Date: 29 November 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Rapibloc

International non-proprietary name: landiolol hydrochloride
Pharmaceutical form: powder for solution for infusion
Dosage strength(s): 300 mg
Route(s) of administration: intravenous
Marketing Authorisation Holder: OrPha Swiss GmbH
Marketing Authorisation No.: 68611
Decision and Decision date: approved on 19 October 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

EMA	European Medicines Agency
ERA	Environmental Risk Assessment
INN	International nonproprietary name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance landiolol hydrochloride of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

- 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.

Landiolol is not intended for use in chronic settings.

2.2.2 Approved Indication

- 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.

Landiolol is not intended for use in chronic settings.

2.2.3 Requested Dosage

Summary of the applied standard dosage:
Posology
Landiolol is intended for intravenous use in a monitored setting. Only a well-qualified healthcare professional should administer landiolol. The dosage of landiolol 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 2 - 16 min.
If rapid onset of the heart rate-lowering effect is desired (within 1 to 4 min), an optional loading dose of 100 micrograms/kg/min for 1 min can be considered, followed by continuous intravenous infusion of 10 - 40 micrograms/kg/min.

Maximum dose: The maintenance dose may be increased up to 80 micrograms/kg/min for a limited time period (see "Pharmacokinetics") 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).

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

In case of an adverse reaction (see “Undesirable effects”), the dose of landiolol 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 landiolol can be restarted at a lower dose after the blood pressure or heart rate has returned to an acceptable level. In patients with 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 landiolol is replaced by an alternative medicinal product, the physician should carefully consider the labelling and dosage of the alternative drug. If switched to an oral beta-blocker, the dosage of landiolol can be reduced as follows:

- Ten minutes after administration of the alternative medicinal product, the infusion rate of landiolol can be reduced by one-half (50%).
- The patient’s response should be monitored, and if satisfactory control is maintained for at least 20 minutes, the landiolol infusion can be discontinued.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	20 July 2021
Formal control completed	12 August 2021
List of Questions (LoQ)	8 December 2021
Answers to LoQ	9 March 2022
Predecision	7 June 2022
Answers to Predecision	21 July 2022
Final Decision	19 October 2022
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

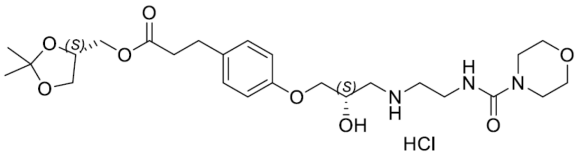
Endogenous catecholamines are released as a physiological response to stress conditions. Stress due to various clinical procedures, among them anaesthesia, intubation and surgery, triggers a substantial catecholamine surge with the associated sympathetic effects, including marked elevations in heart rate and blood pressure. In the perioperative setting in particular, these responses are potentially deleterious, as they can lead to haemodynamic instability and to myocardial ischaemia and can also precipitate cardiovascular events. In the subgroup of patients with pre-existing coronary artery disease, the most important individual predictor of morbidity is perioperative ischaemia. Postoperative ischaemia is associated with a nine-fold increase in the risk of unstable angina, myocardial infarction or cardiovascular death, and thus forms an important target for remediation in the pre- and perioperative setting. In individuals with pre-existing coronary artery disease, beta-blockers reduce perioperative ischaemia by balancing myocardial oxygen supply and demand mismatch. It is crucial to avoid tachycardia without reducing blood pressure and/or inducing bradycardia because both adequate blood pressure and cardiac output are required to maintain coronary perfusion. However, most currently available β1-antagonists show a high likelihood of inducing such unfavourable side effects, which is further complicated by the fact that these effects cannot readily be adapted to the individual situation of the patient due to their pharmacologic properties (oral administration, long duration of action). Such activity may even lead to excess mortality, as reported for perioperative beta-blockade in patients with risk factors for ischaemia undergoing noncardiac surgery.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality Aspects

4.1 Drug Substance

INN:	Landiolol hydrochloride
Chemical name:	(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 3-[4-[(2S)-2-hydroxy-3-[2-(morpholine-4-carbonylamino)ethylamino]propoxy]phenyl]propanoate, hydrochloride
Molecular formula:	$C_{25}H_{39}N_3O_8$*HCl
Molecular mass:	546.06 g/mol
Molecular structure:	



Landiolol hydrochloride is a white crystalline powder. It is very soluble in water.
Landiolol hydrochloride has two stereogenic centres and is synthesised as the single (S,S)-isomer.
The drug substance is manufactured by multiple step chemical synthesis with final isolation by crystallisation.
The drug substance specification includes relevant tests for proper quality control, encompassing e.g. tests relating to identification, optical rotation, assay and related substances.
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

Rapibloc is presented as a sterile lyophilisate (powder) for solution for infusion, filled into a colourless glass vial closed with a rubber stopper and sealed with an aluminium flip-off cap.
Each vial contains 300 mg Landiolol hydrochloride, corresponding to 280 mg Landiolol free base, and mannitol as bulking agent.
The qualitative and quantitative composition of the drug product is adequately described.
The lyophilisate is reconstituted with 50 mL of 0.9% sodium chloride (normal saline) solution, 5% glucose solution, Ringer's solution or lactated Ringer's solution. After reconstitution, the concentration is 6 mg/mL Landiolol hydrochloride.
Suitable pharmaceutical development data have been provided for the drug product composition and manufacturing process.
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data, and including batch manufacturing formula and in-process controls.
Adequate validation data pertaining to the commercial manufacturing process is presented.
The drug product specification covers relevant physicochemical characteristics as well as identification, assay and purity tests. The drug product is tested for sterility and bacterial endotoxins.
The analytical procedures are validated according to the recommendations of international guidelines.
Batch data show consistent quality of the finished product.
The container closure system consists of a colorless glass vial of 50 mL, which is closed with a rubber stopper and sealed with an aluminium flip-off cap.
Appropriate stability data have been generated in the packaging material intended for marketing and following the relevant international guidelines. The data allow for a distinct assignment of the shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical Aspects

Regarding the marketing authorisation application for Rapibloc (landiolol as landiolol hydrochloride), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the Decentralised Procedure Final Assessment report (Procedure No. NL/H/3368/001/DC, dated 29 June 2021 and finalised on 14. April 2021) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Rapibloc in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised and all nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals and in the RMP.

There are no safety concerns regarding impurities and excipients.

According to the ERA, the risk of landiolol to the environment is considered to be low.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Clinical and Clinical Pharmacology Aspects

Swissmedic has not assessed the primary data relating to clinical pharmacology and clinical aspects of this application and relies on the assessment of the reference member state (RMS) in the EU. The current SwissPAR relating to the clinical pharmacology and clinical aspects refers to the publicly available Assessment Report: RMS NL Assessment Report NL/H/3368/001/DC dated 29 June 2016.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the Information for healthcare professionals relating to Rapibloc was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the Information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Rapibloc 300 mg powder for solution for infusion

Composition

Active substances

Landiolol hydrochloride

Excipients

Mannitol, sodium hydroxide (equiv. to max. 4.6 mg sodium).

Pharmaceutical form and active substance quantity per unit

White to almost white powder for solution for infusion for intravenous use.
A vial contains 300 mg landiolol hydrochloride which is equivalent to 280 mg landiolol.
After reconstitution (see “Other information / Instructions for handling”), 1 ml solution for infusion contains 6 mg landiolol hydrochloride.

Indications/Uses

- 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.

Landiolol is not intended for use in chronic settings.

Dosage/Administration

Landiolol is intended for intravenous use in a monitored setting. Only a well-qualified health care professional should administer landiolol. The dosage of landiolol should be titrated individually.
The infusion is usually started with an infusion rate of 10 – 40 mcg/kg/min, which will establish the heartrate lowering effect within 2 – 16 min.

If rapid onset of the heartrate lowering effect is desired (within 1 to 4 min), an optional loading dose of 100 mcg/kg/min for 1 min can be considered, followed by continuous intravenous infusion of 10 – 40 mcg/kg/min.

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

Maximum dose: The maintenance dose may be increased up to 80 mcg/kg/min for a limited time period (see “Pharmacokinetics”), 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., an infusion of 40 mcg/kg/min over 24 hours).

Conversion formula for continuous intravenous infusion: mcg/kg/min to ml/h (Rapibloc 300 mg/50 ml= 6 mg/ml):

Target dose (mcg/kg/min) x body weight (kg)/100 = infusion rate (ml/h)

Conversion table (example):

	Range for cardiac dysfunction patients							
kg body weight	1 mcg/kg/ min	2 mcg/kg/ min	5 mcg/kg/ min	10 mcg/kg/ min	20 mcg/kg/ min	30 mcg/kg/ min	40 mcg/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 mcg/kg/min to ml/h (Rapibloc 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 = 70 ml/h)

Dose adjustment following undesirable effects/interactions

In case of an adverse reaction (see “Undesirable effects”), the dose of landiolol should be reduced or the infusion be discontinued, and patients should receive appropriate medical management if needed. In the event of hypotension or bradycardia, administration of landiolol can be restarted at a lower dose after the blood pressure or heart rate have 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 landiolol is replaced by alternative medicinal products, the physician should carefully consider the product information and dosage of the alternative drug. When switching to an oral beta-blocker, the dosage of landiolol can be reduced as follows:

- 10 minutes after the alternative medicinal product has been administered, the infusion rate of landiolol can be reduced by one half (50%).

The patient's response must be monitored, and if satisfactory control is maintained for a least 20 minutes, the landiolol infusion can be discontinued.

Special dosage instructions

Patients with hepatic impairment

Data regarding treatment in patients with hepatic impairment are limited (see "Pharmacokinetics"). Careful dosing starting with the lowest dose is recommended in patients with all degrees of hepatic impairment.

Patients with renal impairment

No dose adjustment is necessary (see "Warnings and precautions" and "Pharmacokinetics").

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 ischaemia or in septic states, lower doses starting from 1 mcg/kg/min and increased in a stepwise fashion under close blood pressure monitoring up to 10 mcg/kg/min have been used to achieve heart rate control. If required, further dose increased can be considered under strict haemodynamic monitoring if the patient's cardiovascular state tolerates this.

Elderly patients (≥ 65 years)

No dose adjustment is necessary.

Children and adolescents

The safety and efficacy of landiolol in children aged 0 to 18 years have not been demonstrated. The available data can be found in the "Pharmacokinetics" section. Consequently, no dosage recommendation can be derived from the data.

Mode of administration

Rapibloc must be reconstituted before administration (for instructions see "Other information/Instructions for handling") and used immediately after opening (see "Warnings and precautions" and "Other information/Shelf life").
Rapibloc must not be mixed with other medicinal products except those listed under "Other information/Instructions for handling".

Landiolol should be administered intravenously via a central line or a peripheral line and must not be administered through the same intravenous line as other medicinal products (see “Other information/Instructions for handling”).
Unlike other beta-blockers, landiolol did not show withdrawal tachycardia in response to abrupt termination after 24 h continuous infusion. Nevertheless, patients should be closely monitored when administration of landiolol is to be discontinued.

Contraindications

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

Warnings and precautions

Rapibloc must be reconstituted before administration and used immediately after opening (see “Other information/Instructions for handling”).
Landiolol should be used with caution in diabetics 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, are not affected.
The most frequently observed side effect is hypotension, which is rapidly reversible with fluid intake and/or dosage reduction or discontinuation.
It is advised to continuously monitor the blood pressure and the ECG in all patients treated with landiolol.
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.
Due to the negative effect on atrioventricular conduction time, beta-blockers should only be given with caution to patients with first degree heart block (see also “Contraindications”).

Concomitant administration of landiolol with verapamil or diltiazem is not recommended in patients with atrioventricular conduction abnormalities (see “Interactions”).
Beta-blockers may increase the number and the duration of angina pectoris attacks in patients with Prinzmetal’s angina (vasospastic angina pectoris) 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.
Landiolol must be used with caution for the control of ventricular response in patients with supraventricular arrhythmias if (pre-existing) heart failure is present or if 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 signs or symptoms of further worsening, the dose should not be increased and, if considered necessary, landiolol should be discontinued and patients should receive appropriate medical management.
The main metabolite of landiolol (M1) is excreted through the kidneys, which could lead to accumulation in patients with renal impairment. Although this metabolite has no beta-blocking activity even at doses 200 times higher than the parent drug, landiolol should be used with caution in patients with insufficient renal function.
Landiolol should be used with caution and only after pre-treatment with alpha-receptor blockers in patients with phaeochromocytoma (see also “Interactions”).
Patients with bronchospastic disease should, in general, not receive beta-blockers. Because of the high relative beta-1 selectivity and titratability, landiolol can be used with caution in such patients. Landiolol 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.
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.
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 also “Interactions”).
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Interactions

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 landiolol and appropriate haemodynamic monitoring is recommended.
Administration of landiolol should be titrated with caution when concomitantly used with verapamil, diltiazem, class I antiarrhythmic agents or amiodarone, since co-administration can result in excessive suppression of cardiac function and/or atrioventricular conduction abnormalities.
Landiolol should not be used concomitantly with verapamil or diltiazem in patients with atrioventricular conduction abnormalities (see “Warnings and precautions”).
Concomitant use of landiolol 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 landiolol, reflex tachycardia may be reduced and the risk of hypotension can increase.
The hypotensive effects of inhalation anaesthetic agents may be increased in the presence of landiolol. The dosage of either agent may be adjusted as needed to maintain the desired haemodynamics.
Administration of landiolol should be titrated with caution when concomitantly used with anaesthetics with heartrate lowering effect, esterase substrates (e.g., suxamethonium chloride) or cholinesterase inhibitors (e.g., neostigmine), since co-administration may intensify the heartrate lowering effect or prolong the duration of action of landiolol.
An *in vitro* study using human plasma found that co-administration of suxamethonium could increase the maximum blood concentration of landiolol hydrochloride by about 20%. The antagonistic inhibition may also cause a prolongation of the duration of suxamethonium chloride induced neuromuscular blockage.

Interactions with other medicinal products

The combination of landiolol with ganglion blocking agents can enhance the hypotensive effect.
NSAIDs may decrease the hypotensive effects of beta-blockers.
Special caution must be taken when using floctafenine or amisulpride concomitantly with beta-blockers.

Concomitant administration of landiolol with tricyclic antidepressants, barbiturates, phenothiazines or antihypertensive agents may increase the blood pressure lowering effect. Administration of landiolol should be adjusted carefully to avoid unexpected hypotension.
The effects of landiolol 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 or antisympathotonic agents (e.g., reserpine, clonidine, dexmedetomidine) may have an additive effect when concomitantly administered with landiolol. 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 landiolol administration for 24 hours, such an effect cannot be excluded if landiolol is used in combination with clonidine.
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 “Warnings and precautions”).
When heparin was administered intravenously during landiolol infusion in patients undergoing cardiovascular surgery, there was a 50% decrease in landiolol plasma levels in conjunction with a heparin induced decrease in blood pressure and an increase in landiolol circulation time. Heart rate values did not change in this situation.
The interaction potential of the landiolol metabolite M1 with concomitant used medicinal products is not known. The pharmacodynamic effects of the metabolites are considered not clinically relevant (see “Pharmacokinetics”).

Children and adolescents

Interaction studies have only been performed in adults.
It is not known if the extent of the pharmacokinetic or pharmacodynamic drug interactions is similar in the paediatric population compared to that in adults.

Pregnancy, lactation

Pregnancy

There are only limited from the use of Rapibloc in pregnant women available. In a placebo-controlled clinical trial, 32 female patients scheduled for a Caesarian section at the time of anaesthesia initiation received 200 mcg landiolol which reduced the haemodynamic reaction induced by endotracheal intubation. Animal studies did not yield evidence of direct or indirect adverse health effects associated with reproductive toxicity in the therapeutic range (see “Preclinical data”). As a precautionary measure, it is preferable to avoid the use of landiolol during pregnancy.

If the treatment with landiolol is considered necessary, the uteroplacental blood flow and foetal growth should be monitored. The newborn must be closely monitored.

Lactation

It is unknown whether landiolol or its metabolites are excreted in human milk. Available pharmacokinetic data in animals have shown excretion of landiolol in milk (see “Preclinical data”). A risk to the newborn/suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from landiolol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available on the effect of Rapibloc on human fertility. Animal studies revealed no evidence of altered fertility (see “Preclinical data”).

Effects on ability to drive and use machines

Not applicable.

Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADR) reported for clinical trials (1,101 patients) and for postmarketing treatment outcome studies/use surveys (1,257 patients) for landiolol were hypotension and bradycardia (≥1 to <10 %).

List of adverse reactions

The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows:
“very common” (≥1/10)
“common” (≥1/100, <1/10)
“uncommon” (≥1/1,000, <1/100)
“rare” (≥1/10,000, <1/ 1,000)
“very rare” (<1/10,000)
“not known” (frequency cannot be estimated from the available data)

Infections and infestations
Uncommon: Pneumonia.
Rare: Mediastinitis.

Blood and lymphatic system disorders

Uncommon: Thrombocytopenia.

Metabolism and nutrition disorders

Uncommon: Hyponatraemia.

Rare: Hyperglycaemia.

Nervous system disorders

Uncommon: Cerebral ischaemia, headache.

Rare: Cerebral infarction.

Cardiac disorders

Common: Bradycardia.

Uncommon: Cardiac arrest, tachycardia, atrial fibrillation, myocardial infarction.

Rare: Ventricular tachycardia, low cardiac output syndrome, atrioventricular block, bundle branch block right, heart failure, supraventricular extrasystole, ventricular extrasystole, sinus arrest.

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.

Rare: Hyperbilirubinemia.

Skin and subcutaneous tissue disorders

Uncommon: Cold sweat.

Rare: 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.

Not known: Application site pain, injection site reaction, sensation of pressure.

Investigations

Common: Blood pressure decreased.

Uncommon: Electrocardiogram ST segment depression, alanine aminotransferase (ALT/GPT) increased, aspartate aminotransferase (AST/GOT) increased, gamma-glutamyltransferase increased, blood bilirubin increased, white blood cell count decreased, 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 decreased, blood cholesterol abnormal, blood triglycerides abnormal, protein urine present, blood chloride increased, blood alkaline phosphatase abnormal.
Rare: Electrocardiogram T wave inversion, electrocardiogram prolonged QRS complex, cardiac index decreased, pulmonary arterial pressure increased, PO_2 decreased, blood chloride decreased, glucose urine present, red blood cell count increased, urine urea increased, white blood cell count increased, blood creatinine decreased, platelet count increased.

Description of selected adverse reactions

Hypotension and bradycardia (see also “Dosage/Administration”) were the most common adverse events observed in landiolol-treated patients. Hypotension was observed in 5,6% of 1,292 patients treated with landiolol 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 landiolol 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 postmarketing treatment outcome studies/use surveys with landiolol, 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 landiolol treatment in the described studies resolved or improved, without any action being taken or within minutes after discontinuation of landiolol and/or additional treatment.

Serious adverse events based on clinical studies/postmarketing use surveys:

Shock due to excessive hypotension was reported in one perioperative clinical trial patient with heavy bleeding (the event resolved 10 minutes after landiolol, prostaglandin and isoflurane discontinuation). Cardiac arrest, complete AV block, sinus arrest, and severe bradycardia reported from clinical trials and post-marketing surveillance for landiolol 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 under “Dosage/Administration”.
There are only limited safety data on the use of landiolol in the elderly. Uncertainties regarding the safety profile of landiolol need to be considered, as adverse advents could also result from the use of co-medications or from the anaesthesia.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

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 landiolol should be discontinued immediately.

Treatment

The time taken for symptoms to disappear following overdosing will depend on the amount of landiolol administered. Although the heart rate reducing effect of landiolol 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: inhalational 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.

Properties/Effects

ATC code

C07AB14

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. Landiolol does not exhibit any membrane-stabilising activity or intrinsic sympathomimetic activity *in vitro*. In preclinical and 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.

Pharmacodynamics

See “Mechanism of action”.

Clinical efficacy

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 postoperative atrial fibrillation and for the treatment or prevention of adverse haemodynamic and/or other reactions to specific stimuli associated with invasive procedures (see “Undesirable effects”). In controlled studies, adverse reactions were observed in 17% of landiolol-treated patients (vs. 14,3% treated with placebo, 38,8% with active comparator treatment and 13% with no treatment). In uncontrolled studies, the adverse event rate in landiolol-treated patients was 15%. In a postmarketing 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%.

Paediatrics

The European Medicines Agency has deferred the obligation to submit the results of studies with Rapibloc in one or more subsets of the paediatric population in the treatment or prevention of supraventricular arrhythmias. See “Dosage/Administration” for information on use in children and adolescents.

Data on the treatment of supraventricular tachyarrhythmias with landiolol in children is limited and is based on published literature. A continuous infusion at 4 mcg/kg BW/min of landiolol decreased the heart rate and returned normal sinus rhythm in a 3-month old infant with postoperative junctional ectopic tachycardia (JET).

Four patients between the age of 14 days and 2 years who developed perioperative JET were treated with landiolol. In all patients, landiolol administration at a dose ranging from 1.0 to 10.0 mcg/kg BW/min achieved successful rate control. No adverse events such as bradycardia, hypotension, or hypoglycaemia were encountered.
In a retrospective analysis, 12 patients between the age of 4 days and 5 years diagnosed with postoperative tachyarrhythmias were treated with landiolol (the mean maintenance dose was 6,8 ± 0,9 mcg/kg BW/min) for heart rate reduction or conversion to sinus rhythm. Tachyarrhythmias were converted to sinus rhythm in 70,0% of the cases and the average time needed to achieve heart rate reduction was 2,3 ± 0,5 hours. Bradycardia was observed in one patient treated with landiolol at a dose of 10 mcg/kg BW/min.

Pharmacokinetics

When administered by continuous intravenous infusion, the concentration of landiolol 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.

Absorption

In healthy volunteers, the mean peak plasma concentration of landiolol was 0.294 mcg/kg/mL following a single landiolol bolus administration of 100 mcg/kg/kg. The respective steady-state plasma levels after 2 h infusion of 10, 20 and 40 mcg/kg/BW/min were 0,2, 0,4 and 0,8 mcg/kg/mL, respectively.
In a study including patients with atrial fibrillation or atrial flutter, one group received doses of 40 mcg/kg/kg/min for up to 190 minutes without dose escalation, resulting in peak plasma concentrations ranging from 0,52 to 1,77 mcg/kg/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 mcg/kg/mL were observed.
Due to the molecular characteristics of landiolol (low molecular weight of approx. 0,5 kDa and low protein binding capacity), no significant reabsorption by active transport via renal uptake transporters OAT1, OAT3 or OCT2 is anticipated.

Distribution

The volume of distribution of landiolol was 0,3 l/kg – 0,4 l/kg following a single bolus administration of 100 – 300 mcg/kg/kg or in steady state during a landiolol infusion of 20 – 80 mcg/kg/kg/min.
Protein binding of landiolol is low (<10%) and dose 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 and carboxylesterases. 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.
Neither landiolol nor the metabolites M1 and M2 showed inhibitory effects on the metabolic activity of different cytochrome P450 molecular species (CYP1A2, 2C9, 2C19, 2D6 and 3A4) *in vitro*. The cytochrome P450 content was not affected in rats after repeated intravenous administration of landiolol. There are no data on a potential effect of landiolol or its metabolites on CYP P450 induction or time-dependent inhibition available.

Elimination

In humans, the main elimination pathway of landiolol 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 landiolol is via urine with a urinary excretion rate for landiolol and its major metabolites M1 and M2 of >99% within 24 hours.
The total body clearance of landiolol was 66.1 mL/kg/min after a single landiolol bolus administration of 100 mcg/kg, and 57 mL/kg/min at steady state after a 20-hour continuous landiolol infusion of 40 mcg/kg/min.
The elimination half-life of landiolol was 3,20 minutes after a single landiolol bolus administration of 100 micrograms/kg, and 4,52 minutes after a 20-hour continuous landiolol infusion of 40 micrograms/kg/min.

Linearity/non-linearity

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

Kinetics in specific patient groups

Hepatic impairment

The impact of liver function on the pharmacokinetics of landiolol 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 landiolol and an increase of landiolol 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 landiolol were observed between a Caucasian and Japanese population.

Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single repeated dose toxicity and genotoxicity. In preclinical studies, adverse reactions were seen only at exposures considered sufficiently far above maximum human exposure, indicating limited relevance for clinical use. In a 4-week study with continuous infusions (24 hours) in dogs, the drug was well tolerated including at the highest tested dose (1 mg/kg/min., equiv. to 1,440 mg/kg/day).

Carcinogenicity

Carcinogenicity studies have not been performed with landiolol.

Reproductive toxicity

In fertility studies in male and female rats, coupling and fertility were not influenced by treatment with IV doses of up to 100 mg/kg/day.
Landiolol did not demonstrate reproductive or developmental toxicity at clinically relevant infusion rates and exposures. The lowest observed No Observed Adverse Effect Level (NOAEL) was 25 mg/kg/day in an embryofoetal study in rats. This is equivalent to 100 times the maximum clinical infusion rate.
In a pre- and postnatal development study in rats, decreased body weight gain and decreased survival at four days after birth were observed in high-dose F1-generation pups at maternally toxic doses. This effect was observed at 400 times the maximum clinical infusion rate and following long-term administration and is therefore of very little relevance. No adverse effects were observed at a dose of 50 mg/kg/day. This is equivalent to 200 times the maximum clinical infusion rate.

Lactation

Following an IV bolus injection of 1 mg/kg landiolol in lactating rats, excretion of landiolol in the milk was observed at concentrations exceeding maternal plasma concentrations.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under “Instructions for handling”.

Shelf life

Do not use this medicine after the expiry date “EXP” stated on the pack.

Shelf life after opening

Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at 25°C.
For microbiological reasons, the diluted solution should be used immediately, unless the reconstitution has taken place in controlled and validated aseptic conditions.
If the solution is not used immediately, in-use storage times and conditions are the responsibility of the user. Do not freeze.

Special precautions for storage

Do not store above 25°C.
Keep out of the reach of children.

Instructions for handling

Rapibloc may be administered only after reconstitution.
Instructions for use
Reconstitute 1 vial with 50 ml of one of the following solutions:

- NaCl 9 mg/ml (0,9%) solution
- Glucose 50 mg/ml (5%) 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 may be used.

Authorisation number

68611 (Swissmedic)

Packs

The 50 mL vial is made from colourless glass (Type 1) with a bromobutyl or chlorobutyl rubber stopper and an aluminium flip-off seal.
Pack size: 1 vial includes 300 mg (the colour code of the flip-off seal is yellow) powder for solution for infusion. (B)

Marketing authorisation holder

OrPha Swiss GmbH, 8700 Küsnacht, Switzerland

Date of revision of the text

June 2022