnormalities.

Rapiblyk should not be used concomitantly with verapamil or diltiazem in patients with atrioventricular conduction abnormalities (see Section 4.4 Special Warnings and Precaution for Use).

Antidiabetic drugs

Concomitant use of Rapiblyk and insulin or oral antidiabetic medicinal products may affect the blood sugar lowering effect. Attention should be given to the blood sugar levels when these

medicinal products are administered concomitantly, as beta-adrenergic blockade may mask signs of hypoglycaemia such as tachycardia.

Medicinal products used during anaesthesia

Continuation of the beta-blocker use during induction of narcosis, intubation and termination of narcosis reduces the risk of arrhythmia.

In case the patient's intravascular volume status is uncertain or antihypertensive medicinal products are concomitantly administered with Rapiblyk, reflex tachycardia may be attenuated, and the risk of hypotension can increase.

The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of Rapiblyk. The dosage of either agent may be adjusted as needed to maintain the desired haemodynamics.

Administration of Rapiblyk should be titrated with caution when concomitantly used with anaesthetics with heart rate lowering effect, esterase substrates (e.g. suxamethonium chloride) or cholinesterase inhibitors (e.g. neostigmine) since co-administration may intensify the heart rate lowering effect or prolong the duration of action of Rapiblyk.

Landiolol is hydrolysed by pseudocholinesterase in human plasma and liver to form metabolite M1. An *in vitro* study using human plasma found that co-administration of suxamethonium could prolong the half-life of landiolol by approximately 3-fold and increase the value of apparent K_m by about 20%. The antagonistic inhibition may also cause a prolongation of the duration of suxamethonium chloride induced neuromuscular blockage.

Nonsteroidal anti-inflammatory drugs (NSAID)

NSAIDs may decrease the hypotensive effects of beta-blockers.

Special caution must be taken when using floctafenine concomitantly with beta-blockers.

Drugs with antihypertensive effects (including antidepressants, antipsychotics etc)

Concomitant administration of Rapiblyk with tricyclic antidepressants, barbiturates, phenothiazines or antihypertensive agents may increase the blood pressure lowering effect. Administration of Rapiblyk should be adjusted carefully to avoid unexpected hypotension. Special caution must be taken when using amisulpride.

The combination of Rapiblyk with ganglion-blocking agents can enhance the hypotensive effect.

Sympathomimetic drugs

The effects of Rapiblyk may be counteracted if concomitantly administered with sympathomimetic medicinal products having beta-adrenergic agonist activity. The dose of either agent may need to be adjusted based on patient response or use of alternate therapeutic agents considered.

Catecholamine-depleting agents

Catecholamine-depleting agents or antisympathotonic agents (e.g. reserpine, clonidine, dexmedetomidine) may have an additive effect when concomitantly administered with Rapiblyk. Patients treated concurrently with these agents should be closely monitored for evidence of hypotension or marked bradycardia.

Concomitant use of clonidine and beta-blockers increase the risk of “rebound” hypertension. Although a rebound hypertensive effect was not observed after Rapiblyk administration for 24 hours, such an effect cannot be excluded if Rapiblyk is used in combination with clonidine.

Heparin

When heparin was administered intravenously during Rapiblyk infusion in patients undergoing cardiovascular surgery, there was a 50% decrease in Rapiblyk plasma levels in conjunction with a heparin induced decrease in blood pressure and an increase in Rapiblyk circulation time. Heart rate values did not change in this situation.

Interactions with other medicinal products

Anaphylactic reactions caused by other medicinal products may be more serious in patients taking beta-blockers. These patients can be resistant to treatment with epinephrine at the normal dose, but intravenous injection of glucagon is effective (see also Section 4.4 Special Warnings and Precaution for Use).

Landiolol is not a substrate for CYP450 enzymes and inhibitors/inducers of these enzymes are unlikely to affect landiolol exposures. Landiolol is not considered to be a substrate for renal transporters (OAT1, OAT3, OCT2, MATE1 and MATE2-K) or hepatic uptake transporters (OATP1B1 and OATP1B3). There is no information regarding landiolol as a substrate of P-gp or BCRP.

In vitro, landiolol and its metabolites M1 and M2 showed no clinically relevant inhibitory effects on the metabolic activity of cytochrome P450 enzymes (CYP 1A2, 2C9, 2C19, 2D6, and 3A4), but their potential to induce CYP enzymes was not investigated. The potential for landiolol and its metabolites to inhibit transporters were not studied.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There were no effects on reproductive performance in male or female rats following dosing with landiolol at doses up to 100 mg/kg/day (IV bolus) for 21 days resulting in exposures estimated to be clinically relevant at the MRHD based on AUC.

Use in pregnancy – Pregnancy Category C

There are no adequate and well controlled studies in pregnant women. Data on the use of Rapiblyk in pregnant women is limited. In a placebo-controlled clinical study in 32 patients scheduled for caesarean delivery, 200 micrograms/kg Rapiblyk administered at time of anaesthesia induction attenuated the haemodynamic response caused by tracheal intubation. No adverse events were reported. No differences were observed in fetal Apgar scores at 1 minute and 5 minutes between Rapiblyk-treated and untreated patients. Because of its high beta-1 selectivity, Rapiblyk did not affect uterine contractions.

In rats, landiolol was not teratogenic at doses up to 50 mg/kg/day (IV) throughout organogenesis (yielding exposures estimated to be clinically relevant at the MRHD based on AUC). At

50 mg/kg/day and higher doses, embryofetal findings included decreased survival and decreased ossification on post natal day 4. The clinical relevance of this may be limited because in clinical practice, landiolol will only be administered in acute settings.

In rabbits, no evidence of harm to the fetus was observed with landiolol in a developmental toxicity study at once daily IV bolus injections up to 100 mg/kg throughout organogenesis. The resulting systemic landiolol exposure was not determined in this study.

Landiolol is expected to cross the placenta, with drug-related radioactivity detected in the placenta and at low levels in the fetus. As a precautionary measure, it is preferable to avoid the use of Rapiblyk during pregnancy. Based on the pharmacological action of beta-blocking agents, in the later period of pregnancy, side effects on the fetus and neonate (especially hypoglycaemia, hypotension and bradycardia) should be taken into account. If the treatment with Rapiblyk is considered necessary, the uteroplacental blood flow and fetal growth should be monitored. The newborn must be closely monitored.

Use in lactation

It is unknown whether landiolol or its metabolites are excreted in human milk. In lactating rats, excretion of landiolol into milk was observed following a dose of 1 mg/kg landiolol IV bolus, with milk excretion corresponding to approximately 70% of the concentration in maternal plasma. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No specific studies have been conducted to assess the direct effect of Rapiblyk on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most frequently observed adverse drug reactions (ADRs) reported for clinical trials (2,329 patients) and for post-marketing treatment outcome studies/use surveys (1,257 patients) for Rapiblyk were hypotension and bradycardia (≥1 to <10 %).

ADRs are tabulated below by system organ class and frequency; very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Table 2. Adverse reaction rates in clinical trials and post-marketing surveys

Infections and infestations	*uncommon*: pneumonia *rare*: mediastinitis
Metabolism and nutrition disorders	*rare*: hyperglycaemia
Nervous system disorders	*uncommon*: cerebral ischemia, headache *rare*: cerebral infarction
Cardiac disorders	*common:* bradycardia *uncommon*: cardiac arrest, tachycardia, atrial fibrillation, ventricular extrasystole *rare*: ventricular tachycardia, low cardiac output syndrome, atrioventricular block, bundle branch block right, cardiac failure, supraventricular extrasystole, sinus arrest, myocardial infarction

Vascular disorders	*common:* hypotension *uncommon*: hypertension *rare*: shock, hot flush, embolic stroke
Respiratory, thoracic and mediastinal disorders	*uncommon*: asthma *rare*: respiratory distress, respiratory disorder, bronchospasm, dyspnoea, hypoxia
Gastrointestinal disorders	*uncommon*: vomiting, nausea *rare*: abdominal discomfort, oral discharge, breath odour
Hepatobiliary disorders	*uncommon*: liver disorder
Skin and subcutaneous tissue disorders	*uncommon*: cold sweat, erythema
Renal and urinary disorders	*uncommon*: renal failure *rare:* oliguria, acute kidney injury
General disorders and administration site conditions	*uncommon*: pyrexia *rare*: chills, chest discomfort, administration site pain, application site pain, injection site reaction, sensation of pressure
Investigations	*common*: blood pressure decreased *uncommon:* alanine aminotransferase (ALT /GPT) increased, aspartate aminotransferase (AST /GOT) increased, gamma-glutamyl transferase increased, blood bilirubin increased, red blood cell count decreased, haemoglobin decreased, haematocrit decreased, platelet count decreased, blood lactate dehydrogenase increased, blood urea abnormal, blood creatinine increased, blood creatine phosphokinase increased, protein total decreased, blood albumin decreased, blood sodium decreased, blood potassium abnormal, blood cholesterol abnormal, blood chloride increased, white blood cell count increased *rare:* ejection fraction decreased, electrocardiogram ST segment depression, electrocardiogram T wave inversion, electrocardiogram QRS complex prolonged, cardiac output decreased, pulmonary arterial pressure increased, partial pressure of oxygen (PO2) decreased, blood chloride decreased, glucose urine present, red blood cell count increased, urea urine increased, blood creatinine decreased, platelet count increased, blood triglycerides abnormal, protein urine present, blood alkaline phosphatase abnormal

Description of selected adverse reactions

Hypotension and bradycardia (see also Section 4.2 Dose and Method of Administration) were the most common adverse events observed in Rapiblyk treated patients. Hypotension was observed in 5.6% of 1,292 patients treated with Rapiblyk in controlled clinical studies (vs. 1.1% treated with placebo, 12.9% with comparator treatment and 0% with no treatment) and in 7.8% of 809 patients in uncontrolled studies. Bradycardia was observed in 2.3% of 1,292 patients treated with Rapiblyk

in controlled clinical studies (vs. 0.1% treated with placebo, 4.8% with comparator treatment and 3.9% with no treatment) and in 0.3% of 809 patients in uncontrolled studies. In post-marketing treatment outcome studies/use surveys with Rapiblyk, the adverse event frequency for hypotension and bradycardia was 0.8% and 0.7%, respectively (of 1,257 patients). All cases of hypotension and bradycardia related to Rapiblyk treatment in the described studies resolved or improved, without any action being taken or within minutes after dose adaptation or discontinuation of Rapiblyk and/or additional treatment.

Serious adverse events based on clinical studies/post-marketing use surveys

Shock due to excessive hypotension was reported in one perioperative clinical trial patient with heavy bleeding (the event resolved 10 minutes after Rapiblyk, prostaglandin and isoflurane discontinuation). Cardiac arrest, complete AV block, sinus arrest, and severe bradycardia reported from clinical trials and post-marketing surveillance for Rapiblyk treatment were mainly associated with elderly patients or with patients having hypertension or cardiac diseases as complications.

Measures to be taken if these specific adverse reactions occur are described in Section 4.2 Dose and Method of Administration.

There are limited safety data for the use of Rapiblyk in the elderly. Uncertainties regarding the safety profile of Rapiblyk need to be considered, as adverse events could also result from the use of co-medications or from the anaesthesia.

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

In case of overdose the following symptoms can occur: Severe hypotension, severe bradycardia, AV block, heart insufficiency, cardiogenic shock, cardiac arrest, bronchospasm, respiratory insufficiency, loss of consciousness to coma, convulsions, nausea, vomiting, hypoglycaemia, hyperkalaemia.

In case of overdose, administration of Rapiblyk should be discontinued immediately.

The time taken for symptoms to disappear following overdosing will depend on the amount of Rapiblyk administered. Although Rapiblyk's heart rate reducing effect decreases rapidly after the end of administration, this may take longer than 30 minutes as seen with discontinuation at therapeutic dose levels.

Artificial respiration may be necessary. Based on the observed clinical effects, the following general measures should be considered:

- *Bradycardia*: atropine or another anticholinergic medicinal product should be given intravenously and then a beta-1-stimulant (dobutamine, etc.). If bradycardia cannot be treated sufficiently, a pacemaker may be necessary.
- *Bronchospasm*: nebulised beta-2-sympathomimetics should be given. If this treatment is not sufficient, intravenous beta-2-sympathomimetics or aminophylline can be considered.

- *Symptomatic hypotension*: fluids and/or pressor agents should be given intravenously.
- *Cardiovascular depression or cardiac shock*: diuretics (in case of lung oedema) or sympathomimetics can be administered. The dose of sympathomimetics (depending on the symptoms e.g. dobutamine, dopamine, noradrenaline, adrenaline, etc.) depends on the therapeutic effect. In case further treatment is necessary, the following agents can be given intravenously: atropine, inotropic agents, calcium ions.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Beta-blocking agents, selective

Mechanism of action

Landiolol is a highly selective beta-1-adrenoreceptor antagonist (the selectivity for beta-1-receptor blockade is 255 times higher than for beta-2-receptor blockade) that inhibits the positive chronotropic effects of the catecholamines adrenaline and noradrenaline on the heart, where beta-1-receptors are predominantly located. Landiolol, as other beta-blockers, is thought to reduce the sympathetic drive, resulting in reduction in heart rate, decrease in spontaneous firing of ectopic pacemakers, slowing the conduction and increase the refractory period of the AV node. In clinical studies, landiolol controlled tachycardia in an ultra-short acting manner with a fast onset and offset of action and further demonstrated anti-ischaemic and cardioprotective effects.

Clinical trials

Based on the data in published clinical studies, 1,192 patients with perioperative or paroxysmal supraventricular tachyarrhythmias (SVT) were treated with landiolol. The efficacy endpoint was determined as heart rate reduction and/or conversion to sinus rhythm for the treatment of sinus tachycardia or SVTs. Control of heart rate was the main efficacy parameter in these studies. A significant reduction in heart rate was observed in landiolol treated patients. From the clinical studies, safety data are available for 2,101 patients including patients treated for the prevention of postoperative atrial fibrillation and for the treatment or prevention of adverse haemodynamic and other responses to specific stimuli related to invasive procedures (see Section 4.8 Adverse Effects). In controlled studies, adverse events were observed in 17% of landiolol treated patients (vs. 14.3 % treated with placebo, 38.8% with active comparator treatment and 13.4% with no treatment). In uncontrolled studies, the adverse event rate in landiolol treated patients was 15%. In a post-marketing treatment outcome/user survey, 1,257 patients with peri/postoperative SVT (including atrial flutter) were treated with landiolol. The adverse event rate was 8.0%.

In three studies on healthy Caucasians, the most common AE was headache (4 cases, 9%), ventricular extrasystoles and hypotension were observed in 3 volunteers each (6.7%), injection site reaction was reported for 2 participants (4.4%), ventricular tachycardia, breath odour, nausea, vomiting, sensation of pressure, application site pain reported in single volunteers (2.2%). In a clinical study in patients with atrial fibrillation or atrial flutter (n=20), 6 AEs were assessed as related to Rapiblyk including 1 event (5%) of acute kidney injury, 3 (15%) events of hypotension, 2 (10%) events of injection site erythema, and 1 event (5%) of injection site pain.

The AE of acute kidney injury was severe, while all other events were mild or moderate in intensity.

5.2 PHARMACOKINETIC PROPERTIES

When administered by continuous intravenous infusion, the concentration of Rapiblyk in blood reached steady-state values about 15 minutes after initiation of administration. Steady-state can also be achieved faster (up to 2 - 5 minutes) with regimens that use a higher loading dose infused for 1 minute followed by continuous infusion at a lower dosage.

Rapiblyk showed a linear pharmakokinetic - pharmacodynamic (concentration-effect) relationship across the range of the recommended dosages.

Absorption

In healthy volunteers, the mean peak plasma concentration of Rapiblyk was 0.294 micrograms/mL following a single Rapiblyk bolus administration of 100 micrograms/kg. The respective steady state plasma levels after 2 hour infusion of 10, 20 and 40 micrograms/kg/min were 0.2, 0.4 and 0.8 micrograms/mL, respectively.

In a study including patients with atrial fibrillation or atrial flutter, one group received doses of 40 micrograms/kg/min for up to 190 minutes without dose escalation, resulting in peak plasma concentrations ranging from 0.52 to 1.77 micrograms/mL. In the study group receiving doses escalated to 80 micrograms/kg/min for 14 to 174 minutes, peak plasma concentrations ranging from 1.51 to 3.33 micrograms/mL were observed.

Distribution

The volume of distribution of Rapiblyk was 0.3 L/kg - 0.4 L/kg following a single bolus administration of 100 – 300 micrograms/kg or in steady state during a Rapiblyk infusion of 20 - 80 micrograms/kg/min.

The *in vitro* protein binding of landiolol is low (<10%) and concentration dependent.

Metabolism

Landiolol is metabolised via hydrolysis of the ester moiety. *In vitro* and *in vivo* data suggest that landiolol is mainly metabolised in the plasma by pseudocholinesterases in humans. Hydrolysis releases a ketal (the alcoholic component) that is further cleaved to yield glycerol and acetone, and the carboxylic acid component (metabolite M1), which subsequently undergoes beta-oxidation to form metabolite M2 (a substituted benzoic acid). The beta-1-adrenoreceptor blocking activity of landiolol metabolites M1 and M2 is 1/200 or less of the parent compound indicating a negligible effect on pharmacodynamics taking into account the maximum recommended landiolol dose and infusion duration.

Excretion

In humans, the main excretion pathway of Rapiblyk is urine. After intravenous administration, about 75% of the administered dose (54.4% as metabolite M1 and 11.5% as metabolite M2) is excreted within 4 hours. The primary excretion/elimination pathway of Rapiblyk is via urine with a urinary excretion rate for Rapiblyk and its major metabolites M1 and M2 of >99% within 24 hours.

The total body clearance of Rapiblyk was 66.1 mL/kg/min after a single Rapiblyk bolus administration of 100 micrograms/kg, and 57 mL/kg/min in steady state after a 20 hour continuous Rapiblyk infusion of 40 microgams/kg/min.

The elimination half-life of Rapiblyk was 3.2 minutes after a single Rapiblyk bolus administration of 100 micrograms/kg, and 4.52 minutes after a 20 hour continuous Rapiblyk infusion of 40 micrograms/kg/min.

Special populations

***Hepatic impairment*:** The impact of liver function on the pharmacokinetics of Rapiblyk was investigated in six patients with mild to moderate hepatic impairment (5 patients Child-Pugh class A, one patient Child-Pugh class B, mean plasma cholinesterase level -62%) and six healthy volunteers. Patients with hepatic impairment show a reduction in the volume of distribution of Rapiblyk and an increase of Rapiblyk plasma levels by 40%. The half-life and elimination of the drug is not different from healthy adults.

***Renal impairment*:** The pharmacokinetics in patients with renal impairment has not been evaluated.

***Caucasian and Asian population*:** No major differences in the pharmacokinetics of Rapiblyk were observed between Caucasian and Japanese population.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Landiolol was not mutagenic *in vitro* in the bacterial reverse mutation (Ames) assay, a chromosomal aberration assay *in vitro* (lymphoma cells) and *in vivo* (mouse and rat bone marrow). Based on the weight of evidence from these studies landiolol is not considered to be genotoxic.

Carcinogenicity

Because of its short term usage, no carcinogenicity studies have been performed with landiolol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Rapiblyk contains mannitol and sodium hydroxide.

6.2 INCOMPATIBILITIES

Rapiblyk must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and Method of Administration, for list of compatible diluents.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG)[1]. The expiry date can be found on the packaging.

[1] AUST R 463165

Rapiblyk contains no antimicrobial agent and should be used only once and any residue discarded.

Refer to Section 4.2 for in-use storage conditions. Do not freeze.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25˚C.

6.5 NATURE AND CONTENTS OF CONTAINER

Rapiblyk is supplied in Type I clear 50 mL glass vials with a grey chlorobutyl rubber stopper and an aluminium flip-off cap. Each carton contains 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

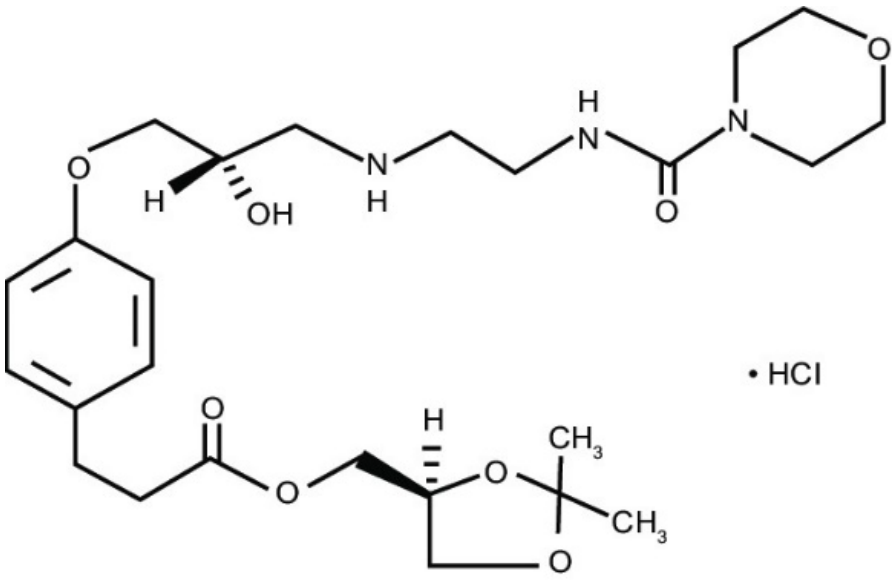
Single use in one patient only. Discard any unused content.

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical structure of landiolol hydrochloride is:



Chemical name (IUPAC): [(4S)-2,2-dimethyl-1,3-dioxolan-4-yl] methyl 3-[4-[(2*S*)-2-hydroxy-3-[2-(morpholine-4-carbonylamino) ethylamino] propoxy]phenyl]propanoate; hydrochloride

Empirical formula: $C_{25}H_{39}N_3O_8.HCl$

Molecular weight: 546.06 g/mol.

CAS number

The CAS number for landiolol hydrochloride is 144481-98-1.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine).

8 SPONSOR

Phebra Pty Ltd,
19 Orion Road,
Lane Cove West,
NSW 2066, Australia.
Ph 1800 720 020

9 DATE OF FIRST APPROVAL

13 June 2025

10 DATE OF REVISION

Not applicable.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	New medicine registration