CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Esmolol HCL Orpha 100 mg/10 ml solution for injection Esmolol HCL Orpha 2500 mg/10 ml concentrate for solution for infusion Orpha-Devel Handels und Vertriebs GmbH, Austria

esmolol (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/779/001-002/MR
Registration number in the Netherlands: RVG 31523, 31526

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Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB09
Route of administration:	intravenous
Therapeutic indication:	short-term treatment of supraventricular tachycardia (except for pre-excitation syndromes), and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter. Treatment of tachycardia and hypertension during the perioperative phase and noncompensatory sinus tachycardia.
Prescription status:	prescription only
Date of authorisation in NL:	2 January 2006
Concerned Member States:	BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, SE, SI, SK, UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Esmolol HCL Orpha 100 mg/10 ml solution for injection (Esmolol HCL Orpha 100) and Esmolol HCL Orpha 2500 mg/10 ml concentrate for solution for infusion (Esmolol HCL Orpha 2500), from Orpha-Devel Handels und Vertriebs GmbH. The date of authorisation was on 2 January 2006 in the Netherlands.
The product is indicated for the short-term treatment of supraventricular tachycardia (except for pre-excitation syndromes), 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. It is also indicated for tachycardia and hypertension during the perioperative phase and noncompensatory sinus tachycardia where, in the physician's judgement the rapid heart rate requires specific intervention. Esmolol is not intended for use in chronic settings.

A comprehensive description of the indications and posology is given in the SPC. Esmolol HCL Orpha 100 is intended for intravenous injection, Esmolol HCL Orpha 2500 is a concentrate for solution intended for infusion and is not for direct intravenous injection and must be diluted before administration.

Esmolol is a parenteral administered, cardioselective beta-inhibitor. In therapeutic doses esmolol does not have intrinsic sympathicomimetic activity (ISA) of importance and no membrane stabilising (local anaesthetic) properties. Based on the pharmacological properties esmolol has a fast and short action by which the dose can be quickly adjusted. After the starting dose a steady state plasma concentration is reached within 5 minutes. However, the therapeutic effect is sooner obtained than the stabile plasma concentration. The infusion rate can then be adjusted to obtain the desired pharmacological effect. Esmolol HCL Orpha has the known hemodynamic and electrophysiologic effect of beta-blockers.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Brevibloc 100 mg/10 ml, solution for injection (RVG 14591), and Brevibloc 2.5 mg/10 ml, solution for injection (concentrate) 250 mg/ml (RVG 13493), which have been registered in the Netherlands by Baxter since 1991 and 1990, respectively. For Brevibloc 2.5 g/10 ml, solution for injection (concentrate) 250 mg/ml registration has been withdrawn in the Netherlands on 31 December 2007. In addition, reference is made to Brevibloc authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Esmolol HCL Orpha 100 and Esmolol HCL Orpha 2500 are products for parenteral use, they are exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of these products prior to granting its national authorisations.

Active substance
The active substance is esmolol hydrochloride, an established active substance not described in the European Pharmacopoeia (Ph.Eur.*), Esmolol hydrochloride is a white to almost white crystalline powder.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Quality control of drug substance
In-house specifications are given, which will ensure the compliance to the required quality as defined during development. The specification is acceptable in view of the synthesis of the drug substance. Batch analytical data demonstrating compliance with this specification have been provided for 3 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 18 months. Based on the data submitted, a retest period could be granted of 2 years when stored in air-tight containers protected from air, moisture and direct heat. The re-test period of the active substance was changed from 30 to 60 months by a post-approval variation (NL/H/0779/001-002/IB/008). See table "*Steps taken after finalisation of the initial procedure*", on page 9.

Medicinal Product

Composition
Esmolol HCL Orpha 100 mg/10 ml solution for injection is a clear and colourless solution. The concentration of this product is 10 mg/ml esmolol hydrochloride.
Esmolol HCL Orpha 2500 mg/10 ml concentrate for solution for infusion is a clear and colourless solution. The concentration of this product is 250 mg/ml esmolol hydrochloride. Esmolol HCL Orpha 2500 must be diluted and used immediately after opening. The administration of Esmolol HCL Orpha 2500 concentrate for solution for infusion undiluted or incorrectly diluted may result in death or disability.

Esmolol HCL Orpha 100 is packed in a clear, colourless, glass vial, with a chlorobutyl rubber stopper, containing 10 ml solution for injection. The vials are packed in an outer cardboard carton.
Esmolol HCL Orpha 2500 is packed in a clear, colourless, glass ampoule, with a break ring, containing 10 ml concentrate for solution for infusion. The ampoule is packed in an outer cardboard carton.
The MAH committed to provide validation data of the integrity of the container closure system (10mg/ml in vials) and data regarding the tightness of the container closure system during the manufacturing process. This post-approval commitment has been fulfilled (see steps taken after finalisation of the initial procedure at page 9).

The excipients for Esmolol HCL Orpha 100 are: sodium acetate trihydrate (E262), acetic acid 99% (E260), hydrochloric acid 10% (E507) for pH adjustment and water for injections.

The excipients for Esmolol HCL Orpha 2500 are: sodium acetate trihydrate (E262), acetic acid 99% (E260), propylene glycol (E1520), ethanol 96%, hydrochloric acid 10% (E507) for pH adjustment and water for injections.

Pharmaceutical development
The products have an established pharmaceutical form and their development is adequately described in accordance with the relevant European guidelines.

The objective was to develop products with the same composition as the innovator product Brevibloc.

Excipients
The excipients are common in the manufacture of parenteral formulations. All excipients comply with the requirements laid down in their respective Ph.Eur. and/or USP* monographs.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 2 pilot and 2 industrial batches from both products in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification of the finished products includes tests for appearance, identification, pH, extractable volume, particulate matter, assay, impurities, bacterial endotoxins and sterility. Limits in the specification have been justified 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 8 batches from both products from the proposed production site(s) has been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 2 pilot scale batches and 2 industrial batch from both products in accordance with applicable European guidelines demonstrating the stability of the product Esmolol HCL Orpha 100 over 18 months and of the product Esmolol HCL Orpha 2500 over 18 months. The results of 18 months long term stability study show a progressing decrease in assay and increase in impurities. However, the results remain within specification. On basis of the data submitted, a shelf life was granted of 18 months for both products.

The labelled storage conditions for Esmolol HCL Orpha 100 are*: "Do not store above 25 °C. Keep the vial in the outer carton in order to protect from light."* The storage conditions of the solution are: *"The opened product is physicochemically stabile during 24 hours at 2-8 °C. From microbiological point of view the product must be used immediately after opening. In case this is not done, the user is responsible for use and administration. Normally the period of use is not more than 24 hours at 2-8 °C, unless opening have taken place under controlled and validated septical circumstances."*

The labelled storage conditions for Esmolol HCL Orpha 2500 are: "*Do not store above 25 °C. Keep the ampoule in the outer carton in order to protect from light."* The storage conditions of the reconstituted solution are: *"The opened and diluted product is physicochemically stabile during 24 hours at 2-8 °C. From microbiological point of view the product must be used immediately after opening and dilution. In case this is not done, the user is responsible for use and administration. Normally the period of use is not more than 24 hours at 2-8 °C, unless opening and dilution have taken place under controlled and validated septical circumstances."*

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.

** Ph. Eur. And USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU or the United States, respectively.*

Non clinical aspects

These products are generic formulations of Brevibloc, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of esmolol hydrochloride released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.2 Clinical aspects

Esmolol hydrochloride is a well-known active substance with established efficacy and tolerability.

During the mutual recognition procedure a concern was raised by one CMS regarding the risk of misidentification of Esmolol HCL Orpha 100 mg/10 ml solution for injection and Esmolol HCL Orpha 2500 mg/10 ml concentrate for solution for infusion, since both products are clear and colourless solutions. In case of misidentification there is a risk of intravenous injection without dilution, which could have lethal complications due to unintended injection of a colourless high esmolol concentrate 2500mg/10ml instead of the 100 mg/10 ml solution for injection. The MAH committed to provide a modification of the concentrate formulation in order to avoid any misidentification compared to Esmolol HCL Orpha 100.

Esmolol HCL Orpha 100 and Esmolol HCL Orpha 2500 are parenteral formulations containing the same active substance in the same concentration as the currently authorized reference medicinal product. As Esmolol HCL Orpha 100 and Esmolol HCL Orpha 2500 are products for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

Risk Management Plan
Esmolol hydrochloride was first approved in 1990 and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of esmolol hydrochloride can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Brevibloc. However during the mutual recogntion procedure some changes were made. In section 4.3 the following contraindications were added: "*severe hypotension", "hypersensitivity to esmolol hydrochloride or to any of the excipients", "pulmonary hypertension", "acute asthmatic attack" and "metabolic acidosis".* In section 4.5 the following warning was introduced in the subsection "Interaction with other medicinal products and other forms of interaction": *"Rate reducing calcium channel blockers (such as verapamil or diltiazem): risk of hypotension and AV-conduction disorders. In common with other beta-blocking agents it is recommended that esmolol be used with caution in combination with verapamil in patients with impaired ventricular function. The combination should not be given to patients with conduction abnormalities and esmolol should not be administered within 48 hours of discontinuing verapamil."*

Readibility test

The package leaflet 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. The test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test is of an acceptable quality.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Esmolol HCL Orpha 100 mg/10 ml, solution for injection, and Esmolol HCL Orpha 2500 mg/10 ml, concentrate for solution for infusion, have a proven chemical-pharmaceutical quality and are generic forms of Brevibloc 100 mg/10 ml, injectievloeistof 10 mg/ml and Brevibloc 2.5 g/10 ml, injectievloeistof (concentraat) 250 mg/ml. Brevibloc is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current products are intended for parenteral use, no bioequivalence study is deemed necessary. The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates. Esmolol HCL Orpha 100 mg/10 ml, solution for injection, and Esmolol HCL Orpha 2500 mg/10 ml, concentrate for solution for infusion are medicinal products used only in hospitals. There is no need to have braille writing on the packaging.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The Board followed the advice of the assessors. Esmolol HCL Orpha 100 mg/10 ml, solution for injection, and Esmolol HCL Orpha 2500 mg/10 ml, concentrate for solution for infusion are authorised in the Netherlands on 2 January 2006. The member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Esmolol HCL Orpha 100 and Esmolol HCL Orpha 2500 with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 11 December 2006.

The first PSUR will cover a 3 year period starting from 11 December 2006 till 11 December 2009. The second PSUR will cover a 2 year period to coincide with the renewal. Hereafter, the PSURs will be submitted three-yearly.

The date for the first renewal will be: 11 December 2011.

The following post-approval commitments have been made during the procedure:

Quality - Medicinal product

- The MAH committed to provide validation data of the integrity of the container closure system (10mg/ml in vials) and data regarding the tightness of the container closure system during the manufacturing process.
- The MAH committed to provide a modification of the concentrate formulation in order to avoid any misidentification compared to Esmolol HCL Orpha 100.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N
The MAH committed to provide validation data of the integrity of the container closure system (10mg/ml in vials) and data regarding the tightness of the container closure system during the manufacturing process. This post-approval commitment has been fulfilled.	NL/H/0779/ 01-02	Post-approval commitment	NA	NA	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of the pharmaceutical forms.	NL/H/0779/ 001-002/IA/ 001	IA	NA	14-1-2008	Non approval	N
Change in the name and/or address of the marketing holder.	NL/H/0779/ 001-002/IA/ 002	IA	NA	14-1-2008	Non approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of the pharmaceutical forms.	NL/H/0779/ 001-002/IA/ 003	IA	19-3-2008	2-4-2008	Approval	N
Change in the name and/or address of the marketing holder.	NL/H/0779/ 001-002/IA/ 004	IA	19-3-2008	2-4-2008	Approval	N
Change in the name of the medicinal product for all countries except NL and UK.	NL/H/0779/ 001-002/IB/ 005	IB	19-3-2008	18-4-2008	Approval	N
Implementation of the final agreed SmPC texts by the CMDh with regard to peadiatric data assessed in the EU Worksharing project.	NL/H/0779/ 001-002/II/ 006	II	1-5-2009	13-7-2009	Approval	Y, Annex I
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.	NL/H/0779/ 002/IA/ 007	IA	5-10-2009	19-10-2009	Approval	N
Change in re-test period of the active substance, from 30 to 60 months.	NL/H/0779/ 001-002/IB/ 008	IB	13-1-2010	12-2-2010	Approval	N
Renewal of the marketing authorisation.	NL/H/0779/0 01-002/R/ 001	Renewal	12-4-2010	28-10-2010	Approval	Y, Annex II

Annex I – Changes in SPC (NL/H/779/001-002/II/006)

I RECOMMENDATION

Based on the review of the data on safety and efficacy, the variation application NL/H/0779/001-002/II/006 for Esmocard/Esmolol HCL Orpha (Esmolol hydrochloride), (1) in the short-term treatment of supraventricular tachycardia (except for pre-excitation syndromes), (2) for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative or other cicumstances where short-term control of the ventricular rate is desirable, (3) for tachycardia and hypertension during the perioperative phase and non-compensatory sinus tachycardia where in the physician's judgement the rapid heart rate requires specific intervention, for the following proposed changes:

"Change in the SPC following a consideration of the available paediatric data assessed in the EU Worksharing project of the CMD(h)."

is approvable.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

Change in the Summary of Product Characteristics following a consideration of the available paediatric data assessed in the EU Worksharing project of the CMD(h).

III SCIENTIFIC DISCUSSION

III.1 Summary of Product Characteristics

The proposed changes are in line with the recommendations of the EU Worksharing project of the CMD(h). A few minor changes were made by the RMS solely for aesthetic reasons.

The following changes were implemented for both strengths:

Red = deleted text
Blue = added text

Section 4.2 Posology and method of administration

(…)
Children ~~and adolescents~~
~~There is no experience in children and adolescents.~~ There are limited data available on the use of esmolol hydrochloride in children (see Sections 5.1 and 5.2). The available data do not support safety and efficacy in the paediatric population and therefore such use is not recommended.

Adolescents
There is no experience in adolescents.

Section 4.4 special warnings and precautions for use

(…)
Use in children
The safety and effectiveness of esmolol hydrochloride in children have not been established.

Section 5.1 Pharmacodynamic properties

(…)

Paediatric Use

An uncontrolled pharmacokinetic/efficacy study was undertaken in 26 paediatric patients aged 2-16 years with supraventricular tachycardia (SVT). A loading dose of 1000 micrograms/kg of esmolol was administered followed by a continuous infusion of 300 micrograms/kg/min. SVT was terminated in 65% of patients within 5 minutes of the commencement of esmolol.

In a randomised but uncontrolled dose comparison study, efficacy was assessed in 116 paediatric patients aged 1 week – 7 years with hypertension following repair of coarctation of the aorta. Patients received an initial infusion of either 125 micrograms/kg, 250 micrograms/kg, or 500 micrograms/kg, followed by a continuous infusion of 125 micrograms/kg /min, 250 micrograms/kg /min, or 500 micrograms/kg /min respectively. There was no significant difference in hypotensive effect between the 3 dosage groups. 54% of patients overall required medication other than esmolol to achieve satisfactory blood pressure control. No difference was apparent in this regard between the different dose groups.

Section 5.2 Pharmacokinetic properties

(…)

A pharmacokinetic study was undertaken in 22 paediatric patients aged 3-16 years. A loading dose of 1000 micrograms/kg of esmolol was administered followed by a continuous infusion of 300 micrograms/kg /min. The observed mean total body clearance was 119 mL/kg/min, the mean volume of distribution 283 mL/kg and the mean terminal elimination half-life 6.9 min, indicating that esmolol kinetics in children are similar to those in adults. However, large inter-individual variability was observed.

III.2 Package leaflet

Section 3 of the currently approved Patient Information Leaflet contains the following text: *"The safety and efficacy of Esmolol HCl Orpha was not established in children and adolescents."* This is equivalent to the agreed wording of section 4.4 of the SPC. Therefore, no changes to the Patient Information Leaflet are considered necessary.

IV OVERALL CONCLUSION

The variation is approvable. No changes to the PIL are required.

Annex II – Renewal of the marketing authorisation (NL/H/0779/001-002/R/001)

I RECOMMENDATION

Based on the review of the data submitted for this renewal application, the RMS is of the opinion that the benefit/risk balance of Esmolol 100 mg/10 ml and 2500 mg/10 ml (esmolol hydrochloride) NL/H/0779/001-002/R001 is positive under the condition that the 2500 mg/10 ml concentration for solution for infusion will be withdrawn from the market and replaced by the Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion since Decentralised Procedure NL/H/799/003/DC has been finalised. Renewal can be granted with unlimited validity.

II SCIENTIFIC DISCUSSION

1 Introduction

Esmolol is a fast and short-acting cardioselective β_1-blocker intended for parenteral use. Its primary applications are in the fields of diagnostics and emergency medicine.

Esmolol hydrochloride is indicated for the short-term treatment of supraventricular tachycardia (except for pre-excitation syndromes), 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.
It is also indicated for tachycardia and hypertension during the perioperative phase and non-compensatory sinus tachycardia where, in the physician's judgement the rapid heart rate requires specific intervention.
Esmolol is not intended for use in chronic settings.

The product is licensed through MR procedure with NL as RMS.

2 Module 1/GMP compliance statements

The MAH has submitted the adequated documentation to comply with the requirements for Module 1. It comprises amongst others:
- valid GMP compliance statements for all manufacturers responsible for batch release and production of the end product listed in the application form
- Declaration of the qualified person as regards the manufacturer of the active substance.
- Contact person for pharmacovigilance
- Contact person with the overall responsibility for product defects and recalls
- Contact person for scientific service in charge of information about the medicinal product

All outstanding issues were resolved at the end of the renewal procedure.

3 Quality

In accordance with the CMD(h) Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedure (version November 2008) a quality expert statement has been submitted for Esmolol confirming:
- That the products are in compliance with the requirements of Directive 2001/83/EC which obliges the MAH "*…. to take account of technical and scientific progress and introduce any changes…*".
- That all changes relating to the quality of the products have been made following applications for variations and that the product conforms to the current CHMP quality guidelines.

The currently authorised specifications for the active substance and the finished products with the qualitative and quantitative composition have been provided.

The remaining quality commitments have been included in section 6.

4 Clinical Efficacy and Safety

4.1 Clinical Efficacy

No new clinical data have become available during the previous period

4.2 Clinical Safety

4.2.1 Summary of cumulative experience 02.01.2006-11.12.2009

Summary of the Clinical overview:
As the application concerns a generic product, the overview consists of a review of literature published from 2004 to present (May 2010).
The reviewed clinical studies have clearly demonstrated that esmolol is effective in the approved indications at the doses recommended in the SPC. The principal adverse effect of esmolol is hypotension (incidence of 0 to 50%), which is frequently accompanied with diaphoresis. The incidence of hypotension appears to increase with doses exceeding 150 µg/kg/min and in patients with low baseline blood pressure. Hypotension infrequently requires any intervention other than decreasing the dose or discontinuing the infusion. Symptoms generally resolve within 30 minutes after discontinuing the drug. In surgical and ethical care settings where clinical conditions are rapidly changing, the pharmacokinetic profile of esmolol allows the drug to provide rapid pharmacological control and minimises the potential for serious adverse effects.
By today there is more than 25 years of clinical experience using esmolol and the efficacy and the safety of this drug is well documented in the published literature, demonstrating a well established use of esmolol as a cardioselective, ultra-short acting beta-receptor antagonist.

The proposed SPC is accurate. Based on the Clinical Overview and the postmarketing experience, the B/R of the product remains positive.

4.2.2 Report of Post Marketing Experience 02.01.2006-11.12.2009

World wide marketing authorisation status

The MAH stated that currently, Esmolol vials (100 mg/10 ml) and ampoules (2500 mg/10 ml) are registered in 20 countries of the EU and are in the process of registration in further three countries of the EU. The product is licensed through MR procedure with NL as RMS. Currently, the product is marketed in 13 countries.

However, from additional data submitted in Module 1 of the renewal application, it was concluded that Esmolol 100 mg/10 ml solution for injection is launched in Germany, Netherlands, Poland, and UK. In the next PSUR, the MAH should clearly describe the market status in the EU and clearly indicate which presentation(s) are launched.

Actions taken for safety reasons

In the PSUR, the MAH states that during the period covered by this review, no actions were taken for safety reasons by Regulatory Authorities or the MAH.

Furthermore, the MAH provided a list with outstanding issues and post approval commitments.

According to the request from one of the Member states the MAH committed to provide a modification of the concentrate formulation in order to avoid any misidentification compared to Esmolol 100 mg/10 ml. A Decentralised Procedure providing a modification of the concentrate formulation is was finalised on 9 September 2010.

Changes to the Reference safety information

The SPC is identical to the CDS and serves as the RSI. There are no changes to the Reference Safety Information.

Patient exposure

During the reporting period, the MAH delivered about 1,075 kg of esmolol. Assuming a DDD of 2.5 g as defined by the WHO, this equals to about 1,176 treatment years.

Adverse reactions

There were no case reports received during the entire reporting period.

Studies

Newly analyzed company-sponsored studies
There were no company-sponsored studies during the reporting period.

Targeted new safety studies planned, initiated or continuing during the reporting period.
There were no new safety studies planned, initiated or continued during the reporting period.

Published safety studies
During the entire reporting period, there was one study published regarding safety and efficacy of esmolol after surgery in infants and children ("The safety, efficacy, and pharmacokinetics of esmolol for blood pressure control immediately after repair of coarctation of the aorta in infants and children: a multicenter, double-blind, randomized trial.") (J Thorac Cardiovasc Surg. 2008 Aug; 136(2):321-8. Epub 2008 Jun 2. PMID: 18692637). In this study with 116 subjects, no serious adverse events occurred.

Overall safety evaluation

There are no reports concerning Interaction, Overdose, Abuse, Misuse, Application during Pregnancy or Lactation, Special Patient Groups, Long-Term Treatment, Medication or Dosage Errors. No Consumer Reports were received.
There is no late braking information. There are no reports of lack of efficacy.

4.2.3 Conclusion on Safety

No case reports of adverse drug reactions have been received.
From the data that are submitted, the benefit-risk balance of esmolol seems to remain positive.
A Clinical Overview to review the clinically relevant information on efficacy and safety of esmolol has been provided by the MAH.

5 Product Information

5.1 Summary of Product Characteristics

Initially, the MAH proposed no changes to the SmPC during this procedure. However, during the response phase, the MAH has harmonized the SmPC according to the recently approved final version of the SmPC for Esmolol Lyo (NL/H/0779/003, Day 210 at 9 September 2010). The Member states agree with these changes.

5.2 Package leaflet and user testing

The Package Leaflet (PL) is harmonised for this product during the initial MR procedure and was also tested during this procedure. No changes have been proposed initially by the MAH during the current procedure. . However, during the response phase, the MAH has harmonized the PL according to the recently approved final version of the PL for Esmolol Lyo (NL/H/0779/003, Day 210 at 9 September 2010). The Member states agree with these changes.

5.3 Labelling

The labelling fir this product was harmonised during the initial MR procedure. No changes were proposed by the MAH.

6 Remaining post-approval commitments to be fulfilled by the MAH

The following post-approval commitments are still outstanding:

Area[1]	Description	Due date[2]
Pharmacovigilance	The next PSUR should be submitted with data lock point December 2011.	February 2012.

[1]Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
[2]Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

From the data that are submitted, the benefit-risk balance of esmolol to remain positive. In line with the Harmonised Birth Date, the renewal date will be August 2010. This is agreed with by the MAH.

Renewal can be granted with unlimited validity under the condition that the 2500 mg/10 ml concentration for solution for infusion will be withdrawn from the market and replaced by the Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion since Decentralised Procedure NL/H/799/003/DC (the concentrate formulation which was brought to the market in order to avoid any misidentification) has been finalised.

List of abbreviations

CDS Core Data Sheet
DDD Defined Daily Dose
RSI Reference Safety Information
WHO World Health Organisation