Paediatric Public Assessment Report

EU Worksharing Project- Assessment of Paediatric Data

Brevibloc
(esmolol hydrochloride)

Marketing Authorisation Holder's: Baxter

Rapporteur:	Finland
Co-Rapporteur:	United Kingdom
Paediatric Data Assessment Procedure start date:	17 February 2007
Date of this report:	20 May 2008

ADMINISTRATIVE INFORMATION

Currently approved indication(s):	short term control of pulse rate in supraventricular tachyarrhythmias, such as atrial flimmer, flutter and sinus tachycardia, and in situations where short acting beta-adrenergic blockade is needed - perioperative treatment of tachycardia and hypertension
Strength(s) and Pharmaceutical form(s) affected by this variation:	10 mg/ml solution for injection and 250 mg/ml concentrate for infusion
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TABLE OF CONTENT

I. RECOMMENDATION

Based on the review of the data on efficacy and safety of pediatric use of Brevibloc, the Rapporteur endorses the Applicant's conclusions, and considers that the data available is insufficient for recommendation the use in pediatric population (children with age less than 12 years). Due to insufficiency of the data, assessment of risk / benefit -ratio can not be made with justifications, and empirical basis for proper dosing instructions does not exist. However, since some safety data exist and no serious concerns have been identified, it is recommended to harmonise the SPC in EU by revising the sections 4.2, 4.3, 4.4, 5.1 and 5.2 of the SPC and removing strict contraindication of pediatric use of Brevibloc (in some countries).

II. EXECUTIVE SUMMARY

II.1 Introduction

Esmolol is a very short-acting beta-1 -selective blocker. It has a short elimination half-life (mean: 9 minutes; range: 4 to 16 minutes) and a total body clearance (285 ml/min/kg) of almost 3 times cardiac output and 14 times hepatic blood flow. The distribution half-life is approximately 2 minutes when given IV. After a bolus injection followed by a continuous infusion, onset of activity occurs within 2 minutes, and 90% of steady-state beta blockade within 5 minutes. Full recovery is observed 18 to 30 minutes after termination of infusion. The elimination of esmolol is independent from renal or hepatic function as it is metabolised by red blood cell cytosol esterases to an inactive metabolite and methanol.
Due to fast elimination, esmolol can be administered only intravenously. In most European countries Brevibloc is available in the following dosage forms:
- 10 mg/ml injection in 10 ml vials – a ready-to-use formulation;
- 250 mg/ml concentrate in 10 ml ampoule – a concentrate which needs to be diluted prior to use.

The indications of esmolol are:
- situations where a brief duration of adrenergic blockage is required, such as tachycardia and/or hypertension occurring in the perioperative period;
- for rapid control of ventricular rate in patients with atrial fibrillation, atrial flutter or sinus tachycardia, in perioperative, postoperative, or other circumstances where short term control of ventricular rate with a short acting agent is desirable.
Posology: In adults, bolus doses of 100 to 200 mg are effective in attenuating the adrenergic responses associated with tracheal intubation and surgical stimuli. For the control of supraventricular arrhythmias doses of up to 300 microgram/kg/min, administered by continuous intravenous infusion, are used.

The principal adverse effect of esmolol is hypotension, which is dose-related. It seldom requires any intervention other than decreasing the dose or discontinuing the infusion. Symptoms generally resolve within 30 minutes after discontinuing the drug.

Brevibloc is approved in Europe through national procedures, the first of which in September 1989.

II.2 Scope of the variation

This assessment of paediatric data has been made according to the EU Work Sharing Project to evaluate if Brevibloc (esmolol hydrochloride) injection (or infusion) is suitable for paediatric use also. The Applicant has carried out two pilot-type studies with children in addition to a literature review. The variation application is based on the application which the Applicant made to the FDA in 2003. In the US, no changes were made to the labelling as a consequence of the Paediatric Exclusivity procedure. It is not indicated in the US for the paediatric population.

III. SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A

III.2 Non clinical aspects

Not applicable.

III.3 Clinical aspects

III.3.1 Literature review on paediatric use of esmolol

Totally 4 different paediatric studies carried out with esmolol could be found in literature. All of them were uncontrolled and open, and had very limited number of children, totally 64.

Vincent *et al.* (1990) studied 7 young patients (7 to 19 years of age) who underwent repair of coarctation of the aorta, and who had post-operative hypertension not controlled by intravenous sodium nitroprusside. Esmolol was given as an adjunct to sodium nitroprusside. Maximal esmolol dosage ranged from 50 to 250 microgram/kg/min. A significant decrease in heart rate and arterial pressure were seen. No safety data were reported.

Wiest *et al.* (1991) investigated the pharmacokinetics and concentration-response relationships of esmolol in 20 children (2.5 to 16 years old) with known or suspected arrhythmias undergoing elective cardiac electrophysiologic testing. Esmolol was titrated until ß-blockade (>10% reduction in heart rate or mean arterial pressure) was seen. The mean maintenance dose needed for beta-blockade was 535 microgram/kg/min (ranging from 300 to 1000 microgram/kg/min), which is higher than in adults. There was no significant association between patient age and dose requirements for ß-blockade based on either body weight or body surface area.. The estimated pharmacokinetic parameters ($T_{½\ elim}$ and Clearance) were comparable to those seen in adults (4.5 ± 2.1 versus 3.69 ± 1.68 minutes and 312.2 ± 238.8 versus 363 ± 184 ml/kg/min). No information on adverse events was mentioned.

Trippel *et al.* (1991) evaluated the cardiovascular and antiarrhythmic effects of esmolol in 20 young patients (2 to 16 years). This publication is likely to be a second publication of the study performed by Wiest et al. (1991). It reports on the hemodynamic, electrophysiologic and adverse effects from this study. Two patients were mentioned to have biopsy evidence of myocarditis while receiving esmolol, but the publication does not provide a causality assessment. The publication concludes that esmolol's effects in children are similar to those in adults.

Cuneo *et al.* (1994) evaluated esmolol's PK and PD properties in 17 young patients (6 months to 14 years) undergoing cardiac catheterization. This study did not show any statistically significant age-related differences in the pharmacodynamics of esmolol. In contrast to the previous publications, this study found lower maintenance dose (118 ± 49 microgram/kg/min) for significant beta-blockade to be similar as in adults, but the half-life was shorter (mean half-life 2.88 ± 2.67 min.) than in adults (9.2 min.). The author hypothesizes that ketamine, which has positive chronotropic effects, may antagonise efficacy of esmolol. Side effects in the study were minimal; only one patient experienced nausea and vomiting.

Wiest *et al.*(1998) investigated the efficacy and disposition of esmolol in 20 children (1 month to 12 years of age) with acute hypertension after cardiac operation. The mean esmolol dose required to normalize blood pressure was 700 microgram/kg/min (range 300 to 1000 microgram/kg/min.), which was related to the degree of hypertension in these patients. The higher doses required in the patients undergoing coarctation repair may be related to their increased norepinephrine (noradrenaline) concentrations, increased clearance or both. An extreme short half-life (mean 2.7 min.) was estimated. No adverse effects were reported.

Assessor's comment
The studies published in literature are explorative and do not provide safety information.

In respect of pharmacokinetics, the kinetics of the parent drug (esmolol) in children are similar to those previously demonstrated in adults. However, one of the metabolic products is methanol, which is of some concern. No data have been provided regarding the rate of formation of methanol when esmolol is given to neonates, infants or children; and no information is provided on the rate of formation of formic acid from this methanol, or on the rate of elimination of the latter in the paediatric population. No information is provided on how the rate of handling of these moieties might change as liver enzyme systems develop with increasing age. In addition, no data have been provided regarding the blood levels of the other (acid) metabolite produced in the paediatric population when esmolol is given. This is of concern, particularly in regard to use in neonates in whom full renal function is not yet established as this moiety is renally eliminated. In this regard it should be noted that the UK SmPC advises caution in adults with impaired renal function as a consequence.

Brevibloc contains sodium acetate and glacial acetic acid as excipients. There is a concern regarding the effect and possible accumulation of these potentially toxic excipients when esmolol is administered at high doses in neonates, infants and children for prolonged periods.
The best quality pk data in children are from study 20,015-005. A summary of the results of this study would be of benefit to prescribers and should therefore be incorporated into the SmPC.

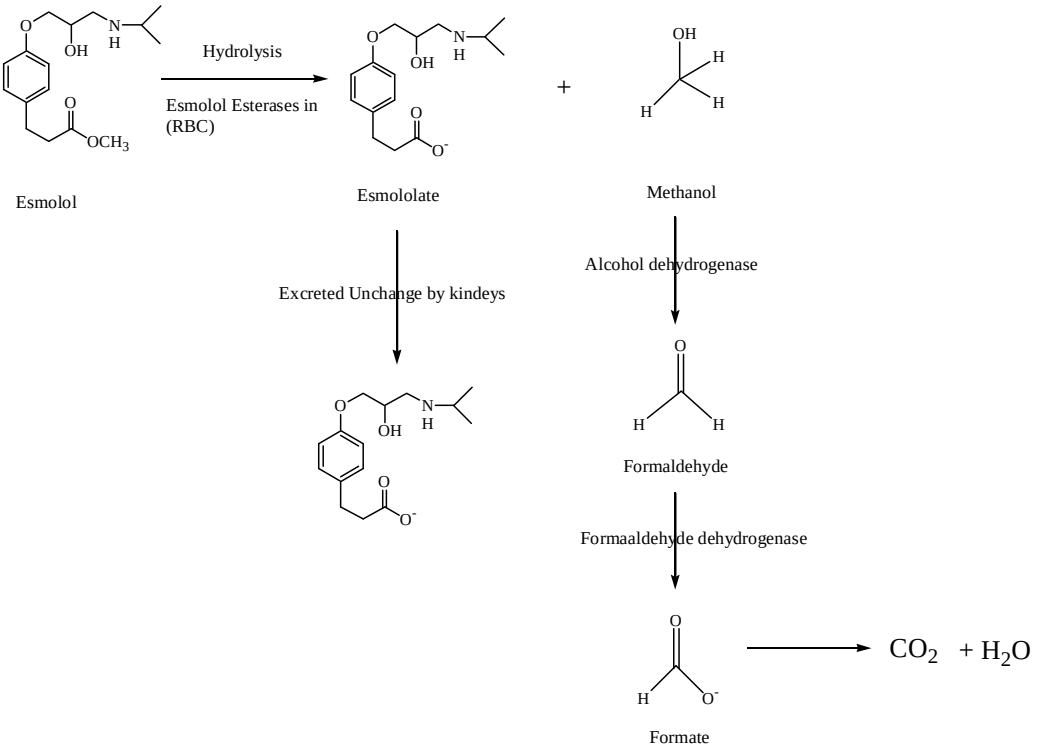
MAH Response:

We agree with the Assessor that there are no studies in published literature for the above items of concern, however we will try to respond with data that we could glean from our NDA studies.

MAH agrees that the pharmacokinetics of esmolol in pediatric population is similar to those of the adult population.

The metabolic pathway of esmolol in the human body has been well established. Esmolol is solely metabolized in the blood stream through hydrolysis by esterases in red blood cells to form the ASL 8123 (acid metabolite) and methanol. The breakdown rate of esmolol is equal to the rate of methanol and ASL formation in the same moles. ASL is excreted through the kidneys unchanged; however methanol in erythrocyte system is further metabolized in multiple steps to yield formate. Figure 1 is the metabolic pathway of esmolol in mammalians.

Figure 1. An illustration of the metabolic pathway of esmolol in mammalians



There is no literature available for the rate of methanol formation and the rate of formation of formic acid from methanol in neonates, infants or children, however, in our adult clinical studies, 300 mcg/kg/min of esmolol infused for 24 hours, the levels of methanol in blood were monitored by gas chromatography. Data gathered indicated low levels of methanol ranging between (2-7 mcg/mL); the limits of quantification and detection for the analytical method were 10 mcg/mL and 2 mcg/mL, respectively. Therefore in the pediatric studies, if the blood methanol levels were taken they would be below quantifiable limits. Data appears to suggest that methanol is rapidly absorbed and oxidized in the liver. Methanol blood levels approximated endogenous levels and were less than 2% of levels usually associated with methanol toxicity.

ASL 8123 does not have any pharmacological activity. It has low protein binding affinity, which is approximately 10%. As such, ASL 8123 is not accumulated in any organ system and is excreted unchanged through the kidneys.

To address the concern on the excipients, we would like to refer to our pediatric studies. In the pediatric studies, the infusions used were diluted from a 250-mg/mL ampul to 20 mg/mL and 10 mg/mL. The 250-mg/mL-ampul concentrate contained 17.0 mg sodium acetate and 0.00715 mL glacial acetic acid. Therefore the total amount of these excipients on the 10 mg/mL and 20 mg/mL dilutions would contain 0.68 - 13.6 mg (7-14%) of sodium acetate and 0.000286 – 0.000572 mg ($2.8 \times 10^{-3} – 5.7 \times 10^{-3}$ %)of glacial acetic acid, respectively.

The FDA Inactive Ingredient Database lists inactive ingredients for all USA approved products. If a particular inactive ingredient has been in an approved product of the same dosage form, the level of inactive ingredient is considered safe for use in a product with the same dosage form. In this database, it lists the approved levels for sodium acetate in IV infusion products at 1.70% to 59.40% and the approved levels of glacial acetic acid used for IV infusion products at levels of 0.05% to 0.44%. Therefore, we consider the levels that we have of these excipients in our product as safe.

MAH agrees to incorporate into the SmPC, a summary of the results of Peds study 20,015-005.

III.3.2 Clinical efficacy of Brevibloc in pediatric population

The Sponsor has carried out two clinical trials in pediatric populations.

Study 20,015-004 was a randomized, double-blind dose-response study comparing efficacy of 3 doses of esmolol (125, 250 or 500 microgram/kg/min) in reducing and controlling intraoperative and postoperative hypertension. No placebo or other active antihypertensive control group was included in the study design. 118 children (neonates to 6 years of age) underwent repair of coarctation of the aorta. Blood pressure - lowering effect was measured 5 minutes after start of esmolol infusion. PK sampling was taken up to 15 minutes. After 15 minutes the investigators were allowed to maintain, titrate or discontinue the blinded esmolol, or switch to open-label esmolol.
Systolic blood pressure decreased in all 3 groups with no statistically significant difference between the groups (in change from baseline). There was also no statistically significant difference across groups in either the percentage of patients meeting rescue criterion or patients receiving rescue therapy.

Study 20,015-005 was an uncontrolled PK study of a 1000 microgram/kg loading dose followed by a 15 minute infusion of 300 microgram/kg/min in children (2-12 years) and adolescents (12-16 years) with supraventricular tachycardia (SVT). Twenty-seven patients were treated with esmolol, of which 26 were included in the efficacy analysis and 22 in the PK analysis. SVT was terminated within 10 minutes (mean time of 2 minutes) after esmolol start in 65% of treated patients. No efficacy conclusion can be drawn from this uncontrolled study.

Assessor's comment
A clear dose-response could not be find in dose interval of 125 – 500 µg/kg/min. Esmolol had surprisingly weak antihypertensive effect in pediatric patients undergoing intrathoracic surgery.

MAH Response:

MAH agrees with the Assessor's comment.

III.3.3 Clinical safety

Patient exposure

In studies found in literature, totally 64 children or adolescents were exposed to esmolol. In two studies carried out by the Sponsor 145 children and adolescents received esmolol

Adverse events

Reported adverse effects in Studies 20,015-004 and 20,015-005 are reviewed individually in the variation application and data from both studies are pooled. Most of the safety findings appear consistent with current esmolol labelling for adults, or are known to be related the surgical operations performed.

Serious adverse events

Two children reported to have myocarditis in one published study. However, the authors do not discuss about causality of the findings and esmolol treatment. No drug-related adverse effects was reported in the two studies carried out by the Sponsor.

Assessor's comment:
No dose-response can be found in scarce safety data reported. Only few unexpected adverse effects, which can not be explained by beta-adrenergic blockade, were seen in the trials reported. All trials were short-term. The Post Marketing Suspected Adverse Reaction data are of poor quality and reports are very few, being limited to 16 in number. In some cases, the actual adverse reaction itself is not recorded. 7 of the 16 reports are from patients aged less than 3 months of age, and 3 of these reports were of extravasation of the drug.

MAH Response:

MAH has verified 15 cases of post marketing pediatric adverse reaction reports against its database from international birth date of December 31, 1986 to May 1, 2008.

The FDA Adverse Event Reporting System (AERS) search which includes all sources – US & foreign database from the Brevibloc marketing approval date of December 31, 1986 through October 19, 2007 had 13 reports for Pediatrics (0-16 years of age).

Assessor's comment:
The MAH has provided narratives for all paediatric cases received through 01 May 2008 and listings from the FDA AERS search. Point resolved.

RESPONSES FROM THE MEMBER STATES

French response

We globally endorse the rapporteurs' conclusions, especially with regard to the request for supplementary information proposed by the co-rapporteur. However we have the following comments.

As stated by both rapporteurs, taking into account the provided PK, efficacy and safety data, a contra-indication in paediatric patients below the age of 12 years is not justified. However, these data are inadequate to support an indication in the paediatric population.

Furthermore, France wants to stress that the studied population doesn't correspond to the real population likely to benefit from this treatment. Indeed, in paediatric population, the occurrence of supraventricular tachycardia (SVT) is mainly observed in children below the age of one year and the children enrolled in study 20,01-005 didn't apparently suffer from underlying cardiopathies for which negative inotropic and hypotensive effects could be at risk. Moreover, notably in France, the surgical repair of coarctation of the aorta is more often performed before the age of three months. Thus, contrary to the co-rapporteur, France considers that the efficacy data from study 20,015-005 and 20,015-004 are too sparse and not of any aid for prescribers and should not be added in section 5.1 of the SPC. Nevertheless, in respect of PK data, France agrees with the text proposed by the co-rapporteur provided that the inter-individual variability is mentioned."

Irish response

The Irish Medicines Board agrees with the overall conclusion and benefit – risk assessment of the Rapporteurs' that the data available is insufficient for the recommendation of the use of esmolol in the paediatric population (children with age less than 12 years).

Czech Republic response

Brevibloc has been studied in limited studies in children. The available data do not support safety and efficacy in the paediatric population and esmolol is not recommended for use in children.

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the review of the data on efficacy and safety of pediatric use of Brevibloc, the Rapporteurs endorse the Applicant's conclusions, and considers that the data available is insufficient for recommendation the use in paediatric population (children with age less than 12 years).
Due to insufficiency of the data, assessment of risk / benefit -ratio can not be made with justifications, and empirical basis for proper dosing instructions does not exist.

V. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RAPPORTEURS

1. The MAH should provide any data which might exist regarding the genetics and development of enzymes responsible for methanol oxidation and formic acid elimination in the newborn, infants and children and any data which exist, on the effect on blood methanol and formic acid levels of administering esmolol at doses up to 250 micrograms/kg/min in neonates, infants and children for prolonged periods, for example up to 24 hours.

MAH Response:

We tried our best to find data requested by the Rapporteurs and there are no available data from literature on the genetics and development of enzymes responsible for methanol oxidation and formic acid

elimination in the newborn, infants and children and the effect on blood methanol and formic acid levels of administering esmolol at doses up to 250 micrograms/kg/min in neonates, infants and children for prolonged periods.

The maximum dose of esmolol that will be exposed to newborn, infants and children at dose of 250 micrograms/kg/min for 24 hour equates to 350 mg/kg (1.05 mmol/kg). When esmolol is metabolized to the above-mentioned dose, the resultant acid moiety (ASL-8123) and methanol will be one molar each of moieties (1.78 m mol/kg of ASL-8123 and 10.9 mmol/kg of methanol).

The enzymes responsible for the oxidation of methanol are alcohol dehydrogenase and formaldehyde dehydrogenase. In humans, methanol is primarily eliminated by oxidation and only 2% of a 50-mg/kg dose of methanol is excreted unchanged by the lungs and kidney (Leaf & Zatman, 1952). The small excretion of unchanged methanol was also observed in methanol-poisoned subjects in whom the renal and pulmonary excretory clearances of methanol were 1 and 6 ml/min, respectively (Jacobsen et al., 1982a, 1983b).

The elimination of formaldehyde in many species, including primates, is extremely rapid with a half-life of approximately 1 min (McMartin et al., 1979). Toxic concentrations of formate (7-8 mM) were detected within 30 min of ingestion in a human case of formaldehyde poisoning, confirming the rapid metabolism of formaldehyde to formate in humans (Eells et al., 1981b). However, consumption of these solutions by alcoholics is still widely seen, exposures of 1-2 weeks being associated with blood methanol concentrations ranging from 1000 to 2000 mg/liter (31-62 mmol/litre) (Heath, 1983).

Since the levels of methanol generated is about 11 mmol/kg for the esmolol dosing it is reasonable to conclude that the methanol content as a metabolite of esmolol is safe.

Assessor's comment:
The response from the MAH is acceptable.

2 The MAH should provide any data which exist regarding the levels of the acid metabolite which are generated in the newborn, infants and children when esmolol at doses up to 250 micrograms/kg/min is given for prolonged periods, for example up to 24 hours.

MAH Response:

There is no available data on studies from literature on the levels of the acid metabolite generated in the newborn, infants and children when esmolol at doses up to 250 micrograms/kg/min is given for prolonged periods.

The maximum dose of esmolol that will be exposed to newborn, infants and children at dose of 250 micrograms/kg/min for 24 hour is 350 mg/kg (1.05 mmol/kg). When esmolol is metabolized to at the above-mentioned dose, the resultant acid moiety (ASL-8123) and methanol will be one molar each of moieties (1.78 mmol/kg of ASL-8123 and 10.9 mmol/kg of methanol). There is no accumulation of ASL in the body and it is excreted unchanged in the urine.

Assessor's comment:
The point is resolved.

3. There is concern regarding the effect and possible accumulation of the excipients sodium acetate and acetic acid when esmolol is administered at high doses in neonates, infants and children for prolonged periods. The MAH should provide any data which exist regarding the levels of acetate and effect on acid-base balance in newborn, infants and children when esmolol is administered at doses up to 250 micrograms/kg/min for periods up to 24 hours.

MAH Response:

We were not able to find available data from literature on the effect and possible accumulation of the excipients sodium acetate and acetic acid when esmolol is administered at high doses in neonates, infants and children for prolonged periods.

To address the concern on the excipients, we would like to refer to our pediatric studies. In the pediatric studies, the infusions used were diluted from a 250-mg/mL ampul to 20 mg/mL and 10 mg/mL. The 250-mg/mL ampul contained 17.0 mg sodium acetate and 0.00715 mL glacial acetic acid. Therefore the total amount of these excipients on the 10 mg/mL and 20 mg/mL dilutions would contain 0.68 - 13.6 mg (7-14%) of sodium acetate and 0.000286 – 0.000572 mg ($2.8 \times 10^{-3} – 5.7 \times 10^{-3}$ %)of glacial acetic acid, respectively.

The FDA Inactive Ingredient Database lists inactive ingredients for all USA approved products. If a particular inactive ingredient has been in an approved product of the same dosage form, the level of inactive ingredient is considered safe for use in a product with the same dosage form. In this database, it lists the approved levels for sodium acetate in IV infusion products at 1.70% to 59.40% and the approved levels of glacial acetic acid used for IV infusion products at levels of 0.05% to 0.44%. Therefore, we consider the levels that we have of these excipients in our product as safe.

Assessor's comment:
The point is resolved.

4. The MAH should provide narratives for the post-marketing suspected adverse reaction reports.

Assessor's comment:
The point is resolved.

5. The presented data are considered to be insufficient to support an indication for *Brevibloc* in the paediatric population.

Assessor's comment:
The point is resolved.

6 The assessment report should be published on the HoA website.
Assessor's comment:
The point is resolved.

ANNEX I:
PROPOSED CHANGES TO THE SPC ANNOTATED WITH THE RAPPORTEUR'S COMMENTS AFTER EACH SECTION

The following changes were proposed by the MAH:

Initial SmPC	**Proposed Revision**
4.3 Contraindications	
Children less than 12 years old	~~Children less than 12 years old~~
4.4 Special warning and precautions for use	
~~The efficacy and safety of Brevibloc in children has not been studied.~~	***Esmolol is not recommended for use in children below the age of 12 years due to insufficient safety and/or efficacy data.***

The recommendations form the Rapporteurs are as follows. It is agreed that the contraindication is removed. It is also acknowledged by the Rapporteurs that the EU SmPC Guideline is for the moment under revision regarding the paediatric data.

Section 4.2

In order to comply with the latest EU SmPC Guidelines the following text should be inserted into this Section.

Use in the elderly:

Special studies in the elderly have not been conducted. However, analysis of data from 252 patients over 65 years of age indicated that no variations in pharmacodynamic effects occurred as compared with data from patients under 65.

The following text should be inserted into this Section:-

Use in children

There are limited data available on the use of Brevibloc 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.

Section 4.4

In order to comply with the latest EU SmPC Guidelines the following text should be deleted from this Section:-

Use in the elderly:

Special studies in the elderly have not been conducted. However, analysis of data from 252 patients over 65 years of age indicated that no variations in pharmacodynamic effects occurred as compared with data from patients under 65.

Use in children

The safety and effectiveness of Brevibloc in children have not been established.

Section 5.1

A summary of the efficacy data from studies 20,015-004 and 20,015-005 should be inserted into Section 5.1 of the SmPC as follows:-

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 300micrograms/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

A summary of the pharmacokinetic data from study 20,015-005 should be inserted into Section 5.1 of the SmPC as follows:-

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 119mL/kg/min, the mean volume of distribution 283mL/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.