CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Esmolol HCl LYO Orpha 2500 mg powder for 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/779/003/DC
Registration number in the Netherlands: RVG 106226

4 January 2011

Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB09
Route of administration:	parenteral
Therapeutic indication:	supraventricular tachycardia (except for pre-excitation syndromes), and 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; tachycardia and hypertension occurring in the perioperative phase and non-compensatory sinus tachycardia where, in the physician's judgement the rapid heart rate requires specific intervention.
Prescription status:	prescription only
Date of authorisation in NL:	8 November 2010
Concerned Member States:	Decentralised procedure with BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, SE, SI, SK, and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(3) Hybrid application

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 member states have granted a marketing authorisation for Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion, from Orpha-Devel Handels und Vertriebs GmbH. The date of authorisation was on 8 November 2010 in the Netherlands. The product is indicated for

- 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.
- tachycardia and hypertension occurring in the perioperative phase and non-compensatory sinus tachycardia where, in the physician's judgement the rapid heart rate requires specific intervention.

Esmolol hydrochloride is not intended for use in chronic settings.

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

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 half an hour. 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.

Rationale for a new pharmaceutical form
Esmolol hydrochloride 2500 mg powder for solution for infusion is a new pharmaceutical form of the registered product Esmolol hydrochloride Orpha 2500 mg/10 ml solution for infusion. Both products contain the same active ingredient as the originator product Brevibloc (Baxter B.V., the Netherlands). The registered and the originator product are concentrates containing several excipients and water, whereas Esmolol hydrochloride 2500 mg is a lyophilised powder of the pure active ingredient. All three products contain the same amount of active ingredient per package unit and need to be diluted or dissolved in appropriate solvents. The development of the new pharmaceutical form was in order to avoid confusions with Brevibloc® 100 mg/10 ml solution for injection and Esmolol hydrochloride 100 mg/10 ml solution for injection, which both are administered directly without dilution.
During mutual recognition procedure NL/H/779/001-002/DC in 2006 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. Therefore, the MAH committed to provide a modification of the concentrate formulation. This modified formulation is subject of this PAR.

Legal basis
This decentralized application for registration concerns a change to the existing marketing authorisation leading to a change or addition of a new pharmaceutical form (line-extension). The existing marketing authorisation is Esmolol HCl Orpha 2500 mg/10 ml concentrate for solution for infusion. The product is registered in the Netherlands under NL license RVG 31526, MAH Orpha-Devel Handels und Vertriebs GmbH (AT). The Netherlands was Reference Member State to obtain registration for this product in a number of European countries (NL/H/0079/002/MR). This application is in accordance with article 10(3) of Directive 2001/83/EC, a hybrid application.
The reference medicinal product is Brevibloc Injection 2500 mg/10 ml of MAH Baxter, which has been registered since 29 May 1991.

The marketing authorisation is granted based on article 10(3) 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 LYO Orpha 2500 mg powder for concentrate for solution for infusion is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product 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 this product, although the options to fulfill the commitment made during the procedure NL/H/0779/02 have been discussed with the RMS and the concerned CMS on 13 December 2007. It was decided that the MAH will develop a powder concentrate for solution for infusion.

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 this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

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 substance is presented as a racemic mixture. Polymorphism has not been reported.

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.

Manufacture
Esmolol HCl is prepared in a five step synthesis. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting material, solvents and reagents.

Quality control of drug substance
The drug substance specification has been established in-house by the active substance manufacturer and 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 drug substance specification have been provided for three full scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three full scaled batches stored at 25 °C/60% and 30°C/65% (up to 18 months) and 40 °C/75% RH (up to 6 months). The batches were adequately stored. The proposed re-test period of 2 years with no specific storage conditions was granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU respectively.*

Medicinal Product

Composition
The drug product is a lyophilised powder for concentrate for solution for infusion, containing 2500 mg Esmolol HCl per vial. No excipients are used, except water for injections during the manufacturing process. The powder is packaged in 50 ml uncoloured glass vials (type I Ph.Eur.) and closed with bromobutyl rubber stopper and blue aluminium seal. The excipient and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of the excipient is justified and its function explained. The development of the lyophilized powder has been explained. The choice of sterilisation by filtration has been justified because of to the well known instability of the active substance in aqueous solutions due to its chemical structure (ester compound). Compatibility of the product with common i.v. administration liquids has been established.

Manufacturing process
The active substance is dissolved in WFI (water for injection), filtered over two 0.22 µm filters and filled into vials. The vials are partly stoppered and loaded into the lyophilisation. After lyophilisation, the vials are closed and sealed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

Excipients
The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification, assay, impurities, uniformity of dosage units, water content, appearance of reconstituted solution, pH of reconstituted solution, sub-visible particulate matter, bacterial endotoxins and sterility. Release and shelf-life requirements are identical except for pH. The specification is acceptable.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scaled batches, demonstrating compliance with the release specification.

Compatibility
The compatibility of the drug with the primary container is guaranteed, as the material is the same as used for marketing of the concentrated product. Stability tests demonstrate that the glass does not affect the drug formulation. There is also no influence of the rubber stopper on the stability of the solution, as tested in in-use stability studies in the upside-down position.

Microbiological attributes
The test for microbial contamination is included as a part of finished product specification to check the microbiological quality of the drug product, since some excipients may tend to support microbial growth. The formulation is a lyophilized powder for single use, not containing preservatives. The sterility of the finished product is guaranteed because in the integral vial closure no microbial contamination may occur.

Stability tests on the finished product
Stability data on the product has been provided on three full scaled batches stored at 25 °C/60% RH (up to 18 months), 30 °C/65% RH (up to 12 months) and 40 °C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in uncoloured glass vials (type I Ph.Eur.) with bromobutyl rubber stoppers and aluminium flip-off seals. A

shelf-life of 30 months can be granted. No specific storage conditions are necessary. The MAH has committed to provide on-going stability data up to 30 months shelf-life.

In-use stability

Stability data has been provided demonstrating that the product remains stable for 24 hours following reconstitution in the appropriate i.v. solvents (glucose 5% solution, glucose 5% Ringer solution, glucose 5% + 0.9% NaCl solution, glucose 5% in Ringer Lactate solution, Ringer Lactate solution and + 0.9% NaCl) at a concentration of 50 mg/ml and at 10 mg/ml). In-use stability has therefore been demonstrated as 24 hours at room temperature for the reconstituted and the diluted product.

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.2 Non clinical aspects

This products is a 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 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.3 Clinical aspects

The development of the new pharmaceutical form was in order to avoid confusions with Brevibloc 100 mg/10 ml solution for injection and Esmolol hydrochloride 100 mg/10 ml solution for injection, which both are administered directly without dilution.

Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "*5.1.6 parenteral solutions*", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

Esmolol 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 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
During the procedure the product information of Esmolol HCl LYO has been brought in line with the innovator. The product information of the innovator was recently (April 2010) harmonised via a decentralised procedure (UK/H/3966/001/MR and UK/H/3967/001/MR, with BE, CZ, DE, DK, ES, FI, FR, HU, IE, LU, LI, NL, NO, PL, PT and SE as CMS).

Readability test
Esmolol HCl LYO 2500 mg powder for concentrate for solution for infusion is a new pharmaceutical form of the already registered product ESMOLOL HCL 2500 mg/10 ml concentrate for solution for infusion. In contrast to the concentrate for solution for infusion the powder does not contain any excipients and does not require any special storage conditions. In addition the powder is packed in a vial whereas the concentrate was packed in an ampoule. There is no difference in the indication and administration of both products.
For the registration of Esmolol HCL Orpha 2500 mg/10 ml concentrate for solution for infusion a readability study for the package leaflet was conducted. For Esmolol HCl LYO the package leaflet of the concentrate was amended only with regard to the name of the product, information on the pharmaceutical form and packaging. All other sections of the text remain the same. Therefore, an additional readability test for Esmolol HCl LYO 2500 mg powder for concentrate for solution for infusion is not considered necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of 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 product are intended for parenteral use, no bioequivalence study is deemed necessary.

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

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

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 essential similarity has been demonstrated for Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 9 September 2010. Esmolol HCl LYO Orpha 2500 mg powder for concentrate for solution for infusion is authorised in the Netherlands on 6 October 2010.

A European harmonised birth date has been allocated 31 December 1986 and subsequently the first data lock point for Esmolol is December 2011. The first PSUR will cover the period from approval to December 2011, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be August 2012.

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

Quality - medicinal product
- The MAH has committed to provide on-going stability data up to 30 months shelf-life.

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
PIL	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
WFI	Water for Injection

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 the procedure	Approval/ non approval	Assessment report attached