Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rapibloc 300 mg powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

After reconstitution (see section 6.6), each ml contains 6 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

Landiolol 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.

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 an appropriately 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 –10 - 20 min.

If rapid onset of the heart rate lowering effect is desired (within 2 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.

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), 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 landiolol infusion durations beyond 24 hours for doses >10 µg/kg/min.

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

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

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 hemodynamically stable patients:
Conversion formula from 100 micrograms/kg/min to ml/h (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), 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. If switched to an alternative medicinal product 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 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 landiolol infusion can be discontinued.

Special populations

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

Renal impairment: no dose adjustment is necessary (see sections 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 (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 hemodynamic monitoring if required and tolerated by the patient´s cardiovascular status.

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

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

Landiolol 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 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

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

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

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

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 also section 4.3).

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.

Heart failure and hemodynamically compromised patients
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.

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

Diabetic patients
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.

Renal impairment
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.

Phaeochromocytoma
Landiolol should be used with caution and only after pre-treatment with alpha-receptor blockers in patients with phaeochromocytoma (see also section 4.3).

Bronchospastic disease
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.

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.

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).

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

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 landiolol and appropriate hemodynamic monitoring is recommended.

Antiarrhythmic drugs
Administration of landiolol 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.
Landiolol should not be used concomitantly with verapamil or diltiazem in patients with atrioventricular conduction abnormalities (see section 4.4).

Antidiabetic drugs
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 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 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 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.

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 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. Special caution must be taken when using amisulpride.
The combination of landiolol with ganglion-blocking agents can enhance the hypotensive effect.

Sympathomimetic drugs
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
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.

Heparin
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.

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).
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 section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited data from the use of landiolol in pregnant women available. In a placebo-controlled clinical study in 32 patients scheduled for caesarean delivery 200 micrograms/kg landiolol administered at time of anaesthesia induction attenuated the hemodynamic response caused by tracheal intubation. No adverse events were reported. No differences were observed in foetal Apgar scores at 1 min and 5 min between landiolol-treated and untreated patients. Because of its high beta-1selectivity, landiolol did not affect uterine contractions. 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 (for details see 5.3). 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 reactions (ADR) reported for clinical trials (2,329 patients) and for postmarketing treatment outcome studies/use surveys (1,257 patients) for landiolol were hypotension (blood pressure decreased) 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).

b. Tabulated summary of adverse reactions

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-glutamyltransferase 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, 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

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 5.6% of 1292 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 1292 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 dose adaptation or 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 in section 4.2.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail:medsafety@hpra.ie.

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. 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 efficacy and safety
Based on the data in published clinical studies, 1192 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 2101 patients including patients treated for the prevention of postoperative atrial fibrillation and for the treatment or prevention of adverse hemodynamic and other responses to specific stimuli related to invasive procedures (see section 4.8). 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 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%.
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 landiolol 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.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Landiololin 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 9 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.
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.

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 microgams/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 pharmakokinetic - 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 were observed between Caucasian and Japanese populations.

5.3 Preclinical safety data

Non-clinical data revealed no special risk for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, and genotoxicity.
Landiolol did not demonstrate reproductive or developmental toxicities at clinically relevant infusion rates and exposure levels. The lowest identified NOAEL was 25 mg/kg/min in an embryo-fetal study in rats, which is 100-fold above the maximum clinical infusion rate.

Excretion of landiolol into milk was observed after 1 mg/kg landiolol i.v. bolus administration to lactating rats, whereas the levels in milk exceeded the maternal plasma concentrations.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol E421
Sodium hydroxide E524 (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

2 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 chlorobutyl rubber stopper and an aluminium flip-off seal.

Pack size of 1 vial contains a powder for solution for infusion, including 300 mg landiolol hydrochloride. The vial is contained in an outer cardboard carton.

6.6 Special precautions for disposal and other handling

Landiolol 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

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

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