

SUMMARY OF PRODUCT CHARACTERISTICS

▼ 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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Rapibloc 300 mg powder for solution for infusion

Rapibloc 600 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A vial contains 300 mg or 600 mg landiolol hydrochloride which is equivalent to 280 mg or 560 mg landiolol.

After reconstitution (see section 6.6), each ml contains 6 mg or 12 mg landiolol hydrochloride.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- 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.

4.2 Posology and method of administration

Posology

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.

Initiate the intravenous infusion by a loading dose of 100 micrograms/kg body weight (BW) for 1 min, followed by continuous intravenous infusion of 10 - 40 micrograms/kg BW/min.

If no rapid onset of the bradycardic effect (within 2 to 4 min) is required, starting the infusion with the maintenance infusion rate of 10 - 40 micrograms/kg BW/min will establish the effect within 10 - 20 min.

Maximum dose: Should the desired therapeutic response not be achieved with this dosing regimen, the maintenance dose may be increased up to 80 micrograms/kg BW/min, if the cardiovascular status of the patient requires and allows such an increase of the dose.

Conversion table for the initial intravenous infusion from micrograms/kg/min to ml/h (Rapibloc 300 mg/50 ml = **6 mg/ml strength**):

kg body weight	100 µg/kg for 1 minute	
40	40	ml/h
50	50	ml/h
60	60	ml/h
70	70	ml/h
80	80	ml/h
90	90	ml/h
100	100	ml/h

Conversion table for continuous intravenous infusion: micrograms /kg/min to ml/h (Rapibloc 300 mg/50 ml = **6 mg/ml strength**):

kg body weight	10 µg/kg/min	20 µg/kg/min	30 µg/kg/min	40 µg/kg/min	80 µg/kg/min	
40	4	8	12	16	32	ml/h
50	5	10	15	20	40	ml/h
60	6	12	18	24	48	ml/h
70	7	14	21	28	56	ml/h
80	8	16	24	32	64	ml/h
90	9	18	27	36	72	ml/h
100	10	20	30	40	80	ml/h

Conversion table for the initial intravenous infusion from micrograms/kg/min to ml/h (Rapibloc 600 mg/50 ml = **12 mg/ml strength**):

kg body weight	100 µg/kg for 1 minute	
40	20	ml/h
50	25	ml/h
60	30	ml/h
70	35	ml/h
80	40	ml/h
90	45	ml/h
100	50	ml/h

Conversion table for continuous intravenous infusion: micrograms /kg/min to ml/h
(Rapibloc 600 mg/50 ml = **12 mg/ml strength**):

kg body weight	10 µg/kg/min	20 µg/kg/min	30 µg/kg/min	40 µg/kg/min	80 µg/kg/min	
40	2	4	6	8	16	ml/h
50	2.5	5	7.5	10	20	ml/h
60	3	6	9	12	24	ml/h
70	3.5	7	10.5	14	28	ml/h
80	4	8	12	16	32	ml/h
90	4.5	9	13.5	18	36	ml/h
100	5	10	15	20	40	ml/h

The maximum recommended daily dose of landiolol is 8,064 mg/subject/day (based on 80 micrograms/kg BW/min for a 70 kg patient and a maximum infusion duration of 24 hours).

There is limited experience with landiolol infusion durations beyond 24 hours.

In case of an adverse reaction (see section 4.8), 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 labelling and dosage of the alternative drug, and the dosage of landiolol 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 landiolol should 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 a least one hour, the landiolol infusion can be discontinued.

Special populations

Elderly population (≥ 65 years)

No dose adjustment is necessary.

Renal impairment

No dose adjustment is necessary (see section 4.4 and 5.2).

Hepatic impairment

Data regarding the treatment in patients with hepatic impairment is limited (see section 5.2). 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 (LEVF <40%, CI <2.5 L/min/m², NYHA 3-4) e.g. after cardiac surgery, during ischemia or in septic states, lower doses starting from 1 microgram/kg BW/min and increased in a stepwise fashion under close blood pressure monitoring up to 10 micrograms/kg BW/min have been used to achieve heart rate control.

Paediatric population

The safety and efficacy of landiolol in children aged 0 to 18 years have not yet been established. Currently available data are described in section 5.2, but no recommendation on posology can be made.

Method of administration

Rapibloc must be reconstituted before administration (for instructions see section 6.6) and used immediately after opening (see sections 4.4 and 6.3).

Rapibloc must not be mixed with other medicinal products except those listed in section 6.6.

Landiolol 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 (see section 6.6).

Contrary to 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- 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 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

Rapibloc must be reconstituted before administration and used immediately after opening (see section 6).

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, may not be affected.

The most frequently observed side effect is hypotension which is rapidly reversible with 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 its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block (see also section 4.3).

Concomitant administration of landiolol with verapamil or diltiazem is not recommended in patients with atrioventricular conduction abnormalities (see section 4.5).

Beta-blockers may increase the number and the duration of anginal attacks in patients with Prinzmetal's 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.

The use of landiolol 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 hemodynamically 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, landiolol should be discontinued and patients should receive appropriate medical management.

The use of landiolol for the control of ventricular response in patients with supraventricular arrhythmias should be undertaken with caution when the patient is compromised hemodynamically 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 main metabolite of landiolol (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, 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 pheochromocytoma (see also section 4.3).

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 section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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 hemodynamic monitoring is recommended.

Administration of landiolol should be titrated with caution when concomitantly used with verapamil, diltiazem, class I antiarrhythmic agents, amiodarone or digitalis preparations 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 section 4.4).

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 attenuated and the risk of hypotension can increase.

The anaesthesiologist should be informed when the patient is receiving a beta-blocking agent in addition to landiolol.

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 hemodynamics.

Administration of landiolol should be titrated with caution when concomitantly used with anaesthetics with bradycardic effect, esterase substrates (e.g. suxamethonium chloride) or cholinesterase inhibitors (e.g. neostigmine) since co-administration may intensify the bradycardic 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 antisymphatonic 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 section 4.4).

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 metabolites M1 and M2 with concomitant used medicinal products is not known. The pharmacodynamic effects of the metabolites are considered not clinically relevant (see section 5.2).

Paediatric population

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Rapibloc in pregnant women available. Animal studies do not indicate clinically relevant effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of landiolol during pregnancy.

Based on the pharmacological action of beta-blocking agents, in the later period of pregnancy, side effects on the foetus and neonate (especially hypoglycaemia, hypotension and bradycardia) should be taken into account.

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

Breastfeeding

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. A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from landiolol therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Landiolol was not shown to alter fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequently observed adverse drug reaction (ADR) reported for clinical trials (1,569 patients) and for postmarketing treatment outcome studies/use surveys (1,257 patients) for landiolol was hypotension and bradycardia (≥ 1 to < 10 %).

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

b. *Tabulated summary of adverse reactions*

Infections and infestations	<i>uncommon</i> : Pneumonia <i>rare</i> : Mediastinitis
Blood and lymphatic system disorders	<i>rare</i> : Thrombocytopenia, platelet disorder
Metabolism and nutrition disorders	<i>uncommon</i> : Hyponatraemia <i>rare</i> : Hyperglycaemia
Nervous system disorders	<i>uncommon</i> : Cerebral ischemia, headache <i>rare</i> : Cerebral infarction, cerebrovascular accident, seizure
Cardiac disorders	<i>common</i> : Bradycardia <i>uncommon</i> : Cardiac arrest, sinus arrest, tachycardia <i>rare</i> : Myocardial infarction, ventricular tachycardia, atrial fibrillation, low cardiac output syndrome, atrioventricular block, bundle branch block right, supraventricular extrasystole, ventricular extrasystole
Vascular disorders	<i>common</i> : Hypotension <i>uncommon</i> : Hypertension <i>rare</i> : Shock, hot flush
Respiratory, thoracic and mediastinal disorders	<i>uncommon</i> : Pulmonary oedema <i>rare</i> : Asthma, respiratory distress, respiratory disorder, bronchospasm, dyspnoea, hypoxia
Gastrointestinal disorders	<i>uncommon</i> : Vomiting, nausea <i>rare</i> : Abdominal discomfort, oral discharge, breath odour
Hepatobiliary disorders	<i>uncommon</i> : Liver disorder <i>rare</i> : Hyperbilirubinemia
Skin and subcutaneous tissue disorders	<i>rare</i> : Erythema, cold sweat
Musculoskeletal and connective tissue disorders	<i>rare</i> : Muscle spasms
Renal and urinary disorders	<i>rare</i> : Renal failure, acute kidney injury, oliguria
General disorders and administration site conditions	<i>rare</i> : Pyrexia, chills, chest discomfort, administration site pain <i>not known</i> : Application site pain, injection site reaction, sensation of pressure
Investigations	<i>common</i> : Blood pressure decreased <i>uncommon</i> : Electrocardiogram ST segment depression, cardiac index abnormal, alanine aminotransferase (ALT /GPT) abnormal, aspartate aminotransferase (AST /GOT) abnormal, blood bilirubin abnormal, white blood cell count abnormal, red blood cell count abnormal, haemoglobin abnormal, haematocrit abnormal, platelet count abnormal, blood lactate dehydrogenase abnormal, blood urea abnormal, blood creatinine increased, blood creatine phosphokinase abnormal, protein total abnormal, blood albumin abnormal, blood sodium abnormal, blood potassium abnormal, blood cholesterol abnormal, blood triglycerides abnormal, protein urine present <i>rare</i> : Blood pressure increased, electrocardiogram T wave inversion,

	<p>electrocardiogram: prolonged QRS complex, heart rate decreased, pulmonary arterial pressure increased, PO2 decreased, neutrophil count abnormal, blood alkaline phosphatase abnormal, leukocyte alkaline phosphatase, free fatty acids abnormal, blood chloride abnormal, glucose urine</p>
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c. Description of selected adverse reactions

Hypotension and bradycardia (see also section 4.2) were the most common adverse events observed in landiolol treated patients. Hypotension was observed in 8.5% of 948 patients treated with landiolol in controlled clinical studies (vs. 2.1% treated with placebo, 8.5% with comparator treatment and 5.7% with no treatment) and in 8.6% of 581 patients in uncontrolled studies. Bradycardia was observed in 2.1% of 948 patients treated with landiolol in controlled clinical studies (vs. 0% treated with placebo, 2.5% with comparator treatment and 2.4% with no treatment) and in 0.5% of 581 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, prostaglandine 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 in section 4.2.

Laboratory parameters: Abnormal changes in laboratory values were reported in the context of adverse events but were also reported separately. In controlled studies abnormal changes in ALT, AST or bilirubin were reported in 5% of landiolol treated patients (n=241) and in 7% of the control group (n=243). The overall frequency of changes in laboratory parameters in these studies was 8.7% in landiolol treated patients and 13.6% in the control group. The changes in laboratory values were resolved or remitted and were not considered clinically relevant.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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 landiolol should be discontinued immediately.

The time taken for symptoms to disappear following overdosing will depend on the amount of landiolol administered. Although landiolol'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*: nebulized 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-blocking agents, selective
ATC code: C07AB14

Mechanism of action / Pharmacodynamic effects

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-stabilizing 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.

Clinical efficacy and safety

Based on the data in published clinical studies, 991 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. For the prevention of perioperative atrial fibrillation and for the treatment or prevention of adverse hemodynamic and other responses to specific stimuli related to invasive procedures, 3,039 patients were treated with landiolol. Control of heart rate and blood pressure were the main efficacy parameter in these studies. A significant reduction in heart rate or prevention of heart rate surges were observed in landiolol treated patients. From the clinical studies, safety data are available for 1,569 subjects (see section 4.8). In controlled studies, adverse events were observed in 12% of landiolol treated patients (vs. 5.8 % treated with placebo, 20.5% with active comparator treatment and 6.1% with no treatment). In uncontrolled studies, the adverse event rate in landiolol treated patients was 16%. 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%.

Paediatric population

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 section 4.2 for information on paediatric use.

Data on the treatment of supraventricular tachyarrhythmias with landiolol in children is limited and is based on published literature. A continuous infusion at 4 micrograms/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 micrograms/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 micrograms/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 micrograms/kg BW/min.

5.2 Pharmacokinetic properties

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 micrograms/ml following a single landiolol bolus administration of 100 micrograms/kg. The respective steady state plasma levels after 2 h infusion of 10, 20 and 40 micrograms/kg/min were 0.2, 0.4 and 0.8 micrograms/ml, respectively.

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 micrograms/kg or in steady state during a landiolol infusion of 20 - 80 micrograms/kg/min. Protein binding of landiolol is low (<10%) and dose dependent.

Biotransformation

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 excretion 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 micrograms/kg, and 57 ml/kg/min in steady state after a 20 hour continuous landiolol infusion of 40 micrograms/kg/min.

The elimination half-life of landiolol was 3.2 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.

Special populations

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 are observed between a Caucasian and Japanese population.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, genotoxicity, toxicity to reproduction and development. In reproductive and development toxicity studies, landiolol did not impair fertility in rats and did not adversely affect embryofetal development up to maternally toxic doses. In a peri- and postnatal development study in rats, decreased body weight gain and decreased survival at 4 days after birth were observed in high-dose F1 pups at maternally toxic doses. This effect is likely not clinically relevant because it occurred after repeated administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol E421
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Chemical and physical in-use stability after reconstitution has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and condition prior to use are the responsibility of the user. Do not freeze.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless glass (Type 1) 50 ml vial with a bromobutyl rubber stopper and an aluminium flip-off seal.

Pack size of 1 vial includes 300 mg (the colour code of the flip-off seal is yellow) or 600 mg (the colour code of the flip-off seal is red) powder for solution for infusion.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Rapibloc must not be administered without 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-lactate solution

Information on the pH and osmolality of the landiolol solutions ready for administration:

Rapibloc 300 mg / 600 mg reconstituted with	pH	Osmolality [Osm/kg]
	Reconstituted solution (free from visible particles)	
NaCl 9 mg/ml (0.9%) solution	6.5/6.5	0.341/0.401
Glucose 50 mg/ml (5%) solution	6.6/6.1	0.358/0.412
Ringer's solution	6.4/6.0	0.342/0.391
Ringer-lactate solution	6.5/6.2	0.313/0.360

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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

{Name and Address }

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT