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 20 mg/2 ml concentraat voor oplossing voor injectie

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the concentrate contains 10 mg landiolol hydrochloride which is equivalent to 9.35 mg landiolol.

Each ampoule of 2 ml concentrate for solution for injection contains 20 mg landiolol hydrochloride which is equivalent to 18.7 mg landiolol.

After dilution (see section 6.6) the concentration of the solution is 2 mg/ml landiolol hydrochloride.

Excipients with known effect:
Rapibloc concentrate contains 672 mg ethanol (96%) per maximum single dose (calculated for a 70 kg patient). See section 4.4.

This medicinal product contains less than 1 mmol sodium (23 mg) and less than 1 mmol potassium (39 mg) per ampoule, i.e. it is essentially ‘sodium- and potassium- free’.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection.

Clear and colourless to yellowish solution free from visible particles.

Rapibloc concentrate has a pH of 6.9 and an osmolality of 8.13 Osm/l.

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 adjusted individually.

Administer an intravenous bolus injection of 0.1 – 0.3 mg/kg body weight (BW). As a starting dose 0.1 - 0.2 mg/kg BW is recommended. The bradycardic effect may last between 5 and 20 min. In case of insufficient efficacy, increase the dose to 0.2 or 0.3 mg/kg BW. Bolus administration may be repeated when necessary up to a maximum daily dose of 100 mg/patient/day. This dose may be subdivided into 5 - 15 doses per day (5 × 20 mg/subject/dose corresponding to 5 × 0.3 mg/kg BW to 15 × 7 mg/subject/dose corresponding to 15 × 0.1 mg/kg BW).

For longer administration use a landiolol infusion prepared from Rapibloc powder for solution for infusion.

In case of an adverse reaction (see section 4.8), additional doses of landiolol should be reduced or avoided and patients should receive appropriate medical management if needed. In patients with a low systolic blood pressure, extra caution is needed when adjusting the dose.

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 are limited (see section 5.2). Careful dosing starting with the lower dose is recommended in patients with all degrees of hepatic impairment.

Rapibloc concentrate contains alcohol (see section 2 and 4.4).

Paediatric population

The safety and efficacy of landiolol in children aged 0 to 18 years have not yet been established. Rapibloc concentrate contains ethanol and is therefore not recommended for the use in the paediatric population (see section 4.4). Another pharmaceutical form (i.e. Rapibloc powder for solution for infusion) may be more appropriate for administration to this population. Currently available data from this formulation are described in section 5.2 but no recommendation on posology can be made.

Method of administration

Rapibloc concentrate ampoules are for single use only. The medicinal product must be diluted before administration (for instructions see section 6.6).

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

Landiolol must be administered intravenously. Subcutaneous or venous perivascular or intra-arterial injection must be avoided. To avoid the risk of local toxicity, intravenous landiolol should be injected
directly into a large central or peripheral vein through a large-gauge needle or intravenous catheter. Landiolol should not be administered through the same intravenous line as other medicinal products (see section 6.6).

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
- Pulmonary hypertension
- Non-treated phaeochromocytoma
- Acute asthmatic attack
- Severe, uncorrectable metabolic acidosis

4.4 Special warnings and precautions for use

Rapibloc concentrate must be diluted before administration (see section 6).

Rapibloc concentrate is hyperosmolar and may cause a risk of thrombophlebitis, the injection site should be monitored. Extravasation should be avoided, and if detected should be treated appropriately. In case of accidental extravascular injection, another injection site should be used.

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 also 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.

In congestive heart failure, beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. At the first sign or symptom of impending cardiac failure, no further landiolol doses should be administered 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 medicinal products 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 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 phaeochromocytoma (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 adjusted to obtain the lowest possible effective dose. In the event of bronchospasm, no further landiolol doses should be administered 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 towards 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).

Rapibloc concentrate contains 672 mg ethanol (96%) per maximum single dose (calculated for a 70 kg patient) equivalent to 17 ml beer or 7 ml wine per dose. This dose may be harmful for those suffering from alcoholism, and has also to be taken into account in pregnant or breast-feeding women and high-risk groups, such as patients with severe liver disease or epilepsy.

**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 adjustment of landiolol and appropriate hemodynamic monitoring is recommended.

Administration of landiolol should be adjusted 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 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 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 concentrate 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 hypoglycemia, 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.

Rapibloc concentrate contains alcohol (see section 2 and 4.4).

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.

Rapibloc concentrate contains alcohol (see section 2 and 4.4).

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 in published literature 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 (≥ 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

<table>
<thead>
<tr>
<th>Infections and infestations</th>
<th>uncommon: Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>rare: Mediastinitis</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>rare: Thrombocytopenia, platelet disorder</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>uncommon: Hyponatraemia</td>
</tr>
<tr>
<td>rare: Hyperglycaemia</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>uncommon: Cerebral ischemia, headache</td>
</tr>
<tr>
<td>Disorder Category</td>
<td>Common Adverse Reactions</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cerebral infarction, cerebrovascular accident, seizure</td>
<td>rare: Cerebral infarction, cerebrovascular accident, seizure</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>common: Bradycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>common: Hypotension</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>uncommon: Pulmonary oedema</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>uncommon: Vomiting, nausea</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>uncommon: Liver disorder</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>rare: Erythema, cold sweat</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>rare: Muscle spasms</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>rare: Pyrexia, chills, chest discomfort, administration site pain</td>
</tr>
<tr>
<td>Investigations</td>
<td>common: Blood pressure decreased</td>
</tr>
</tbody>
</table>

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 active 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 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 advents 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, hyperkalemia.

In case of overdose, no further landiolol doses should be administered.

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 the 30 minutes seen with discontinuation at therapeutic dose levels. 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 tachyarrhythmia (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 use of Rapibloc concentrate is not recommended in the paediatric population (see section 4.2).

Data on the treatment of supraventricular tachyarrhythmias with a different landiolol formulation (i.e. powder for solution for infusion) 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

Absorption
The mean peak plasma concentration of landiolol was 316 ng/ml, 847 ng/ml and 1,269 ng/ml, respectively, following a single bolus administration of 0.1 mg/kg, 0.2 mg/kg or 0.3 mg/kg to healthy volunteers over 15, 30 and 45 seconds. 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 of landiolol. 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.

Neither the parent substance 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, 57.3 ml/kg/min, and 54.1 ml/kg/min after a single bolus administration of 0.1 mg/kg, 0.2 mg/kg or 0.3 mg/kg to healthy volunteers. The elimination half-life of landiolol was 3.20 – 3.63 minutes after a single bolus administration of 0.1 mg/kg, 0.2 mg/kg or 0.3 mg/kg.

Linearity/non-linearity
Landiolol showed a linear dose plasma concentration 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

Hydroxypropylbetadex
Macrogol 300
Ethanol 96%
Sodium chloride
Potassium chloride
Disodium phosphate, anhydrous
Potassium dihydrogen phosphate
Water for injections

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

18 months

Chemical and physical in-use stability after dilution 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

Do not store above 25°C. For storage of the diluted product, see section 6.3.

6.5 Nature and contents of container

Colourless glass (Type 1) 3 ml ampoule.

Pack size of five ampoules per outer carton.

6.6 Special precautions for disposal and other handling

Rapibloc concentrate must not be administered without dilution.

For single use only.
Instructions for use

Prepare a solution of 2 mg/ml by diluting 2 ml of the concentrate with 8 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:

<table>
<thead>
<tr>
<th>Landiolol hydrochloride 20 mg/2 ml concentrate diluted with</th>
<th>pH</th>
<th>Osmolality [Osm/kg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluted solution (free from visible particles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaCl 9 mg/ml (0.9%) solution</td>
<td>6.3</td>
<td>1.896</td>
</tr>
<tr>
<td>Glucose 50 mg/ml (5%) solution</td>
<td>6.4</td>
<td>1.918</td>
</tr>
<tr>
<td>Ringer’s solution</td>
<td>6.3</td>
<td>1.799</td>
</tr>
<tr>
<td>Ringer-lactate solution</td>
<td>6.4</td>
<td>1.802</td>
</tr>
</tbody>
</table>

Diluted 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

Amomed Pharma GmbH
Storchengasse 1
1150 Wenen
Oostenrijk

8. MARKETING AUTHORISATION NUMBER(S)

Rapibloc 20 mg/2 ml concentraat voor oplossing voor injectie    RVG 116684

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 16 augustus 2016

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 7: 9 januari 2017