COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rapibloc 300 mg and 600 mg powder for solution for infusion Rapibloc 20 mg/2 ml concentrate for solution for injection

(landiolol hydrochloride)

NL/H/3368/001-003/DC

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This module reflects the scientific discussion for the approval of Rapibloc 300 mg and 600 mg powder for solution for infusion and Rapibloc 20 mg/2 ml concentrate for solution for injection. The procedure was finalised on 29 June 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
AFl	Atrial Flutter
ALT	Alanine Transaminase
ASMF	Active Substance Master File
AST	Aspartate Transaminase
AUC	Ares Under the Curve
AV	Atrioventricular
BCF	Bio Concentration factor
bpm	beats per minute
CABG	Coronary Artery Bypass Surgery
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CMR	Carcinogenic, Mutagenic, Reprotoxic
Css	Steady State Concentrate
DT50	Degradation Time for 50% of a substance to be degraded under laboratory conditions
EC	Effective Concentration
ECG	Electrocardiography
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ESC	European Society of Cardiology
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAS	Human Serum Albumin
HCL	Hydrochloride
HR	Heart Rate
ICH	International Conference of Harmonisation
ISO	International Organisation for Standardisation
i.v.	Intravenous
Ki value	Inhibitory Constat
Kow	Octanol-Water Partition coefficient
LAN	Landiolol
MAH	Marketing Authorisation Holder
nM	Nanomolair
NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
ONO	Onoact
OPCAB	Off-Pump Coronary Artery Bypass
PBO	Placebo
PBPK	Physiological Based Pharmacokinetic
PBT	Persistent Bioaccumulative Toxic
PD	Pharmacodynamics
Ph.Eur.	European Pharmacopoeia
Pgp	P-glycoprotein
PK	Pharmacokinetics
PL	Package Leaflet
PSVT	Paroxysmal Supraventricular Tachycardia (PSVT)
Rapibloc Conc	Rapibloc 20 mg/2 ml concentrate for solution for injection
Rapibloc Lyo	Rapibloc 300 mg and 600 mg powder for solution for infusion
RCT	Randomised Control Trial
RH	Relative Humidity

RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
ST	Sinus Tachycardia
SVT	Supraventricular Tachyarrhythmias
t½	Half-life
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Rapibloc 300 mg and 600 mg powder for solution for infusion and Rapibloc 20 mg/2 ml concentrate for solution for injection, from Amomed Pharma GmbH.

The product is indicated 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.

Rapibloc is not intended for use in chronic settings.

A comprehensive description of the indications and posology is given in the SmPC.

Landiolol is a highly selective β1-adrenoceptor antagonist (the selectivity for β1-receptor blockade is 255 times higher than for β2-receptor blockade) that inhibits the positive chronotropic effects of the catecholamines adrenaline and noradrenaline on the heart, where β1-receptors are predominantly located. Landiolol, as other beta-blockers, is thought to reduce the sympathetic drive, resulting in reduction in heart rate, decrease in spontaneous firing of ectopic pacemakers, slowing the conduction and increase the refractory period of the AV node. Landiolol does not exhibit any membrane-stabilising activity or intrinsic sympathomimetic activity *in vitro*. In preclinical and clinical studies, landiolol controlled tachycardia in an ultra-short acting manner with a fast onset and offset of action and further demonstrated anti-ischaemic and cardioprotective effects.
The only short-acting selective beta-blocker registered in the Netherlands is esmolol. Landiolol has the same characteristics with regard to fast onset and offset of effect on heart rate, flexible dosing, rapid dose adaptation together with little influence on blood pressure.

This decentralised procedure concerns a full application, *i.e.* a dossier with administrative, quality, preclinical and clinical data. Landiolol hydrochloride is considered a new active substance as no other known isomer, mixture of isomers, complex derivative or salt of landiolol is currently authorised in the European Union. The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

Landiolol hydrochloride has been authorised, as powder for solution for infusion, in Japan since 2002. An extensive clinical program in Japanese subjects has been performed by Ono Pharmaceutical in support of the registration of Onoact 50 for injection in Japan and in the post-licensing phase of the product. The key clinical studies of Onoact have been published and are available in the public domain. The application for Rapibloc is mainly based on these published studies. Three bridging studies were performed to show that the published clinical pharmacology, efficacy and safety data obtained for Onoact can be extrapolated to the two Rapibloc formulations and to justify the translation of the results obtained in the Japanese population to the Caucasian population.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Finland, France, Croatia, Hungary, Iceland, Italy, Lithuania, Latvia, Malta, Norway, Poland, Romania, Sweden, Slovenia and Slovak Republic.

Paediatric development
The Marketing Authorisation Holder (MAH) has submitted a Paediatric Investigational Plan, which was agreed by the Paediatric Committee of the European Medicines Agency. A deferral was granted, which means that the MAH can delay its study onset in the paediatric population to a later stage.

Scientific advice
In a scientific advice meeting with the Medicines Evaluation Board (MEB) of the Netherlands on 1 November 2013, the dossier requirements were discussed. It was agreed that the application based on MAH's own Modules 3, and Module 4 and 5 with selected non-clinical and clinical studies, completed with literature references can be made according to Article 8(3) of Directive 2001/83/EC (mixed dossier), provided that a solid justification is given for the replacement of own studies by literature references.

II. QUALITY ASPECTS

II.1 Introduction

Rapibloc powder for solution for infusion
Rapibloc powder for solution for infusion is a white to almost white powder. A vial contains 300 mg or 600 mg landiolol hydrochloride which is equivalent to 280 mg or 560 mg landiolol. The powder must be reconstituted with 50 ml of NaCl 9 mg/ml (0.9%) solution, glucose 50 mg/ml (5%) solution, Ringer's solution or Ringer-lactate solution. After reconstitution, each ml contains 6 mg or 12 mg landiolol hydrochloride. The powder dissolves completely and should become a clear and colourless solution with a pH between 6.0-6.6 and osmolality between 0.313-0.412 Osm/L.

The powder for solution for infusion is packed in a colourless glass (Type 1) 50 ml vial with a bromobutyl rubber stopper and an aluminium flip-off seal.

The excipients are mannitol (E421) and sodium hydroxide (for pH adjustment).

Rapibloc concentrate for solution for injection
Rapibloc 20 mg/2 ml concentrate for solution for injection is a clear and colourless solution to yellowish solution, free from particles. Each ml of the concentrate contains 10 mg landiolol hydrochloride which is equivalent to 9.35 mg landiolol. An ampoule of 2 ml concentrate for solution for injection contains 20 mg landiolol hydrochloride which is equivalent to 18.7 mg landiolol.

The concentrate must be diluted with 8 ml of NaCl 9 mg/ml (0.9%) solution, glucose 50 mg/ml (5%) solution, Ringer's solution or Ringer-lactate solution. After dilution, the concentration of the solution is 2 mg/ml landiolol hydrochloride. The pH is between 6.3-6.4 and osmolality is between 1.799-1.918 Osm/L. The osmolality is high and might cause damage to the vein used for injection or cause severe irritation when the product is accidentally injected subcutaneously. However, as the product will only be used by health care professionals in a monitored environment, the risk is manageable.

The concentrate for solution for injection is packed in colourless glass (Type 1) 3 ml ampoules. Although ampoules are not preferred, and the used excipients are not ideal for parenteral preparations, these excipients and packaging materials have been used before for this type of dosage form and have been sufficiently justified.

The excipients are: hydroxypropylbetadex, macrogol 300, ethanol 96%, sodium chloride, potassium chloride, anhydrous disodium phosphate, potassium dihydrogen phosphate and water for injections.

II.2 Drug Substance

The active substance is landiolol, as the hydrochloric acid salt, which is considered a new active substance. It is a white to off-white powder, which is very soluble in water and methanol and practically insoluble in ether. Landiolol is a chiral compound having two asymmetric carbon atoms yielding 4 possible isomers, the required isomer is the SS-isomer. Polymorphism has not been studied, and is not reported in the literature, however, as the drug substance will be dissolved for the preparation of the drug product, the provided information is sufficient.

Manufacturing process
The synthesis of landiolol hydrochloride consists of four synthetic steps and a final purification/crystallisation. No class 1 organic solvents or heavy metal catalysts are used during the proposed synthesis. The proposed starting materials are acceptable. Landiolol has been adequately

characterised, and the correct stereochemistry was demonstrated by a single crystal X-ray study. The specifications for the proposed starting materials, solvents, and reagents are acceptable.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the proposed drug substance specification have been provided for three full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at 5°C (48 months), 25°C/60% RH (6 months) and 30°/65% RH (6 months). Storage under long-term and accelerated conditions did not show any clear up- or downward trends, except for an increase of an impurity in one batch under long term conditions (5°C) after 48 months. Based on the data submitted, a retest period could be granted of 54 months when stored under the condition: “Keep in air tight container and protected from light with storage temperature 2°C to 8°C”.

II.3 Medicinal Product

II.3.1 Powder for solution for infusion

Pharmaceutical development
The development of the product had been described, the choice of excipients is justified, and their functions explained. The excipients are widely used for this kind of formulation. The concentration and the pH of the bulk solution were optimised, and the ratio of active substance and mannitol was set according to the ratio of the Japanese product Onoact. The bulk solution is used to prepare two presentations, i.e. 300 mg and 600 mg, which is diluted with 50 ml diluent to concentrations of 6 mg/ml and 12 mg/ml, respectively. The compatibility with the solutions listed in the SmPC, i.e. NaCl 9 mg/ml (0.9%) solution, glucose 50 mg/ml (5%) solution, Ringer’s solution, and Ringer-lactate solution, is sufficiently demonstrated. All parameters remained well within limits. The method of sterilisation by filtration is sufficiently justified and in line with the decision tree for dry powder products. Overall, the pharmaceutical development is acceptable.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and consists of compounding, pre-filtration, sterile filtration, filling, lyophilisation and capping. It is considered a non-standard process. Process validation data on the product have been presented for three full-scale batches of the 600 mg presentation and two full-scale batches of the 300 mg presentation in accordance with the relevant European guidelines. As the bulk solution is identical for both strengths and the provided validation results on the lyophilisation process do not show a large variability, it is accepted that validation data is provided on only two batches of the 300 mg strength.

Control of excipients
The excipients comply with the specifications of the most recent version of the European Pharmacopoeia (Ph.Eur.). These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, degradation products, uniformity of dosage units, water content, reconstitution time, pH and osmolality of the reconstituted solution, particular matter, sterility and endotoxins. The shelf-life limits for assay and related substances are wider than the release specification, to accommodate for degradation during storage. Limits in the specification for related substances have been qualified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on three full-scale batches of the 600 mg presentation and two full-scale batches of the 300 mg presentation, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from three full-scale batches of the 600 mg presentation and two full-scale batches of the 300 mg presentation stored at 25°C/60% RH (24 – 36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. For both presentations an increase in related substances is seen for almost all impurities. However, all impurities remained within specifications. The photostability study showed the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of 36 months for both presentations. Chemical and physical in-use stability after reconstitution has been demonstrated for 24 hours at 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.3.2 Concentrate for solution for injection

Pharmaceutical development
The development of the product had been described, the choice of excipients is justified, and their functions explained. The used excipients are widely used for this kind of formulation. The concentration and the pH of the bulk solution were optimised, and the ratio of active substance and mannitol was set according to the ratio of the Japanese product Onoact. The bulk solution is used to prepare two presentations, i.e. 300 mg and 600 mg, which will be diluted with 50 ml diluent to concentrations of 6 mg/ml and 12 mg/ml, respectively. The proposed manufacturing process, including sterilisation by filtration is acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and consists of compounding, pre-filtration, sterile filtration, filling and closing. It is considered a non-standard process. Process validation data on the product have been presented for three commercial scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the specifications of the most recent version of the European Pharmacopoeia. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, degradation products, pH, particulate matter, extractable volume, osmolality, sterility, and endotoxins. The shelf-life limits for assay and related substances are wider than the release specification, to accommodate for degradation during storage. The proposed specifications are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from three full-scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three full-scale batches stored at 25°C/60% RH (18 months) and one full-scale batch stored at 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Under both conditions out-of-specification values were observed before the end of the study (12 months at 30°C and 3 months at 40°C), this justifies the storage condition “Store below 25°C”. An increase in related substances is seen for all impurities under long term conditions, nonetheless all impurities stay within specifications up to the period tested so far. A photostability study has shown that the drug product is photostable. Based on the provided information the proposed shelf-life of 18 months with the storage condition “Do not store above 25°C” is acceptable. Chemical and physical in-use stability after dilution has been demonstrated for 24 hours at 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Rapibloc has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Primary pharmacodynamics studies
The specificity of landiolol for β1-receptors was shown *in vitro*, with Ki values of landiolol against β1- and β2-receptors reported as 62.1 and 1890 nM, respectively. The Ki values for β1 were reported to be 993.2 or 834.0 nM for left ventricular muscle and papillary muscle, and 12416 nM for β2 in the lung, resulting in a cardio selectivity about twofold higher than that of esmolol or around 80-fold higher than that of propranolol.
The cardio selectivity (β2/β1-AR activity) of landiolol was shown to be approximately eightfold greater than that of esmolol and 375-fold greater than that of propranolol (ratios of 255 vs. 33 vs. 0.68) in an *in vitro* study using guinea-pig right atria and tracheal strips (Iguchi et al., 1992). Tachycardia induced by sympathetic electrical nerve stimulation or administration of the β1-agonist isoproterenol was inhibited by landiolol in a dose-dependent manner in dogs; the effect of landiolol on isoproterenol-induced tachycardia in dogs disappeared rapidly, with a pharmacodynamic half-life of 11 to 18 minutes compared with approximately 60 minutes reported with propranolol. In a similar study evaluating the effects of a 30-minutes i.v. infusion of landiolol or esmolol on isoproterenol-induced tachycardia in anaesthetised dogs, both drugs had a rapid onset of action (peaking at approximately 10 minutes) and offset of action (approximately 20–30 minutes), indicating that they are ultra short-acting beta-blockers. After termination of the landiolol infusion, 50% recovery from blockade occurred in approximately 10 minutes and complete recovery was observed by 30 minutes. Both drugs achieved the same degree of inhibition of the effects of isoproterenol, but with a much lower dosage of landiolol than esmolol (0.01 vs. 0.1 mg/kg/min). These data are supported by other studies on the effects of landiolol and esmolol in anaesthetised dogs (Motomura et al, 1998; Sugiyama et al, 1999).
Adrenaline-induced tachycardia and low cardiac output in dogs were improved by landiolol, probably as a result of a prolongation of the R–R interval, which leads to improved stroke volume. However, when high doses of landiolol were administered to dogs in an overdose scenario, cardiac output was compromised.

Secondary pharmacodynamics studies
The Ki values of landiolol against α1- and α2-receptors *in vitro* were much higher (81.5 and 180.1 μM), indicating minimal effect on these receptors. Also, the Ki values for 5HT1 and 5HT2 were high (>1000 and 113 μM, respectively). The Ki for M1 and M2 Ach receptors was in the order of 40 μM, making landiolol a very specific beta-blocker.
Landiolol did not demonstrate any membrane stabilising activity or intrinsic sympathomimetic activity *in vitro*, effects that have been shown with some other beta-blockers. In a model of ischemia/reperfusion injury in isolated guinea-pig hearts, landiolol appeared to demonstrate anti-ischemic or cardio-protective effects that were generally similar to those of esmolol or propranolol. Non-clinical data suggest that landiolol may have an anaesthetic-sparing effect when administered intra-operatively. Studies in animal models suggest that landiolol has anti-nociceptive properties (Zhao et al., 2007), but this could not be confirmed by others (Kurita et al., 2008).

Safety pharmacology
No *in vitro* pharmacology data (hERG assay) are available for landiolol. In Rapibloc 20 mg/ml concentrate for solution for injection, HPbCD, polyethyleneglycol and ethanol are included as excipients. From literature data it is clear that these compounds in the hERG assay showed activity

only at exposure levels much higher then the anticipated human systemic exposure levels. The results from the *in vivo* safety pharmacology studies suggest that landiolol HCl has properties of a β1-blocker with very weak intrinsic sympathomimetic and membrane stabilising actions. Further, various changes other than those considered to be related to β1-blocking action of this drug were observed in test parameters with ileac and tracheal muscles excised from guinea pigs, atrial blood vessels excised from rabbits, haematological functions and haemolytic activity. The latter effects are all considered to be nonspecific changes that were observed at millimolar concentrations far above the therapeutic dose/exposure level. Studies investigating safety pharmacology parameters after i.v. bolus administration of landiolol HCl cover the pattern of pharmacological targets adequately.

III.2 Pharmacokinetics

Absorption

Single dose pharmacokinetics were investigated after bolus administration and i.v. infusion in rats and dogs. After single dose administration, the decline of landiolol in plasma was biphasic with a terminal elimination half life of total radioactivity of approximately 30 minutes in rats. In dogs, the terminal elimination half life of landiolol was 5-6 minutes. Terminal elimination half life of metabolite M1 in dogs was 160-180 min and of M2 90-150 min. Clearance of total radioactivity was 419-558 ml/hr/kg in rats. Elimination of landiolol was very rapid in dogs with clearance of 69-83 ml/min/kg. Distribution volume of landiolol in dogs was 370 ml/kg. Distribution volume in rats was not provided. AUC increased approximately dose-proportional in rats and dogs. No gender effects were visible in rats. In dogs, only males were investigated. Following repeated dosing in rats for 7 days at 1 mg/kg, AUC was similar to single dose AUC, indicating no accumulation.
An infusion study in dogs was performed in the presence and absence of anaesthesia. During i.v. infusion, plasma levels and AUC of landiolol were higher when anaesthesia was applied, than without anaesthesia, which may have been due to reduced blood flow and hence a reduced hepatic metabolic clearance in the presence of anaesthesia.

Distribution

Protein binding of landiolol was low in all investigated species. *In vitro* protein binding was 2.7 - 5.3% in rat serum, 14.7 – 21.3% in dog serum, 1.5 – 7.0% in human serum and 2.4 – 11.0% in human serum containing 4.3% HSA (human serum albumin). *In vivo* protein binding in rats was slightly higher than *in vitro*, but still low (15.1 – 15.9%). After i.v. bolus administration of 1 mg/kg of the 14C-landiolol HCl to rats, blood to plasma distribution of radiolabelled drug-related material was 0.5-0.6 up to and including 1 hr after administration, indicating no distribution to red blood cells. Distribution to red blood cells was found at later time points (blood to plasma distribution was 1 at 4 hours and 5 at 24 hours after dosing). However, at these time points plasma concentrations were already low and it is not expected to have a significant impact on pharmacokinetics. In a distribution study in rats, the highest concentrations of drug-related radioactivity were found in lungs, liver, kidney, uterus, ovary and urinary bladder. At 24 hours after dosing, levels were below the limit of detection or only slightly above, except after 7 days of daily bolus injections, where still measurable amounts were found in liver and kidney at 24 hours after the last dose. Drug-related radioactivity was distributed to the brain, but at low levels. A significant level was found in the placenta up to 4 hours after dosing, but fatal levels were low.

Metabolism

The metabolism of landiolol was primarily investigated *in vivo* in rats and dogs. The main metabolite M1 is formed by hydrolysis of landiolol which starts immediately after landiolol enters the plasma. M2 is produced by β-oxidation of M1. In rats, at 5 - 30 min after bolus injection M1 comprised 81.8 - 86.9% of total radioactivity in blood while landiolol comprised only 1.6 – 2.1%. 11.5 – 16.1% was reported unknown, but most likely consisted mainly of M2. In dogs, the percentages in blood as fraction of dose for the metabolites were not given. In urine, up to 24 hours after dosing, 2.7% of dose was recovered as landiolol, 38.1% as M1, and 40.5% as M2 and total recovery in urine after 24 hours was 81.3%. This does not add up to 100%, but a small percentage of the dose must have been excreted in the faeces and at 24 hours after dosing most likely not the whole dose was excreted yet. Although the information regarding metabolism was rather concise, it seems clear that there are no other relevant metabolites than M1 and M2. In a 7-day experiment in rats, it was observed that landiolol did not cause enzyme induction in the liver.

Excretion
In rats, after an i.v. bolus injection, approximately 85% of total radioactivity was excreted in urine and 15% in faeces. In dogs, at least 80% (landiolol + M1 + M2) was excreted in the urine. This is similar to humans, where urine also is the main route of excretion. Landiolol and metabolites were excreted into milk of rats.

III.3 Toxicology

Single dose toxicity
Single dose studies were performed in rats (i.v. infusion up to 1000 mg/kg and bolus i.v. injection of Onoact up to 300 mg/kg) and dogs (bolus i.v. injection of Onoact up to 100 mg/kg). No mortality and no significant adverse effects were observed in the single dose rat study with landiolol infusion up to 1000 mg/kg. Based on AUC, the exposure to landiolol in this study was far below the human exposure. Based on C_{max}, the maximum exposure to landiolol compared to humans was somewhat higher but still below the human exposure. For M1, based on C_{max}, the exposure was higher than the human exposure. In the studies with bolus injection, mortality was observed at 150 mg/kg in rats and 100 mg/kg in beagle dogs. Clinical effects observed were hypoactivity, tremor, gait abnormalities and respiration abnormalities. No toxicokinetic data are available for the studies performed with Onoact. From pharmacokinetic data in the rat it is estimated that also in the Onoact studies, the exposure in the rat was far below the human exposure. In addition, the exposure in the dog studies with Onoact can be considered sufficient.

Repeat dose toxicity
Four-week studies were performed in rats and dogs treated with Onoact (bolus administration) up to 100 (rat) and 50 (dog) mg/kg/day. Mortality occurred at 100 mg/kg/day in rats, as a result of acute toxicity. In rats, bradypnea/dyspnoea, tremor, loss of righting reflex and injection site reactions were observed at 100 mg/kg/day. In dogs, vomiting, nausea and diarrhoea were observed at ≥25 mg/kg/day. No target organ toxicity was observed in rats and dogs following four weeks of administration. In rats, the exposure to landiolol and metabolites was far below the human exposure. In dogs, the exposure was much higher and is estimated, based on limited pharmacokinetic data, to have exceeded the human exposure. No target organ toxicity was observed. For beta-blockers it is known that in general they do not induce target organ toxicity. Moreover, dogs were treated up to four weeks which exceeds treatment period with Rapibloc in clinical practice. Overall, the toxicology data can be considered sufficient.

Genotoxicity
Landiolol was not genotoxic in the Ames test, mouse lymphoma assay and *in vivo* micronucleus test in rats and mice. The exposure in the genotoxicity studies was sufficient. No carcinogenicity studies were performed with landiolol. This is acceptable as Rapibloc is intended for short-term use only.

Reproductive toxicity
A complete package of reproductive toxicity studies was performed with Onoact. The studies did not contain toxicokinetic data but based on pharmacokinetic data in the rat it can be concluded that the exposure in the rat studies was below the human exposure. The exposure in the rabbit study is unknown. No effects were observed on fertility in rats, with animals treated up to a lethal dose. Landiolol caused no adverse effects on the embryofoetal development in rats and rabbits. In the embryofoetal development study in rats, the experiment was continued up to the reproduction of the F1 generation and adverse effects were seen on the post-natal development in F1 rats: decreased survival and decreased ossification on post-natal day 4 and an increase in early resorptions following the reproduction of the F1 animals. The clinical relevance of this may be limited, because in clinical practice Rapibloc will only be administered once. In a peri- and postnatal development study in rats, landiolol reduced body weight gain in high-dose F1 pups as well as decreased survival and decreased ossification on post-natal day 4 in high-dose F1 pups. This occurred in the presence of maternal toxicity. No studies were performed in juvenile animals. Rapibloc is currently not indicated for use in children.

Local tolerance
Intravenous injection of landiolol concentrate was slightly less tolerated than Onoact in rabbits; in some animals very, slight erythema was observed and minimal perivascular inflammatory cell

inflammation, at concentrations five times the intended clinical concentrations. After intramuscular or subcutaneous injection of landiolol concentrate, no dermal reactions were observed.
Histopathologically, minimal (s.c.) or minimal to moderate (i.m.) myofibre degeneration was observed, at concentrations two times the intended clinical concentrations. Intra-arterial and perivenous injection of the vehicle of landiolol concentrate induced severe oedema accompanied by signs of acute inflammation, with excipients at five times the intended clinical concentration. Landiolol concentrate at two times the clinical concentration caused mainly mild irritation. Landiolol lyophilisate was in general well tolerated in rabbits after intramuscular, perivenous, intra-arterial or subcutaneous administration.

Other toxicity studies
Impurities were sufficiently qualified regarding general toxicity in two single dose rat studies. M1 was sufficiently qualified because it is a major metabolite in rats and as such sufficiently studied. Impurities were qualified regarding genotoxicity in an Ames test and an *in silico* structure-activity relationship analysis using Derek Nexus and Leadscope. The Ames test was not sufficient for qualification because levels of tested impurities were too low. The *in silico* analyses revealed no relevant alerts for genotoxicity. Two impurities were investigated in two *in silico* studies in accordance with ICH M7, and did not raise a concern with respect to mutagenicity and carcinogenicity.

Landiolol was not haemolytic in rat and human blood.

Rapibloc concentrate contains 2-hydroxypropyl-β-cyclodextrin (HPβCD), polyethylene glycol 300 (PEG-300) and ethanol. No relevant risk is expected of these excipients, since Rapibloc is intended for single use. The dose of maximally 20 mg/kg HPβCD is below the dose which can cause renal toxicity (>50-300 mg/kg/day) according to the draft Q&A document on cyclodextrins in the context of the revision of the guideline on “Excipients in the label and package leaflet of medicinal products for human use” (CPMP/463/00 Rev 1). PEG is a well-known excipient, also in products for intravenous administration. Rapibloc concentrate contains a considerable amount of ethanol. It is not indicated for use in children. For adults a single dose of 3200 mg ethanol will not cause a relevant risk.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The Persistent Bioaccumulative Toxic (PBT) assessment for landiolol resulted in a log K_{ow} of 1.14 and it can be concluded that there is no PBT concern. The MAH has calculated a refined Fpen, taking into account the different indications for which the drug is intended. The data presented by the MAH are underpinned by the submitted literature publications, most of which are published in recent years. Therefore, it can be agreed that the refined $PEC_{surface\ water}$ is below the action limit of 0.01 µg/L, and that further assessment is not deemed necessary.

III.5 Conclusion on the non-clinical aspects

The data summarised by the MAH and supported by the relevant literature clearly describe the ß1 blocking activity of landiolol, and other aspects of the secondary pharmacology and safety pharmacology. It was indicated that the M1 and M2 metabolites have a much lower pharmacological activity, but the data could not be verified. However, the lack of pharmacological activity is clear from the continuous infusion experiment showing a half-life of activity comparable to the first phase elimination half-life. The data summarised regarding the pharmacokinetics, toxicology and ERA are acceptable. Therefore, the overall non-clinical development was considered adequate to support the marketing authorisation for landiolol.

IV. CLINICAL ASPECTS

IV.1 Introduction

A clinical program in Japanese subjects has been performed in support of the registration of Onoact 50 mg for injection in Japan and in the post-licensing phase of the product. The key clinical studies of Onoact have been published and are available in the public domain. Most clinical data are from these literature references. Onoact is a lyophilised powder of 50 mg landiolol with mannitol. Rapibloc

contains also mannitol. Therefore, the pharmaceutical formulations are considered not significantly different. Only the concentration fluid that will be injected may differ.

To bridge the pharmacodynamics information of landiolol (Onoact) in Japanese subjects to the pharmacodynamics properties of landiolol (Rapibloc) in Caucasian subjects, the MAH performed three bridging studies presented in table 1.

Table 1: Summary of the bridging studies

Study	Design and setting	Number of subjects
PK/PD bridging studies		
CSR-CPA-368-10 EudraCT No. 2010-023311-34	A prospective, randomised, double blinded, crossover, two-treatment, two-sequence, short-term pharmacokinetic, pharmacodynamic and tolerability, single centre study to compare AOP200704 (Onoact 50) vs. Esmolol in healthy subjects	16
CSR-CPA-410-12 EudraCT No. 2012-002127-14	A single centre prospective, randomised, double-blind, crossover, three-treatment periods pharmacokinetic, pharmacodynamic, safety and tolerability study to compare bolus administration of AOP LDL202 (Rapibloc Conc), ONO LDL50 (Onoact 50) and Esmolol in healthy volunteers after a pilot phase of AOP LDL202 safety and local tolerability assessment	15
CSR-CPA-422-12 EudraCT No. 2012-004032-36	A single centre prospective, randomised, double-blind, crossover, pharmacokinetic, safety and tolerability study to compare long-term infusion administration of LDLL600 (Rapibloc Lyo) against Esmolol in healthy volunteers	12

An overview of the submitted literature references for Onoact is presented in table 2.

Table 2: Summary of the clinical studies

Study	Design and setting	Number of subjects
PK/PD studies		
Nakashima and Kanamaru, (2000)	Phase I study of ONO-1101, a new ultra short acting β_1-blocking agent in healthy volunteers	42
Murakami et al., (2005)	Pharmacokinetics and pharmacodynamics of landiolol hydrochloride, an ultra-short-acting beta1-selective blocker, in a dose escalation regimen in healthy male volunteers	16
Honda et al., (2008)	Population pharmacokinetics of landiolol hydrochloride in healthy subjects	47
Atarashi et al., (2000)	Pharmacokinetics of landiolol hydrochloride, a new ultra-short-acting beta-blocker, in patients with cardiac arrhythmias	19
Takahata et al., (2005)	Influence of hepatic impairment on the pharmacokinetics and pharmacodynamics of landiolol hydrochloride, an ultra-short-acting β_1-blocker	6
Matsumoto et al., (2012)	Influence of hemodynamic variations on the pharmacokinetics of landiolol in patients undergoing cardiovascular surgery	18
Phase 3 studies		
Ito et al. (2011)	Comparison vs. Amiodarone. Patients with AF after open heart surgery	n.a.
Goto et al. (2007)	Prospective single-centre observational study. Patients with angina pectoris and intraoperative tachyarrhythmia during OPCAB (LVEF ≥50% and <50%)	56
Goto et al. (2010)	Prospective single-centre double-blind observational study. Patients with angina pectoris and intraoperative tachyarrhythmia during OPCAB (LVEF ≥50% and <50%)	30
Sakamoto et al. (2012); JL-KNIGHT study	Multi-centre open-label parallel-group RCT vs. Diltiazem; GCP-compliant. Patients with AF after open heart surgery	71
Tanaka et al. (2008)	Multi-centre double-blind dose-finding RCT vs PBO; GCP-compliant. Patients with SVT/AF after open heart	12

Study	Design and setting	Number of subjects
	surgery (CV risk patients)	
Nakano et al. (2012)	Multi-centre non-controlled RA. Patients with AF after pulmonary resection	25
Nojiri et al. (2011)	Single-centre RA vs. Standard of Care (verapamil + digoxin). Patients with AF after pulmonary resection	30
Seishima et al. (2010)	Case report. Patients with AF after esophagectomy	5
Harasawa et al. (2006)	Prospective single-centre dose-finding parallel-group RCT vs PBO; GCP-compliant. Intraoperative tachycardia in patients undergoing resection of intracranial or maxillofacial tumors under general anaesthesia	32
Kawaguchi et al. (2010a); ILAST study	Multi-centre open-label RCT vs. Diltiazem; GCP-compliant. Preexisting tachycardia in patients undergoing intracranial aneurysm repair	56
Taenaka & Kikawa (2013a)	Prospective multi-centre open-label dose-finding parallel-group study; GCP-compliant. Patients with SVT after various types of surgery	88
Taenaka & Kikawa (2013b)	Multi-centre double-blind parallel-group RCT vs PBO; GCP-compliant. Patients with SVT after various types of surgery (CV risk patients)	151
Uratsuji et al. (1997)	Prospective single-centre open-label non-controlled study; GCP-compliant. Patients with PSVT after various types of surgery	24
Wariishi et al. (2009)	Prospective single-centre open-label non-controlled study. Patients with PSVT after various types of surgery	40
Ito et al. (2006)	Case report. Patient with perioperative SVT after CABG	1
Yoshiya et al. (2000)	Prospective randomised multi-centre double-blind parallel-group dose-finding phase II study; GCP-compliant. Patients with perioperative tachyarrhythmias (PSVT or AF) after various types of surgery, with or without high risk for cardiac ischemia	134
Yoshiya et al. (1997)	Multi-centre double-blind parallel-group phase III RCT vs PBO; GCP-compliant. Patients with perioperative tachyarrhythmias (PSVT or AF) after various types of surgery, with or without high risk for cardiac ischemia	275
Yoshiya et al. (2002)	Multi-centre double-blind parallel-group phase III RCT vs PBO; GCP-compliant. Patients with perioperative tachyarrhythmia (PSVT or AF) after various types of surgery (with high risk for cardiac ischemia)	54
Fujii et al. (2012)	Single-centre double-blind parallel-group RCT vs. PBO. Patients undergoing OPCAB under general anaesthesia (fentanyl/propofol)	70
Fujiwara et al. (2009)	Single-centre RA vs. no Landiolol. Patients undergoing CABG	55
Ito et al. (2012)	Single-centre RA vs. no Landiolol. Patients with LVEF < 40% undergoing CABG under general anaesthesia (fentanyl/sevoflurane/propofol)	32
Maisawa et al. (2012)	Multi-centre RA vs. no Landiolol. Patients undergoing OPCAB	59
Masayuma et al. (2011) – abstract	Single-centre RCT vs. no Landiolol. Patients undergoing CABG	43
Morishima et al. (2009)	Single-centre trial vs. no Landiolol. Patients undergoing aortic dissection repair	75
Nagaoka et al. (2013)	Single-centre single-blind parallel-group RCT vs. diltiazem. Patients undergoing OPCAB	45
Nakanishi et al. (2013)	Single-centre RA vs. no Landiolol. Patients undergoing CABG or heart valve surgery	105
Osada et al. (2012) - abstract	Multi-centre parallel-group RCT vs. no Landiolol. Patients undergoing open heart surgery (CABG, valve surgery, others)	141
Sakaguchi et al. (2012)	Single-centre parallel-group RCT vs. no Landiolol. Patients undergoing heart valve surgery	60
Sato et al. (2011)	Non-randomised single-centre parallel-group study vs. no Landiolol. Patients undergoing open heart surgery (CABG	38

Study	Design and setting	Number of subjects
	or valve surgery) under general anaesthesia (midazolam/fentanyl)	
Sezai et al. (2011); PASCAL trial	Single-centre double-blind parallel-group RCT vs. PBO. Patients undergoing CABG on cardiopulmonary bypass	140
Sezai et al. (2012); BABYLON trial	Single-centre double-blind parallel-group RCT vs. Landiolol + Bisoprolol (LB) vs. no Landiolol. CABG on cardiopulmonary bypass	101
Sugiura et al. (2009)	Single-centre RA vs. no Landiolol. Patients undergoing CABG	74
Tanaka (2010)	Single-centre RA vs. no Landiolol. Patients undergoing OPCAB	80
To et al. (2012) – abstract	Single-centre RA vs. no Landiolol. Patients undergoing OPCAB	62
Uehara et al. (2010)	Comparison vs. Amiodarone. Patients undergoing open heart surgery	30
Wakamatsu et al. (2010)	Single-centre RA vs. no Landiolol. Patients undergoing OPCAB	96
Wakamatsu & Yokoyama (2011) – abstract	Single-centre RA vs. no Landiolol. Patients undergoing OPCAB	140
Okita et al. (2008)	Single-centre RA vs. no Landiolol. Patients undergoing lung resection	301
Sugimoto et al. (2010) – abstract	Single-centre RA vs. no Landiolol. Patients undergoing lung lobectomy	170
Ishigaki et al. (2012a) – abstract	Multi-centre parallel-group RCT vs. PBO. Catheter ablation	49
Ishigaki et al. (2012b) – abstract	Multi-centre parallel-group RCT vs. PBO. Catheter ablation	55
Tanaka et al. (2011) – abstract	Single-centre parallel-group study vs. no Landiolol. Pulmonary vein isolation by RF catheter ablation	80
Atarashi et al. (1997)	Single-centre pharmacokinetics and dose-finding study; GCP-compliant. Patients with tachyarrhythmias	19
Kato et al. (1997a)	Prospective multi-centre open-label parallel-group dose-finding phase II study; GCP-compliant. Patients with PAF/PAFL or PSVT	123
Kato et al. (1997b)	Multi-centre double-blind parallel-group phase III RCT vs PBO; GCP-compliant. Patients with PAF/PAFL	89
Tachikawa et al. (2012)	Single-centre parallel-group RCT vs. LAN+olprinone. Patients undergoing OPCAB	24
Goyagi et al. (2005)	Single-centre parallel-group RCT vs. PBO. Tracheal intubation under general anaesthesia (propofol/succinylcholine)	22
Hasuo et al. (1998)	Multi-centre parallel-group phase III RCT vs. PBO. Isoflurane inhalation and tracheal intubation under general anaesthesia (thiamylal/isoflurane/N2O)	54
Hirata et al. (2010)	Single-centre parallel-group RCT vs. PBO. Tracheal intubation under general anaesthesia (fentanyl/propofol) in elderly patients (65 - 77 years) with CV risk	30
Ishikawa et al. (2012)	Single-centre RCT vs. PBO and Remifentanil. Tracheal intubation under propofol anaesthesia	60
Kaneko et al. (2009)	Single-centre single-blind RCT vs. PBO. Tracheal intubation in patients undergoing elective otorhinolaryngological surgery under general anaesthesia (fentanyl/propofol)	30
Kawaguchi et al. (2008)	Single-centre single-blind RCT vs. PBO and Remifentanil. Tracheal intubation in patients undergoing elective surgery under general anaesthesia (propofol)	60
Kawaguchi et al. (2010b)	Single-centre RCT vs. PBO. Intraoperative stimuli during craniotomy	30
Kawano et al. (2005)	Double-blind parallel-group RCT vs. PBO. Tracheal intubation under general anaesthesia (propofol)	40
Kitamura et al. (1997)	Single-centre open-label dose-finding RCT vs. PBO. Tracheal intubation under general anaesthesia (thiamylal)	53
Miyazaki et al. (2008)	Single-centre double-blind parallel-group RCT vs.	27

Study	Design and setting	Number of subjects
	Propofol and Nicardipine. Tracheal intubation in patients undergoing general elective surgery under general anaesthesia (propofol/fentanyl)	
Nishiyama (2012)	Single-centre placebo-controlled parallel-group study. Patients undergoing hysterectomy under general anaesthesia (sevoflurane/remifentanil)	20
Oda et al. (2005)	Single-centre double-blind RCT vs. PBO and Esmolol. Tracheal intubation during general anaesthesia (sevoflurane)	45
Onaka & Yamamoto (2006)	Single-centre parallel-group placebo-controlled study. Tracheal intubation under general anaesthesia in the presence of buprenorphine and lidocaine	67
Suehiro & Okutani (2012)	Single-centre single-blind parallel-group RCT vs. PBO. Tracheal intubation under general anaesthesia (thiopental) for Cesarean delivery	64
Sugiura et al. (2007)	(A): Single-centre randomised dose-finding parallel-group study; (B): Single-centre double-blind RCT vs. no Landiolol and Fentanyl. Tracheal intubation under general anaesthesia (propofol) in normotensive (A) and hypertensive patients (B)	87
Yamazaki et al. (2005)	Multi-centre double-blind parallel-group RCT vs. PBO. Tracheal intubation during general anaesthesia (propofol)	64
Horiuchi et al. (2010)	Multi-centre open-label RA vs. no Landiolol. Extubation/emergence from anesthesia	998
Kadoi et al. (2010)	Multi-centre open-label placebo-controlled parallel-group study. Extubation/emergence from general anaesthesia (propofol/remifentanil/sevoflurane) in elderly and middle-aged patients (normotensive and hypertensive) undergoing orthopaedic or gynaecological surgery	119
Kadoi et al. (2011)	Single-centre open-label parallel-group RCT vs. PBO. Extubation/emergence from general anaesthesia (propofol/remifentanil/sevoflurane) in elderly patients (normotensive, controlled hypertensive and uncontrolled hypertensive) undergoing orthopaedic or gynaecological surgery	66
Minamizono et al. (2006)	Single-centre parallel-group RCT vs. PBO. Extubation/emergence from general anaesthesia (fentanyl/sevoflurane/N2O)	32
Miyazaki et al. (2009)	Single-centre double-blind parallel-group RCT vs. PBO. Extubation/emergence from general anaesthesia (propofol/remifentanil/sevoflurane) in elderly patients (>70 years, normotensive or hypertensive) undergoing orthopaedic or gynaecological surgery	63
Nonaka et al. (2006)	Single-centre placebo-controlled study. Neostigmine-atropine administration during emergence/extubation from general anaesthesia (propofol/isoflurane/N2O)	24
Ohata et al. (2004)	Single-centre parallel-group RCT vs. PBO. Neostigmine-atropine administration during emergence/extubation from general anaesthesia	46
Shirasaka et al. (2008)	Prospective randomised single-centre single-blind dose-finding study. Neostigmine-atropine administration during emergence/extubation from general anaesthesia in patients undergoing tympanoplasty	59
Hirota et al. (2005)	Multi-centre parallel-group RCT vs. PBO. Epinephrine infiltration in patients undergoing vaginal total hysterectomy under general anaesthesia (propofol/fentanyl/ketamine)	36
Tanabe et al. (2009)	Single-centre double-blind parallel-group RCT vs. PBO. General anaesthesia (sevoflurane/N2O/fentanyl) in patients undergoing hip arthroplasty	25
Ide et al. (2010)	Multi-centre double-blind RCT vs. PBO. ECT	14
Matsura et al. (2010)	Single-centre open-label crossover RCT vs. PBO. ECT	15
Nomoto et al. (2006)	Single-centre double-blind crossover RCT vs. PBO. ECT	11
Saito et al. (2005)	(A): Randomised double-blind crossover dose-finding	39

Study	Design and setting	Number of subjects
	study; (B): Double-blind crossover RCT vs. PBO and Esmolol. ECT	
Sakamoto et al. (2004)	Single-centre double-blind crossover RCT vs. PBO. Outpatient maintenance ECT	10
Wajima et al. (2010)	Multi-centre double-blind crossover RCT vs. PBO. ECT	32
Hanada et al. (2012)	Single-centre open-label parallel-group RCT vs. PBO. Patients undergoing PCI due to acute myocardial infarction	96
Higuchi (2010) – abstract	Single-centre placebo-controlled study. Patients undergoing PCI due to acute myocardial infarction	26
Hoshi et al. (2012)	Single-centre uncontrolled pilot study. Patients undergoing PCI due to acute coronary syndrome	22
Morita et al. (2009) – abstract	Single-centre double-blind parallel-group RCT vs. PBO. Patients with stable angina undergoing PCI	26
Park et al. (2013)	Single-centre parallel-group RCT vs. PBO. Patients undergoing scheduled PCI	70

Not all of these published papers contain an explicit statement confirming the Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) compliance of the studies. However, The GLP and GCP-statements have been verified by the Japanese medicine board during the marketing authorisation procedure of Onoact. The additional bridging studies have adequate GLP and GCP-statements.

IV.2 Pharmacokinetics

For elucidation of the pharmacokinetics of landiolol, the MAH submitted five published studies (table 2: PK/PD studies). In addition, three non-published studies were submitted (table 3). In two of the non-published studies the Rapibloc formulations were administered, however not in the dosing regimes as proposed in the SmPC.

Table 3: Studies conducted by the MAH

Study	Objective	Population	Formulations administered	Landiolol dosing regime
CPA368-10	Compare pharmacokinetics pharmacodynamics and tolerability of Onoact 50 vs. esmolol	16 healthy Caucasian subjects	• Onoact 50 Lyophilised powder 50 mg • Brevibloc 10 mg/ml solution for infusion	60 min of landiolol at 10 µg/kg BW/min.
CPA410-12	Compare pharmacokinetic, pharmacodynamic, safety and tolerability Rapibloc Concentrate, Onoact 50 and Esmolol	12 healthy Caucasian subjects	• AOPLDLA202 (Rapibloc Conc. 20 mg/ 2 mL • Onoact 50 Lyophilised powder 50 mg • Brevibloc 10mg/mL solution for infusion	Bolus 0.1 mg/kg in an infusion rate of 15 sec Bolus 0.2 mg/kg in an infusion rate of 30 sec Bolus 0.3 mg/kg in an infusion rate of 45 sec
CPA422-12	Compare pharmacokinetic, safety and tolerability of long-term infusion of Rapibloc Lyo and Esmolol	14 healthy Caucasian subjects	• Rapibloc Lyo Lyophilised powder, 600mg/ 50 mL • Brevibloc 10mg/mL solution for infusion 250 mL infusion bag	10 µg/kg/min for 2 h followed by 20 µg/kg/min for 2 h and 40 µg/kg/min for 20 h

Methods

The MAH has provided validation reports on the analytical methods and has compared the different methods used in the different studies. A Physiologically Based Pharmacokinetic (PBPK) model was submitted to predict the pharmacokinetic variables of landiolol to some extent. The results of the simulations seem to be reliable, however, only marginal information on the precision and validation

was submitted. Overall, the statistical methods used throughout the publications and conducted trials are considered acceptable.

Exposure

Study CPA410-12 showed that after bolus administration of Rapibloc 20 mg/ml concentrate for solution for injection (which will be referred to as Rapibloc Conc from here) and Onoact 50 a comparable exposure to landiolol was achieved. The C_{max} and AUC values after 0.1 mg/kg, 0.2 mg/kg and 0.3 mg/kg bolus injections are comparable between both products.

Study CPA422-12 characterised the pharmacokinetics of Rapibloc 300 mg and 600 mg powder for solution for infusion (which will be referred to as Rapibloc Lyo from here), after sequential continuous infusion at low dose (10 µg/kg/min for 2 hours), medium dose (20 µg/kg/min for 2 hours) and high dose (40 µg/kg/min for 20 hours). With use of the PBPK model, the dosing of Rapibloc Lyo with the initial bolus injection proposed in the SmPC was simulated. Also, the pharmacokinetics of the 80 micrograms/kg BW/min dose has been simulated in the model and were considered acceptable.

Distribution

The apparent volume of distribution of landiolol is about 3 l/kg and for the main metabolite 0.3 l/kg. The half-lives for the parent and the main metabolite are 3.5 minutes and 1.6 hours, respectively. The protein binding for landiolol is low (< 10%) and dose dependent.

Elimination

Excretion. As landiolol is rapidly metabolised, only 10% of the dose is excreted in urine. The metabolites are also mainly excreted in urine and 90% is excreted within 24 hours. Landiolol is not considered to be subjected to significant active renal secretion as its low molecular weight is far below the molecular weight cut-off for glomerular filtration.

Metabolism. Landiolol is metabolised by carboxylesterase in liver and pseudocholinesterase in plasma mainly into two metabolites M1 and M2. The β1-blocking activity of landiolol metabolites is 1/200 or less of the parent compound, whereas the β2-blocking activity is 1/10 or less.

Polymorphism. The enzymes responsible for landiolol metabolism are carboxylesterase in liver and pseudocholinesterase in plasma are considered not subjected to genetic polymorphism.

Dose proportionality and time dependency

In the study in Japanese subjects in which the volunteers received landiolol in two different infusion rates of 40 µg/kg and 80 µg/kg for 1 hour, dose proportionality was established in the C_{max} and AUC as well (Murakami et al., 2005). The other studies with different doses are difficult to interpret with respect to the dose proportionality as the starting dose as well as the infusion rate differ in a non-proportional way.

Landiolol and its main metabolite M1 do not show time dependent pharmacokinetics. The pharmacokinetic variables after two administrations of the same dose yield comparative pharmacokinetic variables. The exposure to landiolol and its metabolite M1 was approximately dose proportional over the tested dose range.

Intra- and inter-individual variability

The inter-individual variability in the pharmacokinetic variables is about 15%-30%. An analysis for the intra-individual variability in the pharmacokinetics of landiolol was provided and was estimated to be about 18%. This variability is acceptable.

Target population

The pharmacokinetics of landiolol and its main metabolite M1 was not changed in Japanese and Caucasian patients compared with healthy subjects. The effect of reduced cardiac output on the pharmacokinetics of landiolol was modelled with the PBPK model and the changes were considered of no clinical significance.

Special populations

Renal impairment. The lack of clinical data in patients with renal impairment can be accepted. The impact of renal impairment on the pharmacokinetics is expected to be limited as landiolol is rapidly metabolised, only 10% of the dose is excreted by urine. Despite the fact that the metabolites are mainly excreted in urine the clinical impact of renal impairment on the metabolites is also expected to be limited as the metabolites are both inactive.

Hepatic impairment. Blood concentrations of landiolol were significantly higher in patients with hepatic impairment (increase in geometric mean C_{max}, C_{ss} and $AUC_{0-\infty}$ values in patients compared to healthy volunteers: +42%, +35% and +44%, respectively), but t1/2 was not different from healthy adults.
The PBPK model predicted the influence of hepatic impairment on the pharmacokinetics of landiolol. From the simulation, the effect of hepatic impairment was expected to be only marginal and unlikely to affect the safety and efficacy profile of landiolol significantly.

Gender. Data from several studies and after administration of different doses showed that the exposure to females and males is comparable.
Age. The MAH has submitted an overview of the patients' ages in the different studies. From the tables submitted by MAH it can be concluded that landiolol was also used in elderly patients. However, no stratification could be applied to the pharmacokinetic data found in the studies conducted by the MAH nor in the literature. Therefore, it is not clear what the influence of age is on the pharmacokinetics of landiolol.
Race. The MAH predicted that the differences between the Japanese and Caucasian population are small and probably of no clinical significance. Therefore, the data from studies in the Japanese population can be used for elucidation of the pharmacokinetics in the Caucasian population, especially as the dose will be titrated to the optimum effect.
Weight. As landiolol will be administered on weight base doses, the influence of weight is considered of no clinical significance.

Interactions
In vitro. Landiolol nor its metabolites M1 and M2 exhibited *in vitro* inhibitory activity against human cytochrome P450. No interaction studies investigating the involvement of P-glycoprotein (Pgp) or the renal uptake transporters OAT1, OAT3 or OCT2 have been performed. The lack of these studies has been sufficiently justified.
In vivo. No pharmacokinetic drug interaction studies were performed. This is acceptable as it is not expected that the distribution and metabolism will be affected by other medicinal products. However, it was shown that heparinisation decreased the exposure of landiolol by 50%.

Conclusion
In conclusion, pharmacokinetics of landiolol have been investigated sufficiently in vitro and in vivo in healthy volunteers and patients with cardiac arrhythmias and undergoing cardiovascular surgery.

IV.3 Pharmacodynamics

Mechanisms of action
The mechanism of action is typical for a short-acting selective beta-blocker. The principal pharmacodynamic biomarkers are heart rate and blood pressure which is considered valid. Its mechanism of action closely resembles esmolol, the only short-acting selective beta-blocker currently registered in the Netherlands.

Primary pharmacodynamics
In healthy Japanese subjects, landiolol produced a rapid dose-dependent reduction in resting heart rate, both as an infusion and as a bolus/infusion regimen. Resting heart rate was reduced up to 10% in the intended dose range and recovered within 15-30 minutes after discontinuation. During exercise tolerance testing, landiolol infusion reduced the heart rate in a similar manner by about 10 beats per minute (bpm).
Systolic blood pressure was reduced by 4 to 8%, diastolic blood pressure by 3 to 13% depending on the type of administration (infusion or bolus infusion) and the dose used. No clear dose-response relationship was observed.
A clear inverse relationship was observed between landiolol blood concentrations and both heart rate and blood pressure. Landiolol showed small changes on ECG parameters: a prolongation of the RR interval, the QT interval and in some cases in the QTc interval. According to the MAH, these changes were small and clinically not relevant. The QTc interval in the low-dose group in the study by Murakami et al., 2005 was significantly prolonged 30 to 60 minutes after completion compared to baseline. At that time limited amounts of landiolol were present in the subjects and the QTc prolongation cannot be linked to the study treatment.

Bridging studies
The MAH performed three bridging studies investigating the pharmacodynamics in healthy Caucasian subjects (CPA-368-10, CPA-410-12 and CPA-422-12). The Rapibloc products were only investigated in CPA-410-12 and CPA-422-12. The MAH has not submitted data directly comparing the pharmacodynamics of landiolol in Japanese and Caucasian subjects.

Study **CPA368-10** investigated the PD profile of landiolol (Onoact) in 16 healthy Caucasian volunteers. It assessed the mean dose necessary to suppress elevated heart rates due to dobutamine stimulation. The effect on heart rate started shortly after the start of infusion (8 minutes), remained throughout the infusion period and returned to pre-administration values within 30 minutes.
Dobutamine-elevated heart rates decreased slower after start of landiolol infusion than after esmolol infusion (time to decrease of 20 bpm after start of infusion: 6.6 minutes vs 3.0 minutes) and also returned slower to pre-administration values after discontinuation of infusion (time to increase of 20 bpm after end of infusion: 12.3 minutes vs 2.5 minutes).
Blood pressure was reduced as well but the blood pressure effect disappeared within 15 minutes after discontinuation of landiolol infusion.

Study **CPA410-12** investigated the PD profile of bolus doses of landiolol (Rapibloc Conc) compared to landiolol (Onoact) and esmolol in 15 healthy Caucasian volunteers. Heart rate and systolic blood pressure were decreased in 1-3 minutes after each bolus administration, and there was a good correlation of the decrease in heart rate with the blood concentrations of both study medications. The effect of both landiolol products was similar. The effect on heart rate of both landiolol products was larger at most time-points compared to esmolol. Although it is not clear whether the doses used for landiolol and esmolol should be seen as equivalent.
Blood pressure was decreased as well, showing a correlation with the blood concentrations. No clear dose-response relationship was observed, possibly due to a high variability and insufficient time between bolus administrations for the blood pressure to return to baseline.

Study **CPA422-12** investigated the PD profile of continuous infusion of landiolol (Rapibloc Lyo) compared to esmolol in 14 healthy Caucasian volunteers. In comparison with esmolol, landiolol infusion administration had a more pronounced effect on heart rate observed at most time points, significantly different at 16 minutes of low dose infusion (change from baseline in heart rate: 7.1 bpm vs 2.1 bpm) and sustained throughout the 24h study period. There was no difference in time to reach maximal change between treatments. Blood pressure was decreased for both landiolol and esmolol, without a clear difference between the treatments.

Conclusion
The pharmacodynamics of landiolol has been characterised adequately. The pharmacodynamics profile is very similar in Caucasian subjects and Japanese subjects and is comparable to the other short-acting selective beta-blocker esmolol. It quickly reduces heart rate, in a dose dependent way and with a clear relationship between plasma concentration and effect. Blood pressure is reduced as well, but these changes are not large.

IV.4 Clinical efficacy

The application is primarily based on literature describing the clinical studies conducted in support of the Japanese registration for Onoact and post-licensing phase. Data about 83 clinical studies with landiolol have been included in the dossier. Most clinical data are from these literature references. Therefore, there are no individual data and scarce information on the design and statistical methods.

Main studies
Treatment of perioperative supraventricular tachyarrhythmias
The efficacy of landiolol in the treatment of perioperative supraventricular tachyarrhythmias (SVT) was investigated in two pivotal trials (Yoshiya et al., 1997; Yoshiya et al., 2002), and supported by a dose-finding trial (Yoshiya et al., 2000) and a non-controlled trial (Uratsuji et al., 1997). In both pivotal trials landiolol was superior to placebo in reducing heart rate in both perioperative SVT and sinus tachycardia. The effects were confirmed in the two supportive studies.

Table 4: Efficacy of landiolol in the treatment of (perioperative) SVT

Source	Setting	Efficacy Criterion	Efficacy Result	
			LAN	Comparator
Yoshiya et al., 2000	Perioperative SVT; LAN (125/40)	HR reduction ≥20% after 11 min	90.7%	-
	Low-risk		100%	-
	High-risk		88.9%	-
Yoshiya et al., 1997	Perioperative SVT; LAN (125/40) vs PBO	HR reduction ≥20% after 11 min	80.3%	9.4%
	Low-risk		79.1%	11.9%
	High-risk		82%	6.7%
	All	Responder rate at 5 min (HR reduction >10%)	90.1%	32.6%
	Low-risk		90.6%	31.2%
	High-risk		89.4%	34.1%
Yoshiya et al., 2002	Perioperative SVT, high risk; LAN (125/40) vs PBO	Responder rate at 5 min (HR reduction >10%)	90.1%	25.0%
		HR reduction ≥20% after 11 min	85.7%	10.0%
Uratsuji et al., 1997	Perioperative SVT; LAN (125/40)	HR reduction ≥20% after 11 min	81.8%	-

HR heart rate
LAN landiolol
PBO placebo
SVT supraventricular tachyarrhythmias

Treatment of postoperative and paroxysmal atrial fibrillation

Efficacy of landiolol in the treatment of postoperative and paroxysmal atrial fibrillation was investigated in four pivotal trials. The results of these trials support the efficacy of landiolol in heart rate control in hospitalised patients with atrial fibrillation or flutter (AF/AFl) with or without left ventricular dysfunction, after coronary artery bypass surgery (CABG) and after highly invasive surgery.

In one study digoxin was used as comparator drug. However, the usual treatment target in new-onset atrial fibrillation is restoration of sinus rhythm. For this objective, digoxin is not effective and not recommended in the current European Society of Cardiology (ESC) guideline. Another study used diltiazem as comparator. According to the ESC guideline, diltiazem can be used for acute and chronic rate control, but other agents are more usual. The studies can therefore be seen as placebo-controlled, from an efficacy standpoint. In all the trials, a superior heart rate reduction was observed after landiolol treatment compared to either placebo (42.0% vs 0.0%, Taenaka & Kikawa, 2013b; and 60.0% vs 2.3%, Kato et al., 1997b), digoxin (48.0% vs 13.0%, Nagai et al., 2013) or diltiazem (54.3% vs 30.6%, Sakamoto et al., 2012). These data are supported by similar reductions reported in the dose-finding trials.

Table 5: **Pivotal studies** - Efficacy of landiolol in the treatment of postoperative and paroxysmal atrial fibrillation

Source	Setting	Efficacy Criterion	Efficacy Result	
			LAN	Comparator
Kato et al., 1997b	Paroxysmal AF/AFl; LAN (250/80) vs PBO	At least intermittent termination of paroxysm or HR reduction ≥20% after 11 min	60.0%	2.3%
Nagai et al., 2013	AF, high risk; LAN (1 – 10 µg/kg/min for 2 – 72 h) vs digoxin	HR control (reduction ≥20% and <110 bpm) after 2 h	48.0%	13.0%
Sakamoto et al., 2012	Postoperative AF after cardiac surgery; LAN (0.5 – 40 µg/kg/min for 24 h) vs diltiazem	Conversion to sinus rhythm after 8 h	54.3%	30.6%
Taenaka & Kikawa, 2013b	Postoperative SVT after cardiac surgery, high risk; LAN (125/40) vs PBO	HR control (reduction ≥20% and <100 bpm) after 11 min	42.0%	0.0%

(P)AF (paroxysmal) atrial fibrillation
(P)AFl (paroxysmal) atrial flutter
HR heart rate
LAN landiolol
PBO placebo
(P)SVT (perioperative) supraventricular tachyarrhythmias

Table 6: **Supportive studies** - Efficacy of landiolol in the treatment of postoperative and paroxysmal atrial fibrillation

Source	Setting	Efficacy Criterion	Efficacy Result	
			LAN	Comparator
Kato et al., 1997a	Paroxysmal AF/AFl or SVT; LAN (125/40)			-
	PAF/PAFl	HR reduction ≥20% after 11 min	61.9%	-
	PSVT	At least intermittent termination of paroxysm after 11 min	57.1%	-
Taenaka & Kikawa, 2013a	Postoperative SVT; LAN (125/40)	HR reduction ≥20% after 11 min	87.3%	-
Tanaka et al., 2008	Postoperative SVT after cardiac surgery, high risk; LAN (125/40) vs PBO	HR control (reduction ≥20% and <100 bpm) after 11 min	80.0%	0.0%
		HR change	-26%	+2.3%

(P)AF (paroxysmal) atrial fibrillation
(P)AFl (paroxysmal) atrial flutter
HR heart rate
LAN landiolol
PBO placebo
(P)SVT (perioperative) supraventricular tachyarrhythmias

Prevention of postoperative atrial fibrillation

The efficacy of landiolol in the prevention of AF was investigated in five trials. Four of these trials studied a population of patients undergoing CABG, and one studied patients undergoing heart valve surgery.

The incidence of atrial fibrillation in the landiolol group was compared to diltiazem (4.8% vs 27.0%, Nagaoka et al., 2014), no treatment (20.0% vs 53.3%, Sakaguchi et al., 2013), or placebo (11.1% vs 32.3%, Fuji et al., 2012; 10.0% vs 34.3%, Sezai et al., 2011; 14.5% vs 35.3%, Sezai et al., 2012). One of the placebo-controlled studies (Sezai et al., 2012) also had a patient group receiving landiolol followed by oral bisoprolol.

Prevention and treatment of hyperdynamic responses

Summarised results for 31 literature studies that investigated the efficacy of landiolol on the treatment and prevention of hyperdynamic responses to a variety of stimuli were provided. The majority of these studies were of a small size (n<100), and 27 of them were considered pivotal.

The 27 pivotal studies investigated the response to different stimuli: induction of anaesthesia and intubation (21 studies), emergence from anaesthesia and extubation (3 studies), the response to ECT therapy (4 studies). The studies used different dosing strategies for landiolol (bolus+infusion: 12 studies; bolus: 12 studies; infusion: 3 studies) and used various control treatments, including active comparators (like fentanyl) or placebo, either double or single-blind. The studies investigated hyperdynamic responses in a range of surgical procedures, using a variety of methods for inducing and sustaining anaesthesia, both with anaesthetic drugs, opioids (like fentanyl and remifentanil) and cardiovascular drugs.

All studies investigated the efficacy of landiolol on reduction of increased heart rate due to stimuli. Although there was variation between studies on the exact method of measuring the effect on heart rate (reduced maximum or peak heart rate, or reduction of heart rate at various time points), all studies demonstrated a reduction in stimulus increased heart rate compared to placebo, non treated subjects, diltiazem or nicorandil. Heart rate reduction was comparable to remifentanil, fentanyl, propofol or esmolol. It is not certain if suppression of the response to a stimulus is of equivalent benefit to the patient as blocking the stimulus itself, e.g. by opioids.

Summaries for two studies on the prevention of myocardial damage during PCI were provided. The MAH does not claim an indication in this area, but these trials can be considered as supportive for the other indications.

Clinical studies in special populations

Renal impairment. No information is available about the efficacy of landiolol in patients with renal impairment. Given that the metabolism of landiolol is independent on renal function, that elimination is fast and that no significant changes in blood concentrations of landiolol or its main metabolite were

found when using a pharmacokinetics model, no dose adjustments for patients with renal impairment are needed.
Hepatic impairment. In patients with hepatic impairment, increased blood levels were observed, but these are not likely to influence the efficacy of landiolol, since landiolol is to be used under monitored conditions.

Elderly Although landiolol treatment has been examined in elderly subjects in most trials, the efficacy has only been reported separately for a few of them. This is supplemented by several post-marketing surveys. The results presented, do not suggest that the efficacy is different in elderly. The proposed posology can be equal for elderly and non-elderly. The most important efficacy parameters, heart rate and blood pressure, will be monitored during landiolol use, as mentioned in section 4.2 of the SmPC.
Children As the information on landiolol use in children is limited to 25 patients, no recommendation can be made about the use of landiolol in children.

Conclusion
The use of landiolol in the treatment of perioperative SVTs and sustained ST appears to be effective in both low and high risk patients and it supports the claim for an indication of treatment of perioperative SVTs and ST. Landiolol can be used for rate control in patients with atrial fibrillation, further supporting the claim for an indication of treatment of perioperative tachycardia and SVT.
The studies investigating the prevention and treatment of hyperdynamic responses support an indication of arrhythmias, when 'in the physician's judgment the rapid heart rate requires specific intervention'.
Information on the efficacy in special populations is limited, but the available data suggest no differences in patients with renal impairment and only small differences in elderly and patients with hepatic impairment, which will be manageable because landiolol is used under monitored conditions. Information on landiolol use in children is limited to 25 patients, no recommendation can be made about the use of landiolol in children.

IV.5 Clinical safety

Most safety information on landiolol is obtained from 52 clinical studies performed for the marketing authorisation and several line extensions in Japan and from post-marketing experience in Japanese clinical practice. In total 4094 subjects were exposed to landiolol in a clinical trial setting. However, the MAH did not have full access to safety data as the MAH primarily relies on literature references of these trials. The MAH provided the safety data extracted from these trials.

Adverse events
Hypotension was observed frequently (8.5% in landiolol arms, compared to 8.5% in active control arms, 2.1% in placebo arms and 5.7% in not-treated comparator arms). In the clinical trials referenced by the MAH, it was observed more frequently when compared to placebo. When compared to diltiazem the incidence of hypotension was lower for landiolol, in one study (Sakamoto et al., 2012) but higher in another study (Nagaoka et al., 2013). Hypotension generally resolved within 30 after discontinuation of landiolol.
Bradycardia was observed in 2.1% of the landiolol treated patients. It was observed more often when compared with placebo (0%), but less when compared to active comparators (2.5%) or no treatment (2.4%). The cases of bradycardia resolved upon discontinuation of landiolol. However, these bradycardias were mostly seen in one study (Kawaguchi et al., 2010b). With 56 patients included, the study accounted for 21 of the 30 cases observed in controlled studies. Although not explained by the authors, it was speculated that this high incidence of bradycardias can be due to the study population. Bradycardia has been included as 'common' in the SmPC.

Laboratory tests revealed elevated ALT, AST and total bilirubin levels in several cases. Although the exact height of these levels is not clear, all cases were mild and without any complications and do not indicate a hepatic safety issue.

In the pharmacokinetics and pharmacodynamics studies with Rapibloc, a total of 27 Caucasian patients were treated with the two formulations (Rapibloc Lyo n=12; Rapibloc Conc n=15). In these studies, 5 (18.5%) injection site reactions (1 mild, 4 moderate) were reported and 2 (7.4%) injection site pains. None of them requiring treatment or discontinuation. Injection site reactions are reflected in

the SmPC. However, Rapibloc Conc has a high osmolality which may cause a risk of thrombophlebitis in case of accidental extravasation. Therefore, a warning reflecting this risk was added to the SmPC.

Serious adverse events and deaths
In the clinical program several cardiac disorders and one death due to worsening of pre-existing congestive cardiac failure occurred during landiolol use. However, the frequency in the clinical program is lower than in the comparator arms.

Laboratory findings
In general, the information on adverse events relating to laboratory values is restricted to the result of the tests (*i.e.* lowered or increased). Detailed information is available from three pharmacokinetics and pharmacodynamics studies performed by the MAH, including normal ranges and the actual values at screening and EOS. Abnormal values were measured, but generally these were only slightly outside the normal range and none were considered clinically relevant.
In the pharmacokinetics and pharmacodynamics studies and controlled clinical trials for which the literature reference reported laboratory values, abnormalities were observed in patients treated with landiolol, but in similar frequencies as in the control arm. These abnormalities were mild and resolved without action, and although a relationship with study medication could not be ruled out, an influence of anaesthesia or surgery can be considered as well.
The overall frequencies of laboratory abnormalities, especially hepatic, in these studies were higher than reported in the adverse events tables. In the four controlled studies that the MAH described in detail, there were 241 patients receiving landiolol of which 13 patients (5%) had abnormal changes in ALT, AST or bilirubin. The control arms of these studies (active, placebo or none) consisted of 243 patients and 16 (7%) had abnormal hepatic laboratory values. This is described in the SmPC under a specific subheading 'laboratory parameters'.

Safety in special populations
Gender No differences in adverse events were observed according to gender
Age No differences in adverse events were observed according to Age. The MAH did not have sufficiently detailed safety data to provide an overview of the number of adverse events in higher age categories. Insufficient data in elderly subgroups, most patients being under anaesthesia and the use of co-medications lead to uncertainty of the safety profile, which is reflected by a statement in the SmPC.

Comorbidities An increase in adverse events was observed in several comorbidities present at baseline (heart disease, liver, kidney and respiratory disease) and with increased frequency of use. Most of these AEs were observed in post-marketing surveys, and no comparator data was available. The largest part of these AEs were decreased blood pressure or hypotension, and almost all resolved without further action.

Safety related to drug-drug interactions and other interactions
In clinical studies landiolol was co-administered with a broad range of anaesthetics, sedatives and other drugs. Interactions are based on findings in preclinical and clinical studies, complemented with known class-effects of beta-blockers (especially esmolol). Despite over 10 years of landiolol use in Japan, no case reports have been published describing an unknown interaction of landiolol.

Discontinuation due to adverse events
Rapibloc is intended to be used in a monitored setting, and the dosage should be increased or decreased based on the patient's response (e.g. heart rate). In case of adverse events, the dose should be decreased, or the infusion should be terminated. This is stated in section 4.2 of the SmPC. No frequencies of discontinuations have been supplied.

Conclusion
The safety of landiolol is acceptable.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Rapibloc.

Table 7: Summary of safety concerns as approved in RMP

Important identified risks	- Severe hypotension - Severe bradycardia - Shock - Cardiac arrest, sinus arrest, complete AV block - Interaction with drugs affecting myocardial contractility and conduction, e.g. o calcium channel blockers such as verapamil and diltiazem o class I antiarrhythmic agents such as disopyramide, flecainide and propafenone o amiodarone o digitalis preparations. - Interaction with drugs used during anaesthesia, e.g. o anaesthetics with bradycardic effect such as fentanyl citrate and propofol o esterase substrates such as procaine and suxamethonium o cholinesterase inhibitors such as neostigmine. - Interaction with insulin or oral antidiabetic drugs leading to enhanced blood glucose lowering effect and masking of hypoglycaemic symptoms such as tachycardia
Important potential risks	- Depression of myocardial contractility in patients with congestive heart failure leading to aggravation of heart failure - Sudden increase in blood pressure in patients with untreated phaeochromocytoma - Bronchospasms in patients with bronchospastic diseases - Aggravation of peripheral circulatory disorders (Raynaud's disease or syndrome, intermittent claudication) - Allergic/anaphylactic reactions - Medication errors - Suggested possible influence of heparin on the plasma concentration of landiolol
Missing information	- Paediatric population - Pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. Since landiolol hydrochloride is a new active substance, Rapibloc is placed on the additional monitoring list. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 of the SmPC for how to report adverse reactions.

V. BENEFIT/RISK ASSESSMENT

V.1 Therapeutic context

Disease or condition

Landiolol is intended for use in emergency situations or during anaesthesia. The occurrence of supraventricular tachycardia or supraventricular tachyarrhythmias may be caused by many different stimuli, ranging from pre-existing heart conditions to interventions like intubation. In such cases many therapeutic options are available. If pharmacological intervention is warranted, a short-acting beta-

blocker be considered a symptomatic approach, whereas opioids may represent the primary class of medicines to mitigate the stimulus.

Available therapies and unmet medical need
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. The only short-acting selective beta-blocker registered in the Netherlands is esmolol. Landiolol has the same characteristics with regard to fast onset and offset of effect on heart rate, flexible dosing, rapid dose adaptation together with little influence on blood pressure.
As an alternative to esmolol, landiolol has different pharmacological characteristics and a different pharmaceutical form. The clinical relevance of these differences is out of scope for this assessment.

Main clinical studies
Most data submitted for this application come from the clinical program in Japanese subjects in support of the registration of landiolol (Onoact) in Japan. Approximately 80 clinical studies with landiolol have been performed for which the MAH provided summaries and literature references. To bridge the clinical information of landiolol in Japanese subjects to landiolol (Rapibloc Lyo and Rapibloc Conc) in Caucasian subjects, the MAH performed three bridging studies investigating the pharmacokinetics/pharmacodynamics in healthy Caucasian subjects.

V.2 Favourable and unfavourable effects

Favourable effects
Landiolol is a short-acting beta blocker for intravenous use. Efficacy data support its short-term use for tachycardias peri-operatively and in emergency situations. The MAH provided 83 clinical studies with landiolol and although the majority of the studies were of a small size (n<100), these studies consistently showed the efficacy of landiolol in the treatment and prevention of ST or SVT peri-operatively and in the treatment and prevention of hyperdynamic responses. Landiolol produces a rapid dose-dependent reduction in heart rate, both as an infusion, a bolus/infusion regimen and as a bolus injection. Heart rate recovers within 15-30 minutes after discontinuation.

Treatment of perioperative ST/SVT
In two trials landiolol was superior to placebo in reducing heart rate (reduction ≥20% after 11 minutes 80.3% vs 9.4% and 85.7% vs 10.0%) in both perioperative SVT (HR≥100 bpm persisting for ≥1 minute) and ST (HR≥100 bpm persisting for ≥3 minutes). The reduction of heart rate after landiolol treatment was supported by two uncontrolled trials.

Treatment of postoperative and paroxysmal AF
Four trials support the efficacy of landiolol in heart rate control in hospitalised patients with AF/AFl with or without left ventricular dysfunction, after CABG and after highly invasive surgery. In all the trials, a superior heart rate reduction was observed after landiolol treatment compared to either placebo (42.0% vs 0.0% and 60.0% vs 2.3%), digoxin (48.0% vs 13.0%) or diltiazem (54.3% vs 30.6%). These data are supported by similar reductions in the dose-finding trials.

Prevention of postoperative AF
The efficacy of landiolol in the prevention of AF was investigated in five trials. Four of these trials studied a population of patients undergoing CABG and one studied patients undergoing heart valve surgery. The incidence of AF in the landiolol group was lower compared to diltiazem (4.8% vs 27.0%), no treatment (20.0% vs 53.3%), or placebo (11.1% vs 32.3%; 10.0% vs 34.3% and 14.5% vs 35.3%).

Prevention and treatment of hyperdynamic responses
The response to different stimuli was investigated in 27 studies: induction of anaesthesia and intubation (21 studies), emergence from anaesthesia and extubation (3 studies) and the response to ECT therapy (4 studies). The studies investigated hyperdynamic responses in a range of surgical procedures, using different dosing strategies for landiolol, a variety of methods for inducing and sustaining anaesthesia and various control treatments.
All studies demonstrated a reduction in stimulus increased heart rate compared to placebo, non-treated subjects, diltiazem or nicorandil. Heart rate reduction was comparable to remifentanil, fentanyl, propofol or esmolol.

Uncertainties and limitations about favourable effects

The pharmacokinetics and pharmacodynamics have been studied mostly in Japan. However, data observed in Caucasians are comparable to the results of the Japanese studies. Furthermore, Japanese treatment guidelines are generally based on the European or US guidelines and the recommendations are similar. There is no indication of differences in medical practice or other extrinsic factors that might hamper the bridging.

The MAH has submitted a direct comparison of the pharmacokinetics/pharmacodynamics of landiolol in Japanese and Caucasian subjects. The pharmacokinetics of landiolol and its main metabolite M1 was not changed in Japanese and Caucasian patients compared with healthy subjects. The effect of reduced cardiac output on the pharmacokinetics of landiolol was modelled with the PBPK model and the changes were considered of no clinical significance.

The Rapibloc products were only investigated in two studies. The MAH provided validation reports on the analytical methods and compared the different methods used in the different studies.

Two formulations with a different composition are applied for in this procedure, which might behave differently: Rapibloc Lyo and Rapibloc Conc. Experience with Rapibloc Conc is limited to one PK/PD study. A comparison between Rapibloc Lyo and Onoact has been submitted. The pharmacokinetics of Rapibloc Lyo after administration (10-40 µg/kg/min) have been evaluated, studies were conducted with Rapibloc Lyo in the dosing regime with the initial bolus injection as proposed in the SmPC. The PK of the 80 micrograms/kg BW/min dose has been simulated only in the model but were considered acceptable.

Information on the efficacy in special populations is limited, but the available data suggest no differences in patients with renal impairment and only small differences in elderly and patients with hepatic impairment, which will be manageable because landiolol is used under monitored conditions. Information on landiolol use in children is limited to 25 patients. No recommendation can be made about the use of landiolol in children.

Data on the treatment of postoperative and paroxysmal AF is limited to patients after CABG or highly invasive surgery. Similarly, prevention of AF is only documented for heart surgery patients.

Unfavourable effects

Safety information on landiolol is mainly reported from 52 clinical studies performed for the marketing authorisation and several line extensions in Japan, and from pharmacovigilance information gathered on clinical use in Japan since 2002. The clinical trials and the use in clinical practice cover the population targeted in the proposed indication and the safety information should therefore represent the AE profile of landiolol.

Landiolol has been used in 4.094 patients in clinical trials and in 40 subjects in European PK/PD studies. Safety data are provided for these patients and for 1257 patients exposed to landiolol in post-marketing surveys. Furthermore, landiolol (Onoact) has been in use in Japan and over 4 million units have been sold between 2002 and 2013.

The general AE profile appears to be in line with the experience with short-acting beta-blockers. The most common adverse events were hypotension, bradycardia and increased laboratory values for ALT, AST and bilirubin.

- Hypotension was observed frequently (8.5% in landiolol arms, compared to 8.5% in active control arms, 2.1% in placebo arms and 5.7% in not-treated comparator arms). In the clinical trials referenced by the MAH, it was observed more frequently when compared to placebo. Hypotension generally resolved within 30 minutes after discontinuation of landiolol.
- Bradycardia was observed in 2.1% of the landiolol treated patients. It was observed more often when compared with placebo (0%), but less when compared to active comparators (2.5%) or no treatment (2.4%). The cases of bradycardia resolved upon discontinuation of landiolol.
- Laboratory tests revealed elevated ALT, AST and total bilirubin levels in several cases.

In the PK/PD studies conducted by the MAH, a total of 27 Caucasian patients were treated with the Rapibloc products (Rapibloc Lyo n=12; Rapibloc Conc n=15). In these studies, 5 (18.5%) injection site reactions (1 mild, 4 moderate) were reported and 2 (7.4%) injection site pains. None of these required treatment or discontinuation.

No statistically significant interactions for adverse events were observed in subgroups according to gender or age, with an age cut-off of 65 years.

An increase in adverse events was observed in several comorbidities present at baseline (heart disease, liver, kidney and respiratory disease) and with increased frequency of use.

Comparator data were available for 20 studies. The percentage of patients experiencing an AE while exposed to landiolol was 12.0%. This percentage is higher than that in patients with placebo (5.8%) or no treatment (6.1%) but lower than with active comparator (20.9%).

Uncertainties and limitations about unfavourable effects

The adverse events were derived from 52 clinical studies for which the MAH provided literature references. The quality of this safety information varies:

1) some studies only mention the number of AEs or the number of patients with an AE, not both;
2) it is not always clear whether MedDRA coding was used and if so what version; and
3) not all studies evaluated the relationship of AEs with landiolol (or comparator).

The information on adverse events relating to laboratory values is restricted to the result of the tests (i.e. lowered or increased). Detailed information was available from three PK/PD studies performed by the MAH. Abnormal values were measured, but generally these were only slightly outside the normal range and none were considered clinically relevant.

In the PK/PD studies and controlled clinical trials for which the literature reference reported laboratory values, abnormalities were observed in patients treated with landiolol, but in similar frequencies as in the control arm. These abnormalities were mild and resolved without action, and although a relationship with study medication could not be ruled out, an influence of anaesthesia or surgery can be considered as well.

The overall frequencies of laboratory abnormalities, especially hepatic, in the studies were higher than the AST, ALT and bilirubin increases reported in the adverse events tables: 13/241 patients (5%) had abnormal changes in ALT, AST or bilirubin when using landiolol, compared to 16/243 (7%) control patients.

In the clinical program several cardiac disorders and one death due to worsening of pre-existing congestive cardiac failure occurred. However, the frequency is lower than in the comparator arms in the clinical program.

All clinical studies were performed in Japan, and although not explicitly stated, it can be assumed that most study subjects were of Japanese origin. Only the three bridging studies provide safety information in European subjects. Two of these studies were performed with Rapibloc, one with Rapibloc Lyo and one with Rapibloc Conc. Rapibloc Lyo is a lyophilisate containing mannitol, like Onoact. Thus, safety information obtained with the Japanese product is relevant for Rapibloc Lyo.
Rapibloc Conc, a concentrate for injection containing several excipients, is considerably different in composition from Rapibloc Lyo and Onoact. Experience with Rapibloc Conc is limited to one pharmacokinetics/pharmacodynamics study. Thus, the safety information on Caucasian subjects and on the Rapibloc products, especially Rapibloc Conc, is very limited.

The following concerns regarding Rapibloc concentrate for solution for injection were discussed:

- The osmolality of the concentrate, ready for use, is high and might cause damage to the vein used for injection or cause severe irritation when the product is accidentally injected subcutaneously. However, as the product will only be used by health care professionals in a monitored environment, the risk is manageable. A warning is included in the SmPC.
- The use of ampoules is not preferred as the concentrate has to be withdrawn from the ampoule and then diluted in a separate vial. However, since the stability of landiolol in vials is

limited, the concentrate for solution for injection in ampoules is considered of acceptable quality in relation to its intended use.

Effects table

Table 8: Effects table of Rapibloc

	Endpoint	Unit	Active landiolol	control	Strength of evidence
Favourable effects					
Treatment of perioperative ST/SVT	reducing HR (reduction ≥20% after 11 minutes • perioperative SVT (HR≥100 bpm persisting for ≥1 minute) • ST (HR≥100 bpm persisting for ≥3 minutes)	% responders	80.3 85.7	PBO 9.4 PBO 10.0	Two independent trials Two supporting trials
Treatment of postoperative and paroxysmal AF	HR control in hospitalised patients with AF/AFl with or without left ventricular dysfunction, after CABG and after highly invasive surgery	% responders	42.0 60.0 48.0 54.3	PBO 0.0 PBO 2.3 DIG 13.0 DTZ 30.6	Four independent trials Supporting dose-finding trials
Prevention of postoperative AF	Incidence of AF in CABG or in Heart valve surgery	% with AF	4.8 20.0 11.1 10.0 14.5	DTZ 27.0 NUL 53.0 PBO 32.3 PBO 34.3 PBO 35.3	
Prevention and treatment of hyperdynamic responses	induction of anaesthesia and intubation (21 studies), emergence from anaesthesia and extubation (3 studies) and the response to ECT therapy (4 studies).	stimulus increased HR		Reduction compared to PBO, NUL, DTZ or nicorandil comparable to remifentanil, fentanyl, propofol or esmolol.	
Unfavourable effects					
Any AE		% patients	12.0	ACT 20.9 NUL 6.1 PBO 5.8	20 studies
Hypotension		% patients with AE	8.5	ACT 8.5 NUL 5.7 PBO 2.1	
Bradycardia		% patients with AE	2.1	ACT 2.5 NUL 2.4 PBO 0	

	Endpoint	Unit	Active landiolol	control	Strength of evidence
elevated ALT, AST and total bilirubin		% patients with abnormal laboratory test	13/241 (5%)	16/243 (7%)	
Injection site reaction or pain		% patients with AE	18.5 7.4		

ACT	active comparator
AF	Atrial fibrillation
AFI	Atrial flutter
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CABG	Coronary Artery Bypass Grafting
DIG	digoxin
DTZ	diltiazem
HR	Heart rate
NUL	no treatment
PBO	placebo
ST	Sinus tachycardia
SVT	Supraventricular tachyarrhythmia

V.3 Benefit-risk assessment and discussion

Importance of favourable and favourable effects

For use during anaesthesia and in emergencies, fast onset or offset of effect are important. This applies to both favourable and unfavourable effects and defines the ease of use of the product. For the proposed indications, treatment is successful in the majority of cases. Unfavourable effects can be easily managed and therefore weigh mildly in the B/R balance.

Uncertainties were addressed adequately during the procedure. The most important of these concerns the bridging of efficacy and safety data from Japan to the European setting.

Balance of benefits and risks

Landiolol behaves as expected from a short-acting beta blocker. The main characteristic is fast onset and offset of action, which is an important benefit in the proposed condition. In comparison to the effect on heart rate, the hypotensive effect is limited. The most important adverse reactions are of excessive pharmacological effect and can be easily managed by dose reduction or discontinuation. The balance is positive.

There are no additional considerations on the benefit risk balance

V.4 Conclusion

The benefit-risk balance for both Rapibloc products is positive.

VI. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC for the PL for the powder for solution for infusion. For the concentrate for solution for injection a bridging report was provided.

The results of the readability test show that the PL is clear and understandable for the patient. The package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use. In addition, the bridging report is accepted as both PLs have mainly identical information, apart from the product specific characteristics.

VII. OVERALL CONCLUSION AND RECOMMENDATION

The chemical-pharmaceutical information about the manufacturing, the quality requirements with regard to the substance and the finished product Rapibloc 300 mg and 600 mg powder for solution for infusion and Rapibloc 20 mg/2 ml concentrate for solution for injection have a proven chemical-pharmaceutical quality.

The non-clinical data documentation provided did not give rise to specific concerns for humans that would preclude a recommendation for marketing authorisation.

The results of the clinical studies show that the use of landiolol in the treatment of perioperative SVTs and sustained ST is effective in both low and high-risk patients. The claim for an indication of treatment of perioperative SVTs and ST is sufficiently supported. Landiolol can also be used for rate control in patients with atrial fibrillation, further supporting the claim for an indication of treatment of perioperative tachycardia and SVT. The studies investigating the prevention and treatment of hyperdynamic responses support an indication of arrhythmias, when the physician considers that the rapid heart rate requires specific intervention.
The general adverse events profile is in line with what would be expected for a short-acting selective beta-blocker. An appropriate Risk Management Plan has been laid down.

In the Board meetings of 2 April 2015, 10 March 2016 and 18 May 2016 this application was discussed. The issues that have been discussed, were concerns regarding the external validity of the Japanese study results and the applicability and safety of the product. After the three sessions, all issues have been resolved provided that the product information contains a warning about the risk of medication errors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The member states, on the basis of the data submitted, considered that Rapibloc demonstrated adequate evidence of efficacy in the indications applied for. The decentralised procedure was finalised with a positive outcome on 29 June 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3368/1-3/IA/001/G	– Replacement or addition of a manufacturer responsible for importation and/or batch release; Not including batch control/testing – Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	Yes	14-07-2017	Approved	-
NL/H/3368/1-2/II/002	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data (See Annex I).	Yes	08-12-2017	Approved	-
NL/H/3368/1/II/003/G	- Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; o secondary packaging site o site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes - Change to importer, batch release arrangements and quality control testing of the finished product; replacement or addition of a site where batch control/testing takes place - Change in the batch size (including batch size ranges) of the finished product; up to 10-fold compared to the originally approved batch size	No	19-03-2018	Approved	-
NL/H/3368/1,3/IA/004	- Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product; o secondary packaging site	No	27-05-2018	Approved	
NL/H/3368/1/IB/005	- Other variation	Yes	11-09-2018	Approved	
NL/H/3368/3/IB/006	- Change in test procedure for the finished product; o Other changes to a test procedure (including replacement or addition)	No	10-07-2019	Approved	
NL/H/3368/1/II/007	- Change in the specification parameters and/or limits of the finished product o Change outside the approved specifications limits range	No	19-05-2019	Approved	
NL/H/3368/1,3/IA/008	- Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance o Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	No	21-01-2019	Approved	
NL/H/3368/3/IB/009	- Change in the specification parameters and/or limits of the finished product o Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a	No	22-07-2019	Approved	

	result of a safety or quality issue				
NL/H/3368/1/IB/010/G	- Change in test procedure for the finished product o Minor changes to an approved test procedure o Other changes to a test procedure (including replacement or addition)	No	12-02-2020	Approved	
NL/H/3368/1/IB/013	- Other variation	Yes	17-06-2020	Approved	

ANNEX I – VARIATION

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, the RMS considers that the variation NL/H/3368/1-2/II/002 for Rapibloc (landiolol), in the treatment of tachycardia

is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

The scope of the variation for the 300 & 600 mg lyophilisate presentations of the product is a dose reduction in extended infusion settings for patients with impaired left ventricular function, 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 3- 10 micrograms/kg/min have been used for successful heart rate control (for other patient groups, the current SmPC dosing scheme for continuous infusion recommends 10-40 µg/kg/min up to a maximum of 80 µg/kg/min).

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

III.1.1 Clinical efficacy and safety

The MAH has provided new information clinical overview. With this information the MAH has shown convincingly that in patients with LV dysfunction a lower dose can be used than in the general population. The data are predominantly from Japanese origin, but as no major differences in the pharmacokinetics of landiolol are observed between a Caucasian and Japanese population, these findings may be translated to the European setting. It is useful to add this information to the SmPC.

The proposed variation does not apply to the ready-to-use formulation of landiolol, which is acceptable as the ready-to-use formulation is not intended for slow infusion.

III.2 Product information

III.2.1 Summary of Product Characteristics

Section 4.2:

- The two proposed paragraphs should be merged to a single paragraph under Special populations as follows:

  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 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.

Section 4.3:

- Restrict the contra indication in 4.3 from 'Decompensated heart failure' to 'Decompensated heart failure **when considered not related to the arrhythmia**'

Section 4.4:

- Modify the warnings in 4.4 as follows:

~~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, 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 **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.**

IV. OVERALL CONCLUSION

The variation is considered approvable.