Public Assessment Report for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Metoprolol succinate

Selokeen ZOK controlled release tablets

NL/W/0037/pdWS/001

Rapporteur:	The Netherlands
Finalisation procedure (day 120):	7 June 2013
Date of finalisation of PAR	9 September 2013
Update of the PAR	17 December 2013

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Metoprolol
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	C07AB02
Pharmaceutical form(s) and strength(s):	Controlled release tablets 23.75 mg; 47.5 mg; 95 mg; 190 mg

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2, 5.1 and 5.2.

Summary of outcome

☐ No change

☒ Change

☒ New study data: section 5.1 and 5.2

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: section(s) 5.1 and 5.2

☒ New indication: section 4.1 and 4.2

SmPC for prolonged release metoprolol tablets

Naformátováno: zvýrazněné

4.1 Indication

Children and adolescents 6-18 years of age
Treatment of hypertension

4.2 Posology and method of administration
Children and adolescents
The recommended initial dosage in hypertensive patients ≥6 years is 0.5 mg/kg Seloken ZOK (0.48 mg/kg metoprolol succinate) once daily. The final dose administered in milligrams should be the closest approximation of the calculated dose in mg/kg. In patients not responding to 0.5 mg/kg, the dose can be increased to 1.0 mg/kg (0.95 mg/kg metoprolol succinate), not exceeding 50mg (47.5 mg metoprolol succinate). In patients not responding to 1.0 mg/kg, the dose can be increased to a maximum daily dose of 2.0 mg/kg (1.9 mg/kg metoprolol succinate). Doses above 200 mg (190 mg metoprolol succinate) once daily have not been studied in children and adolescents.
Efficacy and safety of use in children < 6 years have not been studied. Therefore, SelokenZOK is not recommended in this age group.

*Appropriate amendments to the posology should be made for tartrate prolonged release products.

Naformátováno: zvýrazněné

5.1 Pharmacodynamic properties
In 144 paediatric patients (6 to 16 years of age) with primarily essential hypertension, Seloken ZOK has been shown in a 4-week study to reduce systolic blood pressure with 5.2 mmHg with 0.2 mg/kg (p=0.145), 7.7 mmHg for 1.0 mg/kg (p=0.027) and 6.3mmHg for 2.0 mg/kg doses (p=0.049) with a maximum of 200mg/day compared to 1.9 mmHg on placebo. For diastolic blood pressure, this reduction was 3.1 (p=0.655), 4.9 (p=0.280), 7.5 (p=0.017) and 2.1 mmHg, respectively. No apparent differences in blood pressure reduction were observed based on age, Tanner stage, or race.

5.2 Pharmacokinetic properties
The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

Package Leaflet for prolonged release metoprolol tablets

Naformátováno: zvýrazněné

1. WHAT <PRODUCT> IS AND WHAT IT IS USED FOR
Children and adolescents from 6-18 years:
For treating high blood pressure (hypertension)

3. HOW TO TAKE <PRODUCT>
Children and adolescents:

High blood pressure: For children aged 6 years and older, the dose depends on the child's weight. The doctor will work out the correct dose for your child.

The usual start dose is 0.5 mg/kg once a day but not exceeding 50 mg. The dose will be adjusted to the nearest tablet strength. Your doctor may increase the dose to 2.0 mg/kg depending on blood pressure response. Doses above 200 mg once daily have not been studied in children and adolescents.

Seloken ZOK tablets are not recommended for children under 6 years.

II. INTRODUCTION

The MAH Astra Zeneca submitted 2 completed paediatric studies for metoprololsuccinate controlled release in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

(A short critical expert overview has also been provided.)

The MAH stated that the submitted paediatric studies do influence the benefit risk for metoprolol succinate CR and that there is a consequential regulatory action necessary.

The MAH proposed the following regulatory action:

4.2 Posology and method of administration
Children and adolescents
The recommended initial dosage in hypertensive patients ≥6 years is 1.0 mg/kg metoprolol CR/ZOK, not exceeding 50 mg, once daily given approximated by dose strength. In patients not responding to 1.0 mg/kg, the dose can be increased to a maximum daily dose of 2.0 mg/kg. Doses above 200 mg once daily have not been studied in children and adolescents.
Efficacy and safety of use in children < 6 years have not been studied. Therefore, metoprolol CR/ZOK is not recommended in this age group.

5.1 Pharmacodynamic properties
In 144 paediatric patients (6 to 16 years of age) with essential hypertension, metoprolol CR/ZOK has been shown in a 4-week study to reduce placebo-corrected systolic blood pressure for the 1.0 and 2.0 mg/kg doses (4 to 6 mmHg). For diastolic blood pressure, there was a placebo-corrected reduction for the 2.0 mg/kg dose (5 mmHg) and a dose-dependent reduction for the dose range 0.2, 1.0 and 2.0 mg/kg. No apparent differences in blood pressure reduction were observed based on age, Tanner stage, or race.

5.2 Pharmacokinetic properties
The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

Product background
Selokeen ZOK™ (metoprolol succinate) is a β1-selective (cardioselective) adrenoceptor blocking agent formulated to provide controlled and predictable release of metoprolol for once-daily administration. In adults, approved therapeutic indications include hypertension, angina pectoris, symptomatic chronic heart failure, disturbances of cardiac rhythm, myocardial infarction, functional heart disorders and migraine prophylaxis.

Condition to be treated – hypertension in children
The majority of hypertensive children are adolescents with mild to moderate hypertension. In adolescents, the etiology of hypertension is usually unknown (essential hypertension) but is often associated with obesity. Most hypertensive children are evaluated and managed as outpatients. Hypertensive children less than 12 years of age often have hypertension secondary to renal or renal vascular disease, coarctation of the aorta or endocrinopathies. Severe hypertension requiring in-patient care is rare in any age group. The prevalence of hypertension in schoolaged children and adolescents is generally estimated to between 1% and 5% (Andersson 2007) although prevalence estimates may be influenced by methodological issues such as the definition of hypertension and the method of blood pressure measurement.

Current management of hypertension in children
Angiotensin-converting enzyme inhibitors and calcium channel antagonists have been described as preferred therapies in children (Robinson et al 2005). It is expected that these agents will still be used for hypertensive children. There is no expectation that prescription patterns would shift preferentially towards a significantly increased use of beta-blockers in children.

Current status
The two AstraZeneca sponsored studies investigating the efficacy of Seloken ZOK (metoprolol succinate) in hypertensive children discussed in this assessment report were the basis of the documentation on Seloken ZOK in paediatric subjects submitted as a type II variation to a majority of EU Member States with Seloken ZOK approved, in 2008. Dosing recommendations in hypertensive children has therefore already been assessed and granted in the following Member States: BE, CZ, DK, EE, FI, DE, IS, LT, LU, LV, NL, RO, SE and SK.
The application is still pending in NO and PL and has been rejected in AT, BG, CY and ES.
The application was not submitted in HU.

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical study(ies)

In the clinical studies prolonged release tablets were used

III.2 Non-clinical aspects

N/A

III.3 Clinical aspects

III.3.1 1. Introduction

The MAH submitted a report for:

- **Study 307A**: A Dose Ranging, Safety and Tolerability of Toprol-XL® (metoprolol succinate) Extended-release Tablets (metoprolol CR/XL) in Hypertensive Pediatric Subjects: A Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel-group Study
- **Study 307B**: A Safety, Tolerability and Pharmacokinetics Study of Toprol-XL® (metoprolol succinate) Extended-release Tablets (metoprolol CR/XL) in Hypertensive Pediatric Subjects: A Multicenter, Open-Label Extension of Protocol 307A

The MAH submitted an extended synopsis for:

- **Study 307A;**
- **Study 307B.**

2. Clinical studies

III.3.2 Study 307A

- **Description**
  A Dose Ranging, Safety and Tolerability of Toprol-XL® (metoprolol succinate) Extended-release Tablets (metoprolol CR/XL) in Hypertensive Pediatric Subjects: A Multicenter, Double-blind, Placebo-controlled, Randomized, Parallel-group Study

- **Methods**

  - Objective(s)

  To evaluate the dose range, safety, and tolerability of Torpol-XL in hypertensive pediatric patients.

- Study design

This was a multicenter, international, double-blind, placebo-controlled, randomized, parallel-group study.

- Study population /Sample size

The most important inclusion criteria were an age of 6 to 16 years, and have hypertension that is either:

- Newly diagnosed and untreated with a mean sitting SBP or DBP above the 95th percentile for height-adjusted charts for age and gender on 3 consecutive office visits (Visits 1, 2, and 3), or
- Previously diagnosed and currently treated with antihypertensive therapy at Visit 1 and a mean sitting SBP or DBP above the 95th percentile at Visit 3 (off treatment)

A total of 204 patients were enrolled in the study, 144 were randomized to study treatment (n=24, 47, 23, and 50 to placebo, 0.2, 1.0, and 2.0 mg/kg, respectively), 140 were included in the ITT population, and 133 completed the study. A total of 30 sites in the United States and Latin America enrolled patients.

- Treatments

The study included a screening visit; a 1- to 2-week single blind, placebo run-in period; and a 4-week double-blind treatment period. At the end of the placebo run-in period, eligible patients with BP measurements in the qualifying range (sitting SBP or DBP at or above the 95th percentile using height adjusted charts for age and gender) were randomized in a 1:2:1:2 ratio to receive once daily, oral doses of placebo, Toprol-XL 0.2 mg/kg, Toprol-XL 1.0 mg/kg, or Toprol-XL 2.0 mg/kg. Toprol-XL doses of 12.5 to 200 mg were used to approximate the target doses. Patient in the 1.0 mg/kg and 2.0 mg/kg group were up-titrated after 1 week and 2 weeks, respectively, to target dose. At the end of the 4-week double-blind period, all eligible patients had the option to enter the open-label extension study (307B).

- Outcomes/endpoints

Primary variable: Sitting SBP determined at trough at Visit 7 (Week 4). The primary measure of effect was the placebo-corrected change from baseline to the end of treatment (Week 4, Visit 7).

The following secondary variables were evaluated in this study:

- Placebo-corrected change from baseline to end of treatment in trough sitting DBP
- Change from baseline at each post-baseline visit for trough sitting SBP and DBP, and trough standing SBP and DBP
- Percentage of responders at Week 4, defined as trough sitting SBP and DBP less than the 95th percentile

- Statistical Methods

The primary analysis used an intention-to-treat (ITT) population which included all patients who received at least 1 dose of study medication and had baseline and at least 1 post-baseline measurement. For this analysis, missing data were imputed using a last observation carried forward (LOCF) approach.
A simple linear regression analysis was performed on the placebo-corrected change from baseline to Week 4/LOCF in sitting SBP and sitting DBP with dose ratio as the explanatory variable. Given TOPROL-XL doses of 0.2, 1.0, and 2.0 mg/kg, the dose ratio of 1:5:10 was considered a continuous variable for analysis. The slope of the regression line was tested to see if it differed from zero using an F-test at a 0.05 significance level.

- Pharmacokinetic Measurements

Although pharmacokinetics were not a planned objective of this study, a 1.5 mL blood sample was to be collected at Visit 7 into a heparinized Vacutainer tube and obtained at 24 hours (±2 hour) following the last dose of study medication (ie, trough measurement) for determination of plasma metoprolol concentrations.
Plasma samples collected for determination of metoprolol concentrations were analyzed by MDS Pharma Services (St. Laurent, Quebec, Canada). Plasma concentrations of metoprolol were determined using a high performance liquid chromatographic mass spectrometric method. The lower limit of quantitation (LLQ) was 1.0 ng/mL

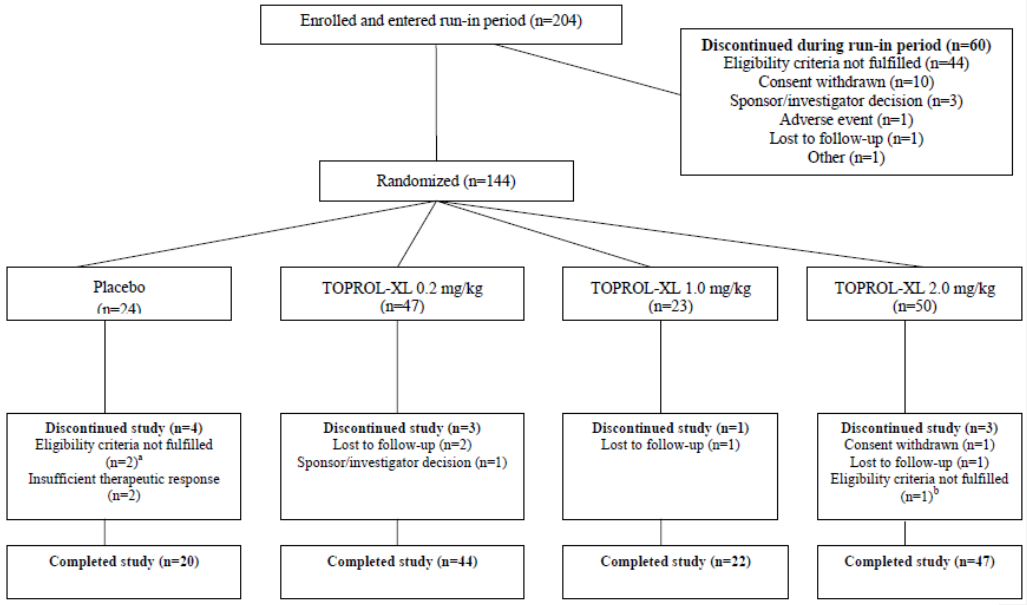
Results

- Recruitment/ Number analysed

144 were randomized at 28 centers to receive double-blind treatment with placebo (n=24), TOPROL-XL 0.2 mg/kg (n=47), TOPROL-XL 1.0 mg/kg (n=23), or TOPROL-XL 2.0 mg/kg (n=50) using a 1:2:1:2 randomization schedule. Sixty patients (29%) discontinued the study during the placebo run-in period, primarily due to eligibility criteria not fulfilled (n=44, 22%).

Despite randomization to a treatment group, 2 patients were excluded from all efficacy and safety analysis populations. One patient in the TOPROL-XL 2.0 mg/kg group was never dispensed double-blind study medication because he was discontinued when the use of a disallowed concomitant medication (PAXIL® [paroxetine HCl]) was discovered. The second patient (TOPROL-XL 0.2 mg/kg group) was lost to follow-up after randomization and did not have any post-randomization data.

Figure 1: Study disposition



The proportion of patients who discontinued study drug early for any reason was comparable in the 3 TOPROL-XL groups (4% to 6%) and lower than that in the placebo group (17%). Lost to follow-up was the most common reason for discontinuation of study drug among the 3 TOPROL-XL groups (n=4) (figure 1).

Of the 144 randomized patients, 142 patients were included in the safety population. For the ITT population, data from 23, 45, 23, and 49 patients in the placebo, TOPROL-XL 0.2 mg/kg, TOPROL-XL 1.0 mg/kg, and TOPROL-XL 2.0 mg/kg groups, respectively, were analyzed for efficacy. For the PP population, data from 19, 39, 21, and 43 patients, respectively, were analyzed for efficacy.

- Baseline data

The 4 treatment groups were generally well matched with respect to demographic and baseline characteristics. Across all patients, the mean age was 12.5 years, all patients were within the stipulated age range of 6 to 16 years, and approximately 40% were ≤12 years of age. The 140 patients comprising the ITT population were equally distributed between younger vs older than Tanner Stage 3 (Table 1).

Within each of the TOPROL-XL groups, at least two-thirds of patients were male (69% to 78%), while the proportion of males and females was more evenly distributed within the placebo group (57% vs 44%). Approximately one-quarter of all patients were black (20% to 33% within each treatment group). The mean BMI at screening ranged from 30 to 32 kg/m2 across the 4 treatment groups and approximately 75% of patients were overweight.

Table 1: Baseline data of study 307A

		TOPROL-XL treatment groups			
	Placebo (N=23)	0.2 mg/kg (N=45)	1.0 mg/kg (N=23)	2.0 mg/kg (N=49)	All patients (N=140)
Age (years), n (%)					
≤12	9 (39.1)	20 (44.4)	7 (30.4)	22 (44.9)	58 (41.4)
>12	14 (60.9)	25 (55.6)	16 (69.6)	27 (55.1)	82 (58.6)
Age, years					
Mean (SD)	12.3 (3.2)	12.5 (2.7)	13.5 (2.5)	12.2 (2.8)	12.5 (2.8)
Median	13.0	13.0	13.0	13.0	13.0
Range	6.0 - 16.0	6.0 - 16.0	6.0 - 16.0	6.0 - 16.0	6.0 - 16.0
Sex, n (%)					
Male	13 (56.5)	35 (77.8)	16 (69.6)	34 (69.4)	98 (70.0)
Female	10 (43.5)	10 (22.2)	7 (30.4)	15 (30.6)	42 (30.0)
Race, n (%)					
Black	5 (21.7)	9 (20.0)	6 (26.1)	16 (32.7)	36 (25.7)
Nonblack	18 (78.3)	36 (80.0)	17 (73.9)	33 (67.3)	104 (74.3)
Caucasian	18 (78.3)	34 (75.6)	17 (73.9)	31 (63.3)	100 (71.4)
Asian	0	1 (2.2)	0	2 (4.1)	3 (2.1)
Other	0	1 (2.2)	0	0	1 (0.7)

Tanner stage, n (%)										
≤3	10	(43.5)	27	(60.0)	10	(43.5)	23	(46.9)	70	(50.0)
>3	13	(56.5)	18	(40.0)	13	(56.5)	26	(53.1)	70	(50.0)
Weight at randomization (kg), n (%)										
≤30	1	(4.3)	1	(2.2)	1	(4.3)	1	(2.0)	4	(2.9)
>30 to ≤45	2	(8.7)	4	(8.9)	2	(8.7)	5	(10.2)	13	(9.3)
>45 to ≤60	2	(8.7)	5	(11.1)	2	(8.7)	6	(12.2)	15	(10.7)
>60 to ≤80	7	(30.4)	15	(33.3)	7	(30.4)	14	(28.6)	43	(30.7)
>80	11	(47.8)	20	(44.4)	11	(47.8)	23	(46.9)	65	(46.4)
Weight at randomization, kg										
Mean (SD)	84.0	(35.3)	79.9	(29.4)	83.7	(31.1)	79.7	(31.2)	81.1	(31.1)
Median	77.0		72.0		80.0		76.0		77.5	
Range	26.0 - 162.0		25.0 - 154.0		23.0 - 160.0		22.0 - 155.0		22.0 - 162.0	
Height at screening, cm										
Mean (SD)	159.0	(18.7)	161.2	(16.8)	162.2	(12.9)	157.4	(16.0)	159.7	(16.2)
Median	161.0		161.0		164.0		160.0		161.5	
Range	114.0 - 184.0		115.0 - 192.0		118.0 - 180.0		121.0 - 181.0		114.0 - 192.0	
BMI percentile at screening, n (%)										
<95th percentile	6	(26.1)	11	(24.4)	7	(30.4)	12	(24.5)	36	(25.7)
≥95th percentile	17	(73.9)	34	(75.6)	16	(69.6)	37	(75.5)	104	(74.3)
BMI at screening, kg/m^2										
Mean (SD)	32.1	(9.6)	30.0	(7.9)	30.8	(9.4)	31.3	(10.8)	30.9	(9.4)
Median	30.8		29.0		29.7		29.9		29.6	
Range	18.5 - 51.4		16.4 - 46.4		15.0 - 49.1		15.0 - 69.9		15.0 - 69.9	
Time since diagnosis of hypertension (years)[a], n (%)										
<1	13	(56.5)	23	(51.1)	13	(56.5)	27	(55.1)	76	(54.3)
1 to 2	6	(26.1)	11	(24.4)	4	(17.4)	13	(26.5)	34	(24.3)
2 to 3	1	(4.3)	3	(6.7)	5	(21.7)	5	(10.2)	14	(10.0)
3 to 4	2	(8.7)	1	(2.2)	0		2	(4.1)	5	(3.6)
4 to 5	0		3	(6.7)	0		0		3	(2.1)
≥5	1	(4.3)	4	(8.9)	1	(4.3)	2	(4.1)	8	(5.7)

Type of hypertension[b], n (%)										
None	0		1	(2.2)	1	(4.3)	0		2	(1.4)
Diastolic only	2	(8.7)	3	(6.7)	2	(8.7)	6	(12.2)	13	(9.3)
Systolic only	11	(47.8)	34	(75.6)	10	(43.5)	30	(61.2)	85	(60.7)
Diastolic and systolic	10	(43.5)	7	(15.6)	10	(43.5)	13	(26.5)	40	(28.6)
Previously treated hypertension[c], n (%)										
No	20	(87.0)	34	(75.6)	19	(82.6)	35	(71.4)	108	(77.1)
Yes	3	(13.0)	11	(24.4)	4	(17.4)	14	(28.6)	32	(22.9)
Sitting SBP										
Mean (SD)	132.7	(8.9)	131.4	(9.0)	135.0	(8.0)	130.6	(9.6)	131.9	(9.1)
Median	133.3		131.3		136.0		130.0		132.0	
Range	110.7 - 152.7		108.0 - 153.3		117.3 - 148.0		98.0 - 151.3		98.0 - 153.3	
Sitting DBP										
Mean (SD)	81.4	(9.0)	76.3	(7.7)	81.0	(7.5)	76.7	(9.1)	78.0	(8.6)
Median	80.0		78.0		82.0		78.0		80.0	
Range	66.0 - 99.3		57.3 - 90.7		62.0 - 91.3		60.0 - 92.0		57.3 - 99.3	

- Pharmacokinetics

Trough plasma samples were collected from 104 patients in the active treatment groups in Study 307A approximately 24 hours after the last dose of Toprol-XL. Of these, 37 samples were unevaluable, including 35 (27 from the Toprol-XL 0.2 mg/kg group) with concentrations below the lower limit of quantitation (LLQ). As shown in Table 2, the evaluable trough plasma levels of metoprolol increased with increasing target dose (in mg/kg).

Table 2 : Summary of though plasma metoprolol concentration (ng/ml) by target dose group (all randomized patients with evaluable data in study 307A

	Toprol-XL target dose group		
	0.2 mg/kg	**1.0 mg/kg**	**2.0 mg/kg**
N	12	15	40
Mean (SD)	4.5 (2.9)	13.9 (14.3)	28.3 (34.5)
Median	3.3	10.8	13.4
Range	1.3 – 15.7	1.3 – 57.1	1.4 – 167.0

SD standard deviation.

- Efficacy results

Effect from baseline

Statistically significant reductions from baseline in sitting SBP and sitting DBP were observed at Week 4/LOCF in the 1 and 2 mg/kg dose groups, whereas no significant reductions in BP were observed at Week 4/ LOCF in the lowest dose group. (Figure 2 and 3).

Figure 2: Changes from baseline to Week 4/LOCF in sitting SBP and DBP with pairwise comparisons to placebo (307A ITT population)

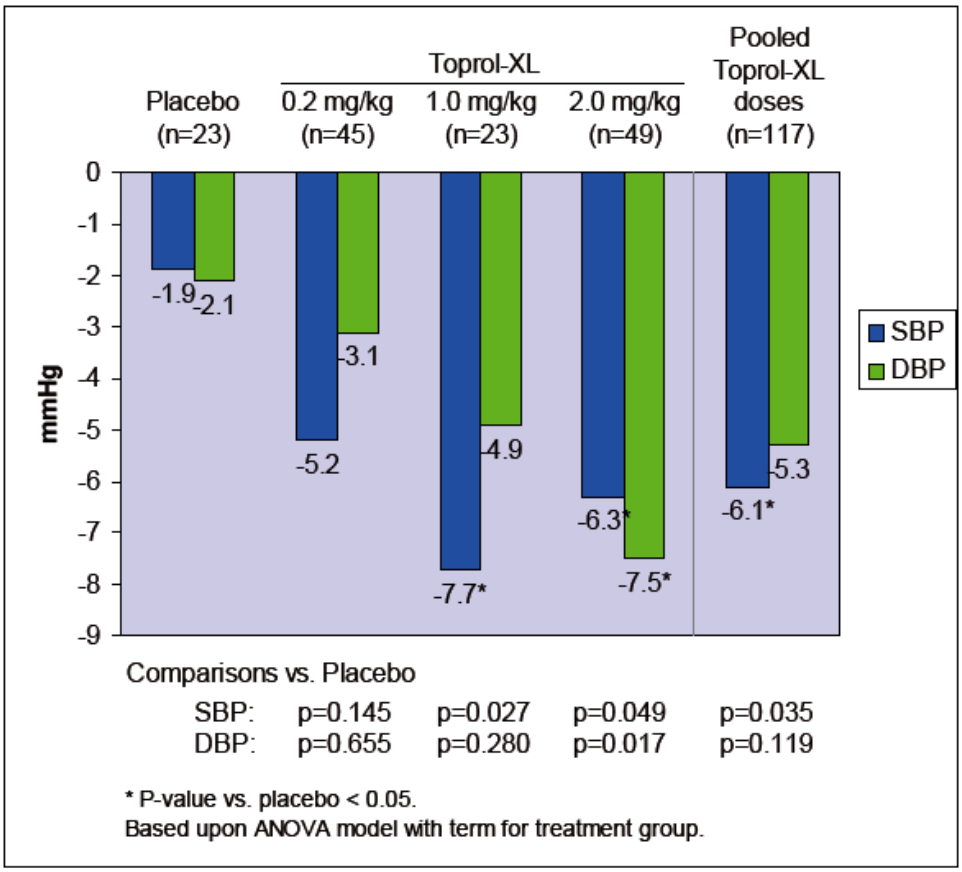
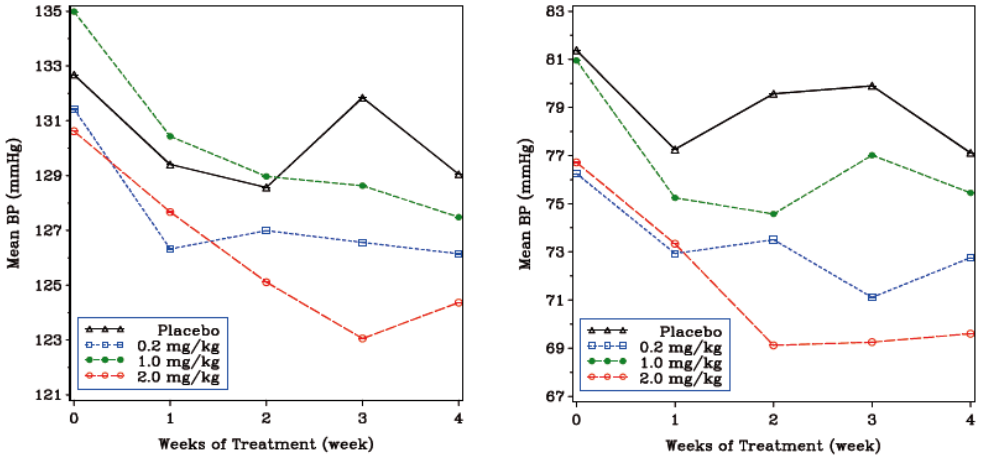


Figure 3: Mean changes over time for sitting SBP and DBP (Study 307A, ITT population**)**



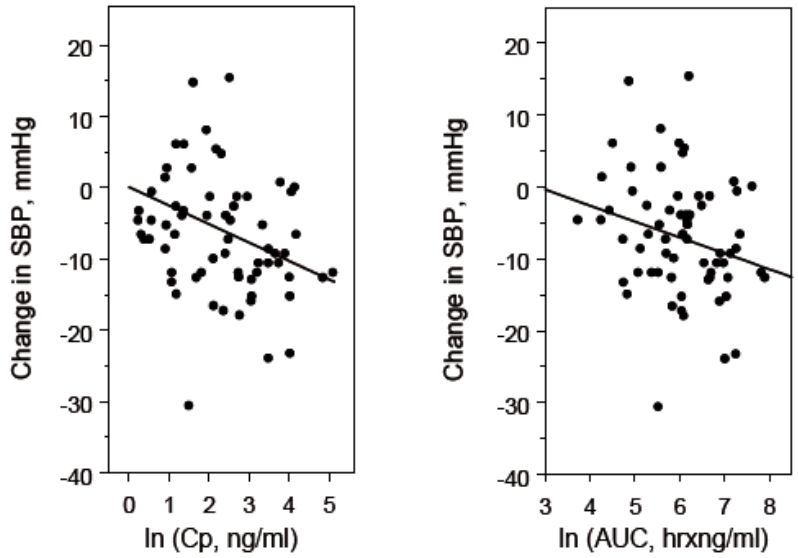
Dose response

The dose response for placebo-corrected changes from baseline in sitting SBP (primary efficacy endpoint) was not significantly different from zero (slope = -0.110, p = 0.573), while a significant dose response was found for placebo-corrected changes from baseline for DBP (slope = -0.485, p = 0.016) (Figure 4).

The finding of a non-significant dose response is likely attributable to a smaller than expected SBP response in the high-dose group (see also figure 2). According to the MAH, there is no apparent biological plausibility to the observation that high-dose Toprol-XL would induce a greater DBP than SBP reduction, and they suspect that the apparently spurious SBP results may be a chance finding. According to the applicant the following reasons could have attributed to these findings:

- the shorter exposure time of patients taking the high dose compared to those taking the low and medium doses, due to the titration steps in the study design (included for safety reasons): the high-dose group received the target dose for only 2 weeks as compared with 2 to 3 weeks for the medium-dose group and 4 weeks for the low-dose group.
- a substantial reduction in SBP even at the chosen low and medium doses, resulting in a flat dose-response curve.

Figure 4: Relationship between change in SBP and trough plasma levels, Cp (p<0.05)or AUC(0–24) (P<0.05) (line generated from model fitting), Studies 307A and 307B



Responders

Nearly one half of the patients in each of the 3 Toprol-XL treatment groups (43% to 47%), as compared to one quarter of patients in the placebo group (26%), were responders at Week 4, defined as sitting SBP and DBP below the 95th percentile (adjusted for height, age, and gender). This was 47%, 44% and 47% for the lowest, mid and highest dose groups, respectively. This particular analysis was not performed using LOCF and assumed that patients with missing BP values at Week 4 were non-responders.

Subgroups

According to the MAH, there was no trend suggesting that the between-group differences in mean reductions in sitting SBP and DBP at Week 4/LOCF differed as a function of age (≤12 years, >12 years), Tanner stage (≤3, >3), or race (black, nonblack). The results for gender, type of hypertension, prior antihypertensive use, and baseline body mass index (BMI) were more variable and meaningful conclusions cannot be drawn due to the small subgroup sample sizes.

- Safety results

Safety results are discussed under study 307B

III.3.3 Study 307B

- **Description**

  A Safety, Tolerability and Pharmacokinetics Study of Toprol-XL® (metoprolol succinate) Extended-release Tablets (metoprolol CR/XL) in Hypertensive Pediatric Subjects: A Multicenter, Open-Label Extension of Protocol 307A

- **Methods**

  - Objectives

  To evaluate the pharmacokinetics and long-term safety and tolerability of Toprol-XL in hypertensive patients.

  - Study design

  This study was begun as a 16-week, multicenter, open-label study to determine the safety, tolerability, and pharmacokinetics of Toprol-XL in hypertensive pediatric patients, and was later amended (because of changes to the Written Request) to include 52 weeks of treatment.

  - Study population /Sample size

  A total of 138 unique patients entered Study 307B (16 week) and/or Study 307B (52 week): 15 were enrolled under both protocols, 37 were enrolled under just the 16-week protocol, and 86 were enrolled under just the 52-week protocol. Of these 138 unique patients, 137 had participated in Study 307A. A total of 45 patients completed 16 week and 81 completed 52 week.

  - Treatments

  The suggested starting dose of study drug was 25 mg, although a starting dose of 12.5 mg was available and could be used based on investigator discretion. The dose was to be increased every 2 weeks in increments of 25 mg or 50 mg, based on tolerability, until BP was controlled as judged by the investigator, or the dose reached 200 mg. If BP was still not controlled at the maximum dose of 200 mg/day, then other antihypertensive medications could be used concomitantly.

  - Pharmacokinetics

  Pharmacokinetic measurements for inclusion in the serial PK portion of the study were to be performed in up to 30 patients, equally divided between the age groups 6 to 12 years and 13 to 16 years. Once enrollment of patients for each age group reached 15, further enrollment or the serial PK evaluation into that age group was to be stopped. Patients who consented to serial PK testing had blood samples obtained at Visit 1 or at any time during the study. A 48-hour washout period prior to sampling was required for all patients, including patients who entered the 52-week study and then decided to participate in the serial PK portion of the study.
  Patients who participated in both the 16-week and 52-week studies and had serial PK blood samples obtained during the 16-week study were not eligible for further PK blood sampling in the 52-week study. The following PK parameters of metoprolol were to be estimated: area under the concentration-time curve from hour 0 to the last quantifiable concentration (AUCt), area under the concentration-time curve from zero to infinity (AUC), maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and terminal phase halflife (T1/2).
  In addition, all patients were to have a trough blood sample obtained 24 hours after the last dose of open-label TOPROL-XL for determination of plasma metoprolol concentrations with the exception of patients who participated in the serial PK portion of the study and had blood sampling performed at Visit 18.
  For patients participating in the serial PK portion of the study, blood samples (1.5 mL) were to be collected into heparinized Vacutainer tubes and obtained at Hour 0 (predose) and at 1, 2, 3, 4, 6, 8, 10, and 24 hours after administration of a single 25 mg dose of TOPROL-XL following a 48-hour

washout period. After the last blood sample was obtained, the patient was to start/resume the prescribed dose of TOPROL-XL he/she was receiving prior to PK sampling.
Plasma samples collected for determination of metoprolol concentrations were analyzed by MDS Pharma Services (St. Laurent, Quebec, Canada). Plasma concentrations of metoprolol were determined using a high performance liquid chromatographic mass spectrometric method. The lower limit of quantitation (LLQ) was 1.0 ng/mL.

- Outcomes/endpoints

This study was designed to examine the pharmacokinetic profile and long-term safety of TOPROL-XL in pediatric patients with hypertension and therefore no single variable was considered primary for this study.

- Statistical Methods

Data were analyzed using observed data. In some instances, additional analyses impute for missing values by using the last value carried forward (LOCF). An LOCF approach was used to determine the percentage of responders at Weeks 16, 32, and 52 because of the large number of patients who did not have data within the time windows for each of these time points.

➢ Results

- Pharmacokinetics

Of the 152 patients in this study, 126 patients had trough plasma samples collected approximately 24 hours after the last dose of Toprol-XL. Of these, 27 patients had trough plasma concentrations that were below the LLQ. The data for the 99 patients with evaluable concentration values are summarized in Table 3. As shown, trough plasma concentrations in tended to increase with increasing dose (in mg), although the results were not always monotonic.

The PK profile of metoprolol following a 25 mg dose of TOPROL-XL was generally comparable among younger (Tanner Stage .3) and older (Tanner Stage >3) patients. Over the age ranges studied, no correlation between Cmax or AUCt and age was observed (7.48 ng/mL and 109.24 ng.hr/mL in patients with a Tanner Stage of .3, respectively compared with 7.00 ng/mL and 95.78 ng.hr/mL in patients with a Tanner Stage >3, respectively). No correlation between body weight and C_{max} and AUCt estimates was observed across the range of body weights examined (44 to 155 kg), nor were any differences in PK parameter estimates noted between males and females in this study.
Dose-normalized Cmax and AUC_t were within the ranges observed in healthy young adult subjects. In addition, Tmax (6.1 hours and 8.8 hours for patients with a Tanner stage .3 and >3, respectively) was similar to that observed in adults. These results suggest that the PK profile of metoprolol among pediatric and adolescent hypertensive patients is comparable to that in adults.

Table 3: Summary of trough plasma metoprolol concentration (ng/ml) by final daily dose in pooled 16-week and 52-week studies (all treated patients with evaluable data in study 307B)

	Final Toprol-XL dose (mg)							
	12.5	**25**	**50**	**75**	**100**	**150**	**175**	**200**
N[a]	1	13	17	10	13	13	1	31
Mean (SD)	1.98 (--)	7.31 (6.85)	16.73 (16.46)	10.22 (11.84)	11.03 (10.49)	32.53 (24.39)	17.3 (--)	98.18 (414.63)
Median	--	4.75	13	6.71	6.31	34.3	--	16.8
Range	--	1.43 – 21.7	1.3 – 63.4	1.02 – 41.4	2.15 – 37.6	1.51 – 66.7	--	1.81 - 2330

[a] Eight patients had plasma concentrations above the LLQ during both the 16-week study and the 52-week study and both samples were included in the analysis of trough plasma metoprolol concentrations.
SD standard deviation.

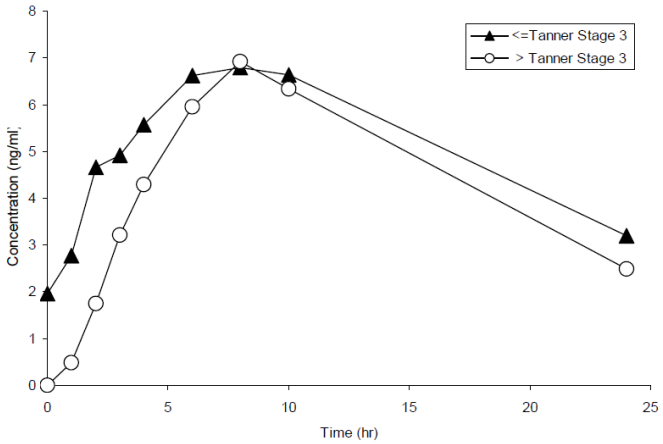
The PK profile of metoprolol following a 25 mg dose of TOPROL-XL was generally comparable among younger (Tanner Stage .3) and older (Tanner Stage >3) patients. Over the age ranges studied, no correlation between Cmax or AUCt and age was observed (7.48 ng/mL and 109.24

ng.hr/mL in patients with a Tanner Stage of .3, respectively compared with 7.00 ng/mL and 95.78 ng.hr/mL in patients with a Tanner Stage >3, respectively) (See Table 4 and Figure 5). No correlation between body weight and C_{max} and AUCt estimates was observed across the range of body weights examined (44 to 155 kg), nor were any differences in PK parameter estimates noted between males and females in this study.
Dose-normalized Cmax and AUC_t were within the ranges observed in healthy young adult subjects. In addition, Tmax (6.1 hours and 8.8 hours for patients with a Tanner stage .3 and >3, respectively) was similar to that observed in adults. These results suggest that the PK profile of metoprolol among pediatric and adolescent hypertensive patients is comparable to that in adults.

Table 4. PK parameters estimated for metoprolol following a 25 mg dose of Toprol-XL. (Mean ± s.d. , tmax median and range)

Parameter	*Tanner stage <3* *n = 13*	*Tanner stage > 3* *n = 14*
AUCt (ng.n/ml)	109 ± 127	95.8 ± 112
Cmax (ng/ml)	7.48 ± 6.35	7.00 ± 7.29
Tmax (h)	6.0 (0.0 - 10.0)	8.2 (0.9 - 24)

Figure 5: Mean plasma concentration of metoptolol versus time following dosing with TOPROL-XL 25 mg (patients with evaluable serial PK samples)



- Population Pharmacokinetic Analysis.

The concentration-time profile of metoprolol after oral administration of Toprol-XL was defined in Study 307B in 27 hypertensive pediatric patients with evaluable serial PK samples.
Since trough plasma samples were collected in other patients at the end of Studies 307A and 307B, the population analysis approach is used to further explore the pharmacokinetics of metoprolol in these hypertensive pediatric patients. The objectives of this population analysis were:

1. To identify the structure of a compartmental model and characterize the population pharmacokinetics of metoprolol in this hypertensive pediatric patient population after administration of Toprol-XL in Study 307A and Study 307B.
2. To estimate population PK and PK/PD parameters, including typical values and random sources (inter-individual and residual) of variability
3. To identify and estimate the effects of individual-specific demographic covariate factors as predictors of inter-individual variability in PK and PK/PD relationships
4. To generate population and individual Bayesian estimates of PK parameters in all patients and individual plasma concentrations over the last dosing interval for patients in Study 307A to obtain their derivative parameters (Cmax and AUC(0–24))

5. To explore the relationships between measured trough metoprolol plasma concentrations or individual Bayesian-estimated PK parameters (Cmax and AUC(0-24)) and hemodynamic effects in the changes of DBP, SBP, and HR in patients in Study 307A.

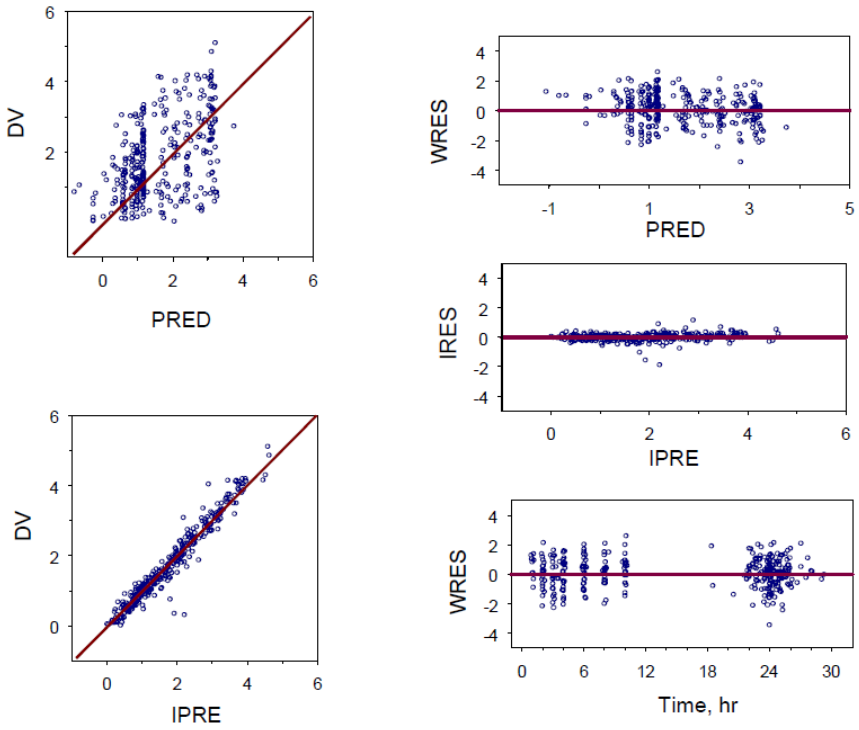
The population PK dataset contained 592 ln-transformed metoprolol plasma concentration measurements obtained from 120 unique patients after oral administration of Toprol-XL in Study 307A or Study 307B . Sixty-seven patients were from Study 307A and 109 patients, including 56 patients who had participated in Study 307A and 53 additional patients, were from Study 307B. Twenty-seven of these 109 patients from Study 307B provided serial samples and 24 patients among them also provided 1 or more trough levels. The remaining 93 of the 120 patients with PK data provided 1 to 3 trough levels. This dataset was used to identify the structural and base population models, evaluate the impact of patient demographic covariates on model parameters, and finalize the optimal population PK model for metoprolol.
The natural logarithms of measured metoprolol plasma concentrations were used as the dependent variable (DV) in NONMEM dataset for PK modeling. Records with missing concentrations, or incomplete date/time of last dosing or plasma sampling were excluded from the datasets. Records with below LOQ were treated as zero for descriptive statistics and treated as missing concentrations in the NONMEM dataset.

Validation of the final population PK model was based solely upon its predictive performance for all patients in the dataset. The goodness-of-fit of the final model was evaluated graphically by comparing population and individual predictions of metoprolol concentrations with observed metoprolol concentrations along the line of unity, and by visual inspection of the following plots of population-weighted residuals (WRES) for the final population model:
1. Population-weighted residuals (WRES) versus population-predicted concentrations (PRED)
2. WRES versus time after first drug administration in each patient
3. WRES versus all covariates evaluated.
WRES were generally expected to be distributed homogenously around zero for PRED, time after administration, and covariates. For those 27 patients with serial samples, goodness-of-fit of the plasma concentration-time profile for each individual was visually inspected. The linear relationship between their AUClast values from the observed data and those from the simulated data (final model) was examined.

The structural model was unable to be clearly identified by visual inspection of individual metoprolol plasma concentration-time profiles of patients with serial blood sampling schedules in normal or logarithmical scales. Concentration-time profiles revealed metoprolol plasma concentrations increased slowly and steadily to their maximal concentrations at about 8 to 10 hours post dosing, and dropped at the last data point sampled at 24 hours. Based on the nature of the sustained-release dosage form, the disposition pharmacokinetics of metoprolol after immediate-release dosage forms, and preliminary estimates of the apparent elimination half-lives from the terminal phase of these plasma concentration-time profiles in this study, one could conclude that Toprol-XL exhibited a flip-flop absorption kinetics.

Compared to the adult mean parameter values published (clearance of 118.4 L/hr, volume of distribution of 720 L, and half-life of 3 to 4 hours; Plosker and Clissold 1992) as well as the preliminary results from noncompartmental analysis of those 27 patients with serial samples in Study 307B, the PK parameter estimates in the base model (clearance of 247 L/hr, volume of distribution of 841 L, and half-life of 3.5 hr) appeared to be reasonable. Goodness-of-fit of the base model is shown in Figure 6. Plots of weighted residuals versus time after the first administration of metoprolol show no trends over time, indicating that PK parameters are time invariant.
Homogenous distributions of weighted residuals along population-predicted concentrations suggest that PK parameters are not concentration dependent, indicating apparent linear pharmacokinetics.

Figure 6: Assessment of the Goodness-of-fit of the base model



The final model best describing the data was a 2-compartment model with first-order flip-flop absorption and an absorption lag time bearing an age effect on Q and a BSA effect on CL/F. The change in MOF of the final model relative to the base model was –36.17 (–53.92 in the base model versus –90.09 in the final model). The following covariates did not affect metoprolol pharmacokinetics: gender, race, ideal body weight, and metoprolol dose. No covariate was found to exhibit impact on V2, V3, Ka, and absorption lag time of metoprolol. AGE had no effect on metoprolol CL/F.

The conclusion from the population pharmacokinetic/pharmacodynamic analysis were:

A 2-compartment PK model with first-order elimination and flip-flop first-order absorption and lag time was identified to best fit metoprolol concentration-time data obtained from these pediatric hypertensive patients.

• Typical values of metoprolol CL/F, V2/F, V3/F, Q/F, Ka, and Tlag1 were 227.5 L/hr, 96.1 L, 620 L, 675 L/h, 0.0467 hr–1, and 0.853 hr, respectively. These values were generally in the same range as those reported in adults.

• Sex, race, ideal body weight, and Toprol-XL dose have no significant effect on metoprolol pharmacokinetics.

• No covariate impacts V2, V3, Ka, or the absorption lag time of metoprolol. Age has no effect on metoprolol CL/F, and body weight has no effect on Q/F.

• Metoprolol CL/F increases linearly with body weight. The clinical implications for hemodynamic effects of the impact of body weight on CL/F of metoprolol are limited, as the dosage of Toprol-XL should be titrated from a low dose at weekly (or longer) intervals to a higher and tolerable dose until optimum BP reduction is achieved. Therefore, no dose adjustment based upon body weight is necessary. Q/F is proportional to age; however, the increase in Q/F with age is not clinically relevant.

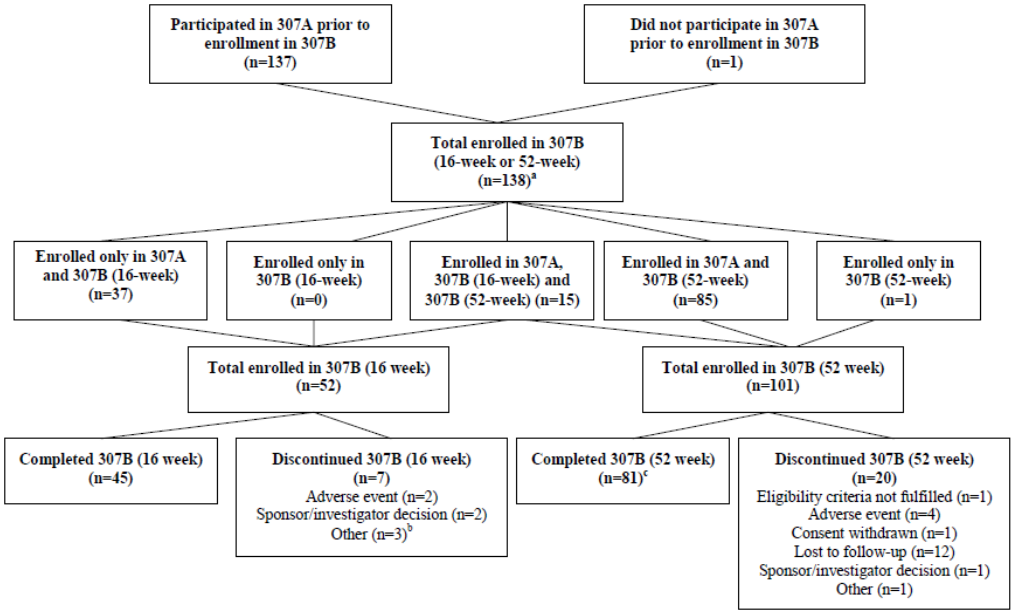
• Weak, but statistically significant, relationships were found between the hemodynamic effects (DBP, SBP, and HR) and some measures of metoprolol exposure (trough plasma levels, Cmax and

AUC(0–24)). This suggests that the oncedaily regimen of Toprol-XL provides appropriate therapeutic coverage in this pediatric patient population, because their hemodynamic measurements were performed at trough time and greater hemodynamic effects can be potentially achieved when higher Toprol-XL doses are given.
• Because of high variability in the hemodynamic data, goodness-of-fit of the PK/PD models was generally poor and the resulting parameter estimates were not considered to be very reliable. Extrapolation of these model parameters in the clinic for dose adjustment is not recommended.
• The clinical implications of the hemodynamic effects of the impact of body weight on CL/F of metoprolol are limited, because of the poor relationship in PK/PD, and the fact that dosages of Toprol-XL are usually titrated from a low dose at weekly (or longer) intervals to a higher and tolerable dose until optimum BP reduction is achieved. Therefore, no dose adjustment based upon body weight is recommended.
• No covariate was identified to exhibit any impact on the parameters delineating the PK/PD relationship between metoprolol exposure and hemodynamic effects.
• Metoprolol Cmax or AUC(0–24), generated from the population PK analysis, did not offer a stronger correlation with hemodynamic effects than did trough plasma levels.

- Recruitment/ Number analysed

A total of 52 patients were enrolled in the original 16-week study and all took at least 1 dose of study medication. Forty-five (87%) patients completed the 16-week study, 12 of whom entered the 52-week study. An additional 3 patients were discontinued from the 16-week study to enroll into the 52-week study.
A total of 101 patients were enrolled in the amended 52-week protocol, 81 of whom completed the study. The most common reason for discontinuation was lost to follow-up (n=12). One patient was excluded from the all treated patients population because although he received study medication, his data could not be verified due to failure on the part of the investigator to sign data queries. Thus, a total of 100 patients are included in the all treated patients population in the 52-week study.

Figure 7: Patient disposition



- Baseline data

Patients enrolled in the 52-week study were primarily male (66%), older than 12 years of age (69%), and nonblack (77%). The mean age of all patients was 13.1 years, and approximately 60%

of patients had a Tanner Stage of >3, with 37% classified as Tanner Stage 5. The mean BMI at screening was 31.4 kg/m^2 and 64% of patients were overweight (BMI ≥95th percentile adjusted for age and gender).

- Efficacy results

Most patients (78%) in 307B (52 week) had treatment with Toprol-XL initiated at a dose of 12.5 to 25 mg. By Week 16, the dose of Toprol-XL had been titrated to an average of 96.6 mg and at Week 52/LOCF, patients were being maintained on an average daily dose of 112.3 mg. Beginning at Week 16 and continuing throughout the study, the mean daily mg/kg dose of Toprol-XL remained stable at 1.2 to 1.3 mg/kg. A total of 16 patients received treatment with a concomitant antihypertensive to maintain BP control during the 52-week study. The most frequently used antihypertensive medications were lisinopril and hydrochlorothiazide.
Approximately 40% of patients (41 of 99) entered the 52-week study as treatment responders; the majority of these patients had received double-blind treatment (Toprol-XL or placebo) in Protocol 307A prior to enrollment in 307B (52 week), a small minority of whom had also received open-label treatment in 307B (16 week). Over 60% were responders at all timepoints following open-label treatment with Toprol-XL. Further information is provided in the table below.

Table 5: Number and proportion of responders at selected timepoints (all treated patients in Study 307B)

	N	Number of responders	Proportion of responders (%)	95% CI
16-week study				
Entry in 307B (16 week)	52	16	30.8	18.2, 43.3
Week 16/LOCF	52	24	46.2	32.6, 59.7
52-week study[a]				
Entry in 307B (52 week)	99[b]	41	41.4	31.7, 51.1
Week 16/LOCF	100	62	62.0	52.5, 71.5
Week 32/LOCF	100	70	70.0	61.0, 79.0
Week 52/LOCF	98[c]	63	64.3	54.8, 73.8

Note: A responder was defined as any patient whose sitting systolic and diastolic BP was less than the 95th percentile (adjusted for height, age, and gender) at the specified timepoint.

[a] Fifteen patients had previously participated in 307B (16 week).

[b] One patient (No. 047-004) was missing BP data upon entry into 307B.

[c] Percentiles are only available for ages up to 17 years. Patient Nos. 034-201 and 047-021 turned 18 during the study and were excluded from the Week 52 and Week 52/LOCF timepoints.

- Safety results

According to the MAH, the tolerability profile of Toprol-XL in children was generally comparable to that reported for adult hypertensive patients, and there were no unexpected adverse drug reactions compared with the known product profile.
A total of 153 unique patients were exposed to Toprol-XL in Study 307A and/or Study 307B and were included in the safety populations. Of these patients, 84 were exposed for at least 241 days, while 69 were exposed for over 360 days. No patient died during either study.

Table 6 : Summary of adverse events in Studies 307A and 307B (safety populations)

	307A (4 weeks)[a]		307B	
	Placebo (N=24)	All Toprol-XL groups (N=118)	Toprol-XL 16 weeks (N=52)	Toprol-XL 52 weeks (N=100)
Category	n (%)	n (%)	n (%)	n (%)
At least 1 AE[a]	12 (50.0%)	56 (47.5%)	35 (67.3%)	83 (83.0%)
Drug-related AE	2 (8.3%)	10 (8.5%)	9 (17.3%)	18 (18.0%)
Serious AE	0	0	0	2 (2.0%)
Discontinued treatment due to AE	1 (4.2%)	0	2 (3.8%)	5 (5.0%)
Death	0	0	0	0

[a] For Study 307A, only treatment-emergent adverse events (AEs) , defined as AEs that began after the first dose of double-blind study medication, are shown.

Table 7: Number (%) of patients who had at least 1 AE by preferred term, occurring with an incidence of at least 5% in the 52-week study (safety populations)

	307A (4 weeks)[a]		307B	
	Placebo (N=24)	All Toprol-XL groups (N=118)	Toprol-XL 16 weeks (N=52)	Toprol-XL 52 weeks (N=100)
Preferred term	n (%)	n (%)	n (%)	n (%)
Headache	4 (16.7%)	15 (12.7%)	9 (17.3%)	30 (30.0%)
Upper respiratory tract infection	1 (4.2%)	8 (6.8%)	0	20 (20.0%)
Cough	2 (8.3%)	3 (2.5%)	2 (3.8%)	19 (19.0%)
Nasopharyngitis	0	3 (2.5%)	7 (13.5%)	13 (13.0%)
Pharyngolaryngeal pain	0	3 (2.5%)	3 (5.8%)	12 (12.0%)
Influenza	0	0	2 (3.8%)	10 (10.0%)
Pyrexia	0	5 (4.2%)	4 (7.7%)	10 (10.0%)
Fatigue	0	3 (2.5%)	2 (3.8%)	9 (9.0%)
Back pain	0	1 (0.8%)	0	8 (8.0%)
Diarrhoea	1 (4.2%)	3 (2.5%)	3 (5.8%)	7 (7.0%)
Nasal congestion	0	2 (1.7%)	1 (1.9%)	7 (7.0%)
Otitis media	1 (4.2%)	2 (1.7%)	1 (1.9%)	7 (7.0%)
Dizziness	1 (4.2%)	5 (4.2%)	3 (5.8%)	6 (6.0%)
Abdominal pain upper	0	3 (2.5%)	2 (3.8%)	5 (5.0%)
Dysmenorrhoea	0	0	2 (3.8%)	5 (5.0%)
Gastroenteritis viral	0	2 (1.7%)	0	5 (5.0%)
Oedema peripheral	0	1 (0.8%)	0	5 (5.0%)
Vomiting	0	2 (1.7%)	1 (1.9%)	5 (5.0%)

[a] For Study 307A, only treatment-emergent adverse events (AEs), defined as AEs that began after the first dose of double-blind study medication, are shown.

Neither of the 2 serious adverse events (SAEs; pneumonia and menometrorrhagia in Study 307B), was considered by the investigator to be causally related to study medication. A total of 7 patients were discontinued prematurely from Toprol-XL treatment due to an AE.
Of note, 6 patients in the 52-week study were reported to have cardiac-related AEs, including 3 patients with bradycardia; and 1 report each of chest pain, atrial dilatation, and sinus tachycardia, each of which was considered mild in intensity and unrelated to study medication by the investigator.
Respiratory events included wheezing (n=2) and dyspnea (n=1), each of which was considered mild in intensity and unrelated to study medication by the investigator. All 9 cases of fatigue were mild in intensity.

Assessors comment

Pharmacokinetics
The trough plasma concentration measured in both studies submitted showed that there is more or less linear relation ship between dose and trough level albeit that the variability in the measured concentrations is very high probably due to the high variability in the demographic characteristics of the population studies.

After dosing of 25 mg in study 307B the pharmacokinetic parameters between the two groups are comparable.
Furthermore, linear regression analysis of the effect of age and body weight showed that over the range of age (7 - 17 years) and body weight (44 to 155 kg) no significant correlation with the age of body weight and AUC of Cmax was observed (data not shown).

The population pharmacokinetic analysis of the data of study 307A and 307B of metoprolol were evaluated in 120 pediatric patients in the age of 6 - 17 years.
The best model to describe the data was a 2-compartment model with first order elimination and flip-flop first order absorptions and a lag-time.
The pharmacokinetic parameters in these patients were in general consistent with those reported for adults.
Sex, age, race and ideal body weight had no significant effect on metoprolol pharmacokinetics. The CL/F was found to increase with increasing body weight while Q/F increased with age.
No dose adjustment was considered necessary based upon body weight as metoprolol is titrated at weekly intervals until optimum blood pressure is achieved.

Efficacy
The MAH provided one large clinical study with an additional 52 week safety data and included a PK evaluation. Furthermore, some literature data and safety reports have been included.
The placebo-controlled data in patients aged 6 to 16 years provided dose finding data for 3 separate doses. Patients with hypertension have been included; however, baseline data do not provide sufficient information. It remains unrevealed what type of hypertensive patients were included (essential or secondary hypertension; of note, more than 75% were overweight as well). Furthermore, the company did not provide information if all ages were represented in the study, because all ages between 6 and 16 should have been sufficiently included in the study. Therefore, the company should reveal the type of hypertension and provide the age distribution.

Dose response data have been presented by the company. All doses showed a blood pressure reduction. However, it can be observed that with a placebo corrected BP lowering of 3.3/1.0 mmHg for the lowest no statistical significance can be demonstrated. There is a lack of further dose reduction on the highest dose for SPB compared to the mid dose, while a dose response across the full dose range for DBP has been demonstrated. The applicant provides some possible explanation for the lack of further BP reduction for the highest dose such as chance finding, short exposure of 2 weeks on highest dose or flat dose response curve. However, this does not explain the curious finding of a similar amount of responders (baseline BP levels are similar) in the lowest and highest dose group (both 47%). So other factors also could have attributed to these findings. For instance, data on the origin of hypertension, age distribution or previous use of hypertensive medication have not been provided or discussed. Although the applicant states that subgroup analysis did not reveal any consistent differences, these factors could have contributed to these findings. The MAH should further explore some possible explanations for these findings.

Although the responder rates were not dose proportional and can be considered moderate in the placebo controlled study (approximately 45% on treatment vs 26% in placebo), this increased to more than 60% in the 52 weeks follow-up study. However, due to the curious finding of an absence between dose and response rate, it would be interesting to know whether each dose step during the open-label phase also increased responder rates. Although these data have not been provided, these could support dose recommendations for the highest dose.

Safety
Open-label long-term safety data up to 52 weeks has been provided in addition to short-term 4 weeks placebo controlled data. Frequency of adverse events was comparable between placebo and treatment. Long-term data on metoprolol did not reveal unexpected adverse events. Serious adverse events were considered not related to study medication.

Overall
Metoprolol moderately reduces blood pressure in patients from 6 to 16 years. However, dose proportionality has not univocally been demonstrated, and some data need to be further addressed to finalize dose recommendation. Safety in these children is sufficiently reassuring.

SmPC

Section 4.2:
The wordings as proposed for section 4.2 could be approvable provided that the questions on further exploration related to dose recommendation are satisfactory addressed..

Section 5.1:
The text is considered acceptable.

Section 5.2:
The text is considered acceptable.

III.3.4 4. Post-marketing experience

Results from literature
In addition to the clinical studies described above, the MAH performed a literature search for the period 1970 to 01 December 2005 to identify publications addressing the use of metoprolol in pediatric patients. This search revealed 13 case reports of individual patients, 1 open-label efficacy and tolerability study, and 1 open-label study examining intracranial pressure targeted therapy in pediatric patients with severe traumatic brain injury were found. The age range of the patients described in the case reports was 1 to 17 years. All patients had secondary forms of hypertension, usually requiring multiple antihypertensive medications to achieve acceptable blood pressure control. The majority of the cases had primary renal disease as the cause of the secondary hypertension. In the majority of publications, no information was provided on metoprolol dose or duration of therapy. Overall, no specific AEs or tolerability issues were identified that were causally related to the use of metoprolol.

Assessor's comment:
The data lock point for the literature search appears to be 01 December 2005, which is almost seven years ago. The MAH is therefore requested to update the literature search with recent data.

Solicited reports
The MAH performed a physician survey among pediatric nephrology and cardiology practices, and from hypertension clinics in the US, New Zealand and Slovakia. A total of 9 physicians participated in the survey. Data were collected from 1 November 2004 until 2 December 2005. A total of 32 reports were submitted, including 4 AEs, which are included in the Clintrace discussion below. The patients were 2 to 19 years old (maximum age 17 years at onset of use), and included 22 boys and 10 girls. Reported daily doses ranged from 12.5 mg to 300 mg per day.

In-house database
The AstraZeneca in-house safety database (Clintrace) contains all SAEs from clinical trials and all spontaneous reports, including reports from the Poison Control Center and solicited post-marketing reports. The database was searched for all reports of metoprolol succinate use in pediatric patients ≤17 years of age.
As of 1 December 2005, 32 case reports had been received, 13 of which were not included in the analysis: the 2 SAEs from Study 307B and 11 case reports regarding drug exposure during pregnancy or lactation. Of the 19 remaining reports, 7 were serious, and 12 were non-serious. No deaths were reported, and in the majority of reports in which outcome was provided, the patient recovered without sequelae. A single case report was received for all but 2 preferred terms—accidental exposure (4 reports) and medication error (3 reports). Three preferred terms were reported that have not been reported in the adult population: accidental exposure, blood amylase increased, and enuresis.
The majority of reports were from adolescents, with both genders represented. The reason for use of or exposure to metoprolol succinate was given in 17 case reports (5 for hypertension, 5 accidental exposures, 3 for migraine, 2 medication errors, 1 for neurocardiogenic syncope, and 1 intentional overdose), and was not provided in 2 case reports. Fifty milligrams was the most

commonly reported dose; however, there were too few reports to assess dose trends. The reports regarding pregnancy and lactation did not reveal significant new or unexpected findings related to metoprolol.

In the table below, the number of events in Clintrace is provided.

Table 8: Number of events in the Clintrace database

Preferred term		Preferred term	
Abdominal pain	1	**Enuresis***	1
Accidental exposure*	4	Face edema*	1
Alopecia	1	Headache	1
Amnesia*	1	Heart rate decreased	1
Asthma*	1	Hypotension	1
Blood amylase increased*	1	Hypotrichosis*	1
Bradycardia	1	Intentional overdose*	1
Chest pain	1	Medication error*	3
Convulsion*	1	Pneumonia	1
Cyanosis	1	Retinal artery occlusion*	1
Depression	1	Somnolence	1
Dizziness	1	Suicide attempt*	1
Dyspnea	1	Weight increased*	1
	1	**Total events**	**31**

* Preferred terms that are not listed in the current US Toprol-XL Package Insert.
Note: Bolded preferred terms have not been reported to AstraZeneca for the adult population.

Assessor's comment:
See also previous comment. The data lock point for the search in the MAH's safety database also appears to be 01 December 2005, which is almost seven years ago. The MAH is therefore requested to update the search with more recent data. Furthermore, the MAH should discuss how these data are linked to the data from the PSURs, as it is expected by the assessor that the cases from the Clintrace database should have been included in the PSURs as well.

Based on the events that were presented from the Clintrace database no new safety issues are revealed. The majority of the events has been reported once and may be considered isolated cases. The events reported > 1 time do not indicate a safety concern, although it is difficult to draw any definite conclusions from these data. In general, we agree with the MAH that the safety profile for paediatrics can be considered comparable to the safety profile of adults.

Cases reported in PSURs
Cumulatively 44 medically confirmed cases of paediatric use of metoprolol have been reported to the MAH since the first market authorisation of the product until 29 February 2012. Reported ADRs are described in the table below, stratified by age group.

Table 9: Reported ADRs in PSURs

	Age group	SOC of reported ADR	PT of reported ADR
2 cases	**Contain insufficient information**		
19 cases	**No ADRs reported.**		
24 cases	**Allow further assessment**		
	Unknown age	Psychiatric disorders	*Nightmares*

Unknown age	Cardiac disorders	*Severe bradycardia*
Unknown age	Cardiac disorders	*Hypotension*
Unknown age	Respiratory disorders	Cough
15 months	Investigations	Blood glucose increased
	Psychiatric disorders	*Lethargy*
2 years	Psychiatric disorders	*Mood altered*
4 years	General disorders and administration site conditions	Sluggishness
5 years	General disorders and administration site conditions	Lack of effect†
7 years	Nervous system disorders	Seizures*
8 years	General disorders and administration site conditions	Lack of effect t†
9 years	Nervous system disorders	*Somnolence*
11 years	Investigations	*Increased aspartate aminotransferase* *Increased alanine aminotransferase*
12 years	Skin and subcutaneous tissue disorders	Pruritus generalised
13 years	Cardiac disorders	*Bundle branch block left*
13 years	Nervous system disorders	Hypoaesthesia
	Eye disorders	Intraocular pressure increased Blindness transient
	Psychiatric disorders	*Depression* Irritability
13 years	Investigations	*Increased aspartate aminotransferase* *Increased alanine aminotransferase*
14 years	Nervous system disorders	Grand mal convulsions
	General disorders and administration site conditions	Multiple drug overdose Drug toxicity
	Cardiac disorders	*Hypotension* *Bradycardia*
	Psychiatric disorders	Completed suicide
15 years	General disorders and administration site conditions	*Fatigue* Drug ineffective
15 years	Cardiac disorders	*Uncontrolled arrthymia †*
16 years	Injury, poisoning and procedural complications	Intentional suicide
16 years	Injury, poisoning and procedural complications	Intentional suicide
16 years	Injury, poisoning and procedural complications	Intentional suicide
	General disorders and administration site conditions	Acute drug poisening
17 years	Injury, poisoning and procedural complications	Intentional suicide
	Nervous system disorders	Coma

	Hepatobiliary disorders	Impaired liver function
	Renal and urinary disorders	Impaired renal function
	Cardiac disorders	*Cardiogenic shock*
17 years	Nervous system disorders	Seizures*

* Drug dispensing error: TOPROL (metoprolol) has been dispensed instead of TEGRETOL (carbamazepine); † metoprolol used for treatment of arrthmias (off-label). ADRs listed in the SPC are presented in italics.

The overall safety profile showed similar reactions as those known in the adult population; however no quantitative comparison is possible considering that the experience was derived from a small number of paediatric patients. The overall documentation of the cases remains limited in order to enable to recognize the respective role of the drug and of the underlying disease for some of the reactions.
According to the applicant, there is no evidence of an increased risk of any adverse reactions in children from the information received during the period since marketing. The safety profile in children is in agreement with the overall drug safety profile for metoprolol.

Assessor's comment
Most of the adverse events reported in the post-marketing Astra Zeneca database are well known adverse effects of metoprolol in adults. These can also be observed in the paediatric population. Most ADRs are listed in section 4.8 of the SmPC or are referred to in section 4.4 or 4.9.

Based on the currently available data, the safety profile for metoprolol in paediatrics can be considered comparable to the safety profile of adults and is considered acceptable for paediatrics from 6 to 16 years.

IV. CONCLUSION AND RECOMMENDATION IN PRELIMINARY ASSESSMENT

- **Overall conclusion**

The data for patients between 6 and 16 years of age are sufficient to include a dose recommendation in section 4.2 and information in section 5.1 and 5.2. However, some additional information is needed.

- **Recommendation**

Based on the data submitted, the MAH should provide additional information as additional questions have been formulated.

- **List of questions**

1. Age distribution, origin of hypertension (primary, secondary), and details on the use of previous hypertensive medication is unknown. These should be provided. Data on whether these characteristics could have influenced current dose response should be provided and discussed.

2. Dose response data after each dose titration during the open-label phase is considered important. This could answer the question whether the highest dose (2 mg/kg) has additional benefit over the mid-dose (1 mg/kg). These data should be provided and discussed.

3. The data lock point for the literature search appears to be 01 December 2005, which is almost seven years ago. The MAH is therefore requested to update the literature search with recent data.

4. The data lock point for the search in the MAH's safety database also appears to be 01 December 2005. The MAH is therefore requested to update the search with more recent data. Furthermore, the MAH should discuss how these data are linked to the data from the PSURs, as it is expected by the assessor that the cases from the Clintrace database should have been included in the PSURs as well.

V. ASSESSMENT OF RESPONSE TO QUESTIONS

Question 1

Origin of hypertension (primary, secondary), and details on the use of previous hypertensive medication is unknown. These should be provided. Data on whether these characteristics could have influenced current dose response should be provided and discussed.

Summary of company response

AZ provides a composite response consisting of:
(a) Identification of aetiology of hypertension (primary and secondary)
(b) Comparison between patients with primary and secondary hypertension
(c) Comparison of results for treatment naïve patients vs. patients with previous antihypertensive pharmacologic therapy

(a) Identification of aetiology of hypertension
Though type of hypertension was not a specified variable in study 307A, the protocol actively excluded secondary hypertension due to

- Coarctation of the aorta
- Phaeochromocytoma
- Hyperthyroidism
- Cushing's syndrome (hypercorticolism)

Furthermore the protocol excluded patients with renal conditions of:

- Bilateral renal artery stenosis
- Renal artery stenosis to a single kidney
- Nephrotic subjects who not were in remission

These exclusion criteria are associated with forms of secondary hypertension where β-blockers are contraindicated or corrective/curative therapy should be offered. Secondary hypertension per se was not an exclusion criterion, as it due to congenital and acquired renal conditions, is common particularly in younger hypertensive children. In the absence of a protocol specified variable, patients who reasonably could have hypertension of secondary nature were identified from their medical history (MEDRA low level terms) and results from clinical chemical laboratory analyses.

(b) Comparison between primary and secondary hypertension (primary and secondary)
In 11 of 144 randomised patients, secondary hypertension was considered not possible to rule out. An additional 12 patients were viewed as not having secondary hypertension, as the conditions of their medical history were past, conditions by expertise not considered provoking hypertension, or their laboratory results were not compatible with secondary hypertension.

Summary statistics by primary or secondary hypertension is presented in Table 1. The differences observed are congruent with that patients who, based on their medical history, were appreciated as having non-primary hypertension, actually, at least to some degree, had secondary hypertension; as these patients weighed less, to a higher degree were previously treated for hypertension, and had hypertension for a longer time. There is no clear indicator that their therapeutic response differed from those defined as having primary hypertension. Nor are there major differences in doses administrated.

In conclusion, other than what is explained by aetiology, no significant differences can be seen between the patients with suspected secondary hypertension and those with primary.

Table 1 **Background data from Study 307A: Primary vs. potential secondary hypertension**

		Primary (n=133)	Secondary (n=11)
Gender	Male	93 (70%)	8 (73%)
	Female	40 (30%)	3 (27%)
Race	Caucasian	92	9
	Black	37	1
	Hispanic	3	
	Mixed	1	1
Age	(years)	12.5±2.73	12.6±3.08
Weight	(Kg)	82.1±30.95	64.6±23.72
Height	(cm)	160.1±15.60	154.8±20.89
Tanner stage	1	24	3
	2	19	1
	3	23	2
	4	29	3
	5	38	2
Previously treated hypertension		27	7
Duration of hypertension	(years)	0.7±1.15	3.0±2.00
Dose group	Placebo	24	–
	0.2 mg/Kg	41	6
	1.0 mg/Kg	22	1
	2.0 mg/Kg	46	4
Max. dose by dose group (mg)	Placebo	90.6±68.69	–
	0.2 mg/Kg	18.9±30.63	12.5±0.00
	1.0 mg/Kg	79.5±26.03	75.0±na
	2.0 mg/Kg	151.7±52.33	150.0±70.71
	Total	87.3±71.01	68.2±77.73
Sitting blood pressure			
Systolic	Baseline	132.3±8.85	128.5±9.57
	4 weeks	126.1±10.87	125.3±13.63
Diastolic	Baseline	78.8±8.80	72.8±9.45
	4 weeks	73.0±8.87	69.1±11.47
Responder		57	4

(c) Comparison of results for treatment naïve patients vs. patients with previous antihypertensive pharmacologic therapy

Out of the 144 randomised patients, 34 were treated for hypertension prior to enrolment, and 110 were not. Of those previously treated, 2 received additional antihypertensive drug treatment, and of the 110 treatment naïve patients, 1 received supplementary antihypertensive drug treatment.

The only additional drugs used by more than 10 patients during the study period were products for temporary pain-relief (ATC codes: M01AE [ibuprofen group] and N02BE [paracetamol group]).

Characteristics and mean sitting blood pressures for treatment naïve vs. previously treated patients are presented in Table 2 and Table 3. The two groups appear congruent and with similar treatment response. The numbers of previously treated patients within each dose groups are small, as to why statistical estimation is considered inappropriate

It is concluded that antihypertensive pharmacologic treatment prior to participation in study 307A has not impacted on other patient properties, or on the therapeutic response.

Table 2 Background data from Study 307A: Naïve vs. previously treated patients

		Naïve (n=110)	Prev. treated (n=34)
Gender	Male	75	26
	Female	35	8
Race	Caucasian	78	23
	Black	29	9
	Hispanic	3	
	Mixed		2
Age	(years)	12.4±2.77	12.8±2.72
Weight	(Kg)	81.6±30.91	77.9±30.50
Height	(cm)	159.5±15.95	160.5±16.52
Tanner stage	1	21	6
	2	18	2
	3	18	7
	4	18	14
	5	35	5
Secondary hypertension		4	7
Duration of hypertension	(years)	0.5±1.00	2.1±1.69
Dose group	Placebo	20	4

		Naïve (n=110)	Prev. treated (n=34)
	0.2 mg/Kg	35	12
	1.0 mg/Kg	19	4
	2.0 mg/Kg	36	14
Max. dose by dose group (mg)	Placebo	95.6±73.03	65.6±37.33
	0.2 mg/Kg	20.0±33.10	12.5±0.00
	1.0 mg/Kg	80.3±24.05	75.0±35.36
	2.0 mg/Kg	146.4±52.91	164.3±53.45
	Total	85.0±69.84	88.6±77.38
Sitting blood pressure			
Systolic	Baseline	132.3±8.76	131.0±9.53
	4 weeks	126.0±10.33	126.2±13.46
Diastolic	Baseline	78.3±8.53	78.7±10.38
	4 weeks	72.5±9.21	73.5±8.80
Responder		48	13

Table 3 **Sitting blood pressures at weeks 0 and 4, by treatment naïve or previously treated blood pressure and dose group**

	Naïve				Prev			
	Systolic		Diastolic		Systolic		Diastolic	
Dose group	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4	Week 0	Week 4
Placebo	133.2±7.75 (n=20)	128.9±10.98 (n=17)	81.9±8.53 (n=20)	78.3±7.84 (n=17)	131.8±14.37 (n=4)	128.9±18.69 (n=3)	84.1±16.31 n=4)	75.8±7.37 (n=3)
0.2 mg/Kg	132.2±8.17 (n=35)	126.6±11.53 (n=32)	77.2±8.15 (n=35)	72.6±9.54 (n=32)	129.2±10.31 (n=12)	124.7±13.57 (n=11)	76.5±9.61 (n=12)	73.2±7.58 (n=11)
1.0 mg/Kg	135.6±7.26 (n=19)	128.7±7.82 (n=18)	81.2±7.55 (n=19)	75.2±7.08 (n=18)	131.8±11.72 (n=4)	121.8±21.58 (n=4)	79.8±8.56 (n=4)	76.7±11.06 (n=4)
2.0 mg/Kg	130.0±10.14 (n=36)	122.5±9.35 (n=35)	75.7±8.58 (n=36)	68.1±8.63 (n=35)	132.1±7.54 (n=14)	128.6±9.75 (n=11)	78.8±10.14 (n=14)	72.2±10.21 (n=11)

Conclusion
It is the position of AstraZeneca, that neither secondary hypertension nor previously treated hypertension has impacted on the robustness of the results and conclusion of study 307A. Furthermore the therapeutic responses in the two sub-groups do not deviate from the overall of the study.

Assessor's comment:
The company provided baseline data for patients according to hypertension etiology (primary vs secondary) and for treatment naïve and previously treated patients.
The BP reduction for patients with secondary hypertension is slightly less than for patients with primary hypertension. However, numbers treated with secondary hypertension is very limited to draw conclusions. For naïve patients a dose response relation is also observed for the SBP effect across the

dose-range, while for the previous treated patients this dose response is less compelling, but this could have been caused by the short 1-2 week run-in period. A dose response for DBP can be observed in total and in the subgroup analyses provided.

Question 2
Dose response data after each dose titration during the open-label phase is considered important. This could answer the question whether the highest dose (2 mg/kg) has additional benefit over the mid-dose (1 mg/kg). These data should be provided and discussed.

Summary of company response
Study 307B recommended a starting dose of 25 mg, increasing at most every 2 weeks in increments of 25 mg or 50 mg, based on tolerability, until BP was controlled or the maximum daily dose of 200 mg was attained. Dose escalation could occur at any visit during the 52- week study. If a patient reached the maximum daily dose of 200 mg and BP remained >95th percentile, a second antihypertensive agent (not a beta-blocker) could be added at the discretion of the investigator to achieve BP control.

Within the Study 307B 52-week protocol, 32% of patients were titrated to daily doses of 175-200 mg (Study 307B CSR Figure 8).

Responder rates for the overall 52-week study population were 41% at study entry and ranged from 62% to 70% throughout the study (Study 307B Table 11.2.1.1). For subjects titrated to 175 mg or higher, similar results were seen regardless of additional antihypertensive use (Table 4).

Table 4 **Number and proportion of responders at selected time points (treated patients titrated to 175-200 mg maximum dose)**

	N	Number of responders	Proportion of responders (%)	95% CI
52-week study				
Entry in 307B (52-week)	34	8	23.53	9.27; 37.79
Week 16/LOCF	34	16	47.06	30.28; 63.84
Week 32/LOCF	34	19	55.88	39.19; 72.57
Week 52/LOCF	34	18	52.94	36.16; 69.72
52-week study - No additional antihypertensive medication at any time				
Entry in 307B (52-week)	19	5	26.32	6.52; 46.12
Week 16/LOCF	19	9	47.37	24.92; 69.82
Week 32/LOCF	19	11	57.89	35.69; 80.10
Week 52/LOCF	19	12	63.16	41.47; 84.85

Note: A responder was defined as any patient whose sitting systolic and diastolic blood pressure was less than the 95th percentile at the specified time point. CI confidence interval; LOCF last observation carried forward.

Conclusion
These results demonstrate that subjects titrated to the highest maximum doses, do receive additional benefit from higher doses of metoprolol over lower doses.

Assessor's comment:

The question was probably misunderstood by the company. It would have been informative if the company could have shown to whether additional dose titration of the study medication during the first 16 weeks provides additional blood pressure reduction, in particular for mid-dose to highest dose .

Question 3
The data lock point for the literature search appears to be 01 December 2005, which is almost seven years ago. The MAH is therefore requested to update the literature search with recent data.

Summary of company response
The original Article 45 submission from May 2012 included a document titled "Paediatric studies with metoprolol". This document covered AstraZeneca sponsored studies and relevant literature findings up to September 2007. In addition, AstraZeneca made a search covering the time period from 2007 to May 2012. No information was found changing the known safety profile of metoprolol in children and no additional literature references were included. A new literature database query covering 2005-October 2012 has now been conducted and is provided below.

Efficacy

Definition literature query
The medical literature databases Embase and Medline were queried using the following search structure

- exp metoprolol/ OR metoprolol.mp/ OR metoprolol tartrate.mp/ OR metoprolol succinate.mp
- AND
- exp child/ OR exp adolescent/ OR exp preschool child/ OR children.mp/
- limit (2005 2012)
- Cushing's syndrome (hypercorticolism)

Result literature query
194 titles were identified using Embase and 50 using Medline. No new studies (in addition to those already listed in the document "Paediatric studies with metoprolol) on efficacy for use of metoprolol in children with hypertension were found.

Safety
Definition literature query

The search terms were 'metoprolol'/exp AND [English]/lim AND [embryo]/lim OR [fetus]/lim OR [newborn]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim OR [child]/lim OR [adolescent]/lim. The dates specified were from 1 December 2005 to 15 November 2012. The searches were done in Embase and KDP.

Result literature query
In general there was scant information on metoprolol in this population. No new safety information has been identified for children with hypertension.

Among publications addressing off-label use of β-adrenergic blocking agents, an abstract presented safety data in patients aged ≤14 years, where the majority (95%) was receiving β-blockers for treatment of an arrhythmia or channelopathy without underlying cardiac disease (Orcutt et al 2010). Cardiomyopathy or structural heart disease was present in 8% and 7%, respectively. The retrospective chart study had been conducted at a single institution to review potential adverse drug reactions in patients receiving β-blockers. To be classified as an adverse drug reaction the symptoms had to persist for more than one week and there had to be a significant improvement or resolution of the adverse reaction after stopping the β-blocker. There were 211 patients with an average age of 6.6 ± 4.4 years. In 44/211 (21%) a reported side effect was observed and in 20/211 (9%) the effect was significant enough to require termination of the β-blocker. The most common side effect was fatigue (55% of side effects) followed by mood changes/aggressive behaviour (39% of side effects). The incidence of side effects was highest in the 6- to 9-year population with 31% having an untoward effect. There was no difference in incidence of side effects between propranolol, atenolol, nadolol, and metoprolol. The authors concluded that although β-blockers are commonly used in children with heart problems, they

have a high incidence of side effects, the most common being fatigue and mood changes, and that surveillance for these side effects should be actively performed in children on β-blockers. Further information has not been published to the knowledge of AstraZeneca. The proportion of patients on metoprolol is not presented and there is no information on the exposure, any concurrent diseases or concomitant medications.

Fatigue and terms reflecting mood changes (e.g. depression, nervousness and anxiety) are among the listed events in the Company Core Data Sheet for metoprolol succinate. Thus, in the opinion of AstraZeneca no safety data changing the benefit-risk profile for the product has been identified in the updated literature search.

Conclusion
It is the opinion of AstraZeneca, that for the period 2005 – 31 October 2012 no previously unknown safety or clinical trial efficacy data for the use of metoprolol in the treatment of hypertension in children has been published.

Assessor's comment:
No new publications addressing the efficacy of metoprolol in children were identified by the MAH for the period 2005-October 2012.

Regarding the updated search for safety-related publications: the MAH did not provide the number of publications that has been identified with the new search, but discussed one publication of Orcutt et al. The adverse events that were reported in this study are in line with the safety profile in adults and does not require further action.

Question 4
The data lock point for the search in the MAH's safety database also appears to be 01 December 2005. The MAH is therefore requested to update the search with more recent data. Furthermore, the MAH should discuss how these data are linked to the data from the PSURs, as it is expected by the assessor that the cases from the Clintrace database should have been included in the PSURs as well.

Summary of company response
The AstraZeneca global safety database Sapphire (former Clintrace) contains all Serious Adverse Events (SAEs) from clinical trials and all spontaneous reports, including reports from the literature and solicited post-marketing reports. The database was searched for all reports of metoprolol succinate (Seloken ZOK) use in paediatric patients ≤17 years of age. In Table 5 below, the number of events (preferred terms (PT), arranged by System Organ Classification (SOC)) is provided for the time period 02 December 2005 to 15 November 2012 and cumulatively up to 15 November 2012. Number of reports by age and gender for the period are presented in Table 6. Numbers of case reports by year are presented in Table 7. The case reports from clinical trials were not included in the analysis, i.e., two reports on SAEs in Study 307B.

For the time period 02 December 2005 to 15 November 2012, 45 case reports from all spontaneous sources (including non-medically confirmed reports) were received. Twenty (20) of the 45 case reports were medically confirmed. Nine case reports were serious (none with fatal outcome) and 36 were non-serious. The 45 case reports were associated with 103 adverse events (AEs), where 34 events (28 PT:s) are considered listed according to the Company Core Data Sheet (CDS) for metoprolol succinate.

Fifteen case reports with the following events: Accidental drug intake by child (7), Accidental exposure (1), Drug dose omission (1), Intentional drug misuse (1), Inappropriate schedule of drug administration (1) and Off label use (6) did not include any other AEs.

The reason for use of or exposure to metoprolol succinate was given in 38 of the 45 case reports (accidental exposures (9), different types of arrhythmias (8), hypertension (6), medication errors (3), drug dispensing errors (2), migraine (2), hypertrophic cardiomyopathy (2), cardiac failure (1), long QT syndrome (1), vasovagal syndrome (1), Basedow's disease (1), chest pain (1), overdose (1)).

Review and comments on individual case reports

The 9 serious case reports (5 medically confirmed) are presented below:

One medically confirmed serious case report *(Case ID 2006AP05017)* concerned a 16-year old male patient, who developed bradycardia and atrioventricular (AV) block, which are listed events for metoprolol. Concomitant medications included verapamil. Verapamil may affect AV conduction and cause bradycardia. The potential for a pharmacodynamic interaction with verapamil is addressed in the CDS of metoprolol.

A medically confirmed serious case report *(Case ID 2010SE36895)* concerned a 16-year old female patient who was treated for a borderline condition and a suspected bipolar disorder. Attempted suicide and drug exposure during pregnancy were reported. On an unspecified date, the patient started to receive quetiapine fumarate, valproate sodium for bipolar affective disorder and lorazepam. As prophylactic treatment for migraine she was also taking metoprolol succinate 100 mg daily. After two weeks and six days of amenorrhoea, she took 33 tablets of lorazepam in an attempted suicide. The care of the patient following this event was delayed and no specific measures were taken. Treatment with valproate sodium and quetiapine fumarate was stopped (after four weeks and two days of amenorrhoea). Treatment with lorazepam and metoprolol succinate was stopped at a later time point of the pregnancy. Outcome of the pregnancy was not reported.

Five of the serious case reports (3 were medically confirmed) were related to medication errors or accidental exposures and the narratives of these cases (*Case IDs 2007AC02486, 2007UW19820, 2008UW05904, 2008UW05916, 2008UW05921*) are provided in the Response to Question 13 b.

A serious, non-medically confirmed, case report *(Case ID 2009UW10176)* concerned a 13- year old female patient, who received metoprolol succinate and topiramate for migraine. Her mother reported that the patient developed increased intraocular pressure, temporary vision loss (PT Blindness transient) of 2 days duration, hand numbness (PT Hypoaesthesia), depression and irritation. Time to onset of the temporary vision loss was four days from start of metoprolol. Metoprolol was discontinued the same day. The information in the case report is limited and it is not reported if the vision loss was associated with a migraine attack.

A serious, non-medically confirmed, case report *(Case ID 2010SE08874)* concerned a 7-year old female patient with trisomy 18 with polypharmacy and multiple events reported – wrong drug administered, overdose, convulsion, unresponsive to stimuli, grand mal convulsion, hallucinations, blood pressure decreased, renal disorder, hepatomegaly, crying, wrong technique in drug usage process. It was stated that during 2005, she was given several doses of crushed metoprolol succinate (Toprol XL) instead of topiramate (Topamax). The patient was given 50 mg of metoprolol succinate on 17 Dec 2005 and on 18 Dec 2005, she got 6 crushed 25 mg tablets. The patient's seizures increased. Her blood pressure dropped and she was unresponsive. She was taken to hospital. Metoprolol succinate was discontinued on 19 Dec 2005. Escalating seizures including grand mal and hallucinations were seen in January 2006. The underlying condition trisomy 18 is considered to be the likely explanation for the convulsions. The seizures increased when the patient did not receive topiramate.

Table 5 Number of spontaneous events (PTs, arranged by SOC) reported in children ≤17 years for metoprolol succinate (Seloken ZOK)

System Organ Class (SOC) Preferred Term (PT)*	Period 02 Dec 2005 - 15 Nov 2012	Total Cumulatively to 15 Nov 2012
Cardiac disorders	**8**	**10**
Arrhythmia (L)	2	2
Atrioventricular block (L)	1	1
Atrioventricular block first degree (L)	1	1
Bradyarrhythmia (L)	1	1
Bradycardia (L)	1	2
Conduction disorder (L)	1	1
Cyanosis	0	1
Sinus bradycardia (L)	1	1
Eye disorders	**1**	**2**
Blindness transient	1	1
Retinal artery occlusion	0	1
Gastrointestinal disorders	**3**	**4**
Abdominal pain upper (L)	0	1
Diarrhoea (L)	1	1
Lip swelling	1	1
Nausea (L)	1	1
General disorders and administration site conditions	**8**	**10**
Chest pain (L)	1	2
Crying	1	1
Drug ineffective	2	2
Face oedema	0	1
Fatigue (L)	1	1
Ill-defined disorder	1	1
Irritability (L)	1	1
Oedema peripheral (L)	1	1
Hepatobiliary disorders	**1**	**1**
Hepatomegaly	1	1

System Organ Class (SOC) Preferred Term (PT)[a]	Period 02 Dec 2005 - 15 Nov 2012	Total Cumulatively to 15 Nov 2012
Infections and infestations	**1**	**2**
Meningitis	1	1
Pneumonia	0	1
Injury, poisoning and procedural complications	**24**	**33**
Accidental drug intake by child	8	8
Accidental exposure	1	4
Accidental overdose	0	1
Drug administration error	1	1
Drug dispensing error	2	2
Drug dose omission	2	2
Drug name confusion	0	3
Inappropriate schedule of drug administration	1	1
Intentional overdose	0	1
Maternal exposure during pregnancy[b]	1	1
Medication error	4	5
Overdose	1	1
Wrong drug administered	1	1
Wrong technique in drug usage process	1	1
Investigations	**12**	**15**
Alanine aminotransferase increased (L)	2	2
Amylase increased	0	1
Aspartate aminotransferase increased (L)	2	2
Blood pressure decreased (L)	1	1
Blood triglycerides increased	1	1
Electrocardiogram delta waves abnormal	1	1
Heart rate decreased (L)	0	1
Heart rate increased	1	1
Intraocular pressure increased	1	1
Opiates	1	1
Weight increased (L)	1	2

System Organ Class (SOC) Preferred Term (PT)[a]	Period 02 Dec 2005 - 15 Nov 2012	Total Cumulatively to 15 Nov 2012
Respiratory, thoracic and mediastinal disorders	**2**	**4**
Asthma (L)	1	2
Bronchitis chronic	1	1
Dyspnoea (L)	0	1
Skin and subcutaneous tissue disorders	**6**	**8**
Alopecia (L)	2	4
Hair colour changes	1	1
Hair disorder	1	1
Pruritus generalised	1	1
Urticaria (L)	1	1
Surgical and medical procedures	**10**	**10**
Off label use	10	10
Vascular disorders	**2**	**3**
Essential hypertension	1	1
Flushing	1	1
Hypotension (L)	0	1
Total	**103**	**136**

a MedDRA version 15.1
b One case report concerns a pregnant 16-year-old female
L=listed according to the CDS

Table 6 Number of case reports in children by age and gender for the period 02 Dec 2005 to 15 Nov 2012

Year	All reports	Male	Female	Unknown gender
≤1	2	1	1	0
>1 to <6	12	6	5	1
≥6 to <12	9	2	7	0
≥12 to ≤17	21	14	7	0
Not provided	1	0	1	0
Total	**45**	**23**	**21**	**1**

Table 7 Number of case reports in children by year from year of first report

Year	Number case reports	Year	Number case reports
1990	1	2005	5
1999	3	2006	5
2000	3	2007	3
2001	2	2008	7
2002	1	2009	6
2003	1	2010	6
2004	7	2011	8
		01 Jan 2012-15 Nov 2012	8

PTs reported in children and not in adults
Cumulatively seven PT:s were reported that have not been previously reported in the adult population: Amylase increased, Electrocardiogram delta waves abnormal, Encephalitis, Enuresis, Opiates, Pneumonia and Petit mal epilepsy.

Such PT:s identified during the time period 02 December 2005 to 15 November 2012 relate to the following cases:

Electrocardiogram delta waves abnormal: A non-serious, non-medically confirmed report on a 5-year old boy, who developed alterations of delta waves on metoprolol after 3 months of treatment. No additional information was provided. An accessory cardiac pathway is a congenital condition, where the delta waves may become more prominent on treatment with a medication potentially prolonging AV nodal conduction (Case ID 2010SE16195).

Encephalitis and opiates were reported in a serious, medically confirmed case concerning a 14-month old male child with multidrug intoxication with multiple symptoms reported after accidental drug intake (Case ID 2008UW0592). The narrative is provided in the Response to Question 13 b.

Petit mal epilepsy: A non-serious, non-medically confirmed case report (Case ID 2006PK02179) received from a relative of a 5-year old female patient treated with metoprolol succinate for hypertension. Two days after starting treatment the patient experienced absence attacks and abnormal behaviour. Limited information was provided.

Linkage to Periodic Safety Update Reports (PSURs)
The AE reports received by AstraZeneca concerning children and use of/exposure to metoprolol are continuously reviewed as part of the routine surveillance activity for metoprolol. The annual PSURs summarises the safety information received and evaluated by AstraZeneca from worldwide sources.

The PSUR includes information for both metoprolol succinate and metoprolol tartrate. The cases that meet the criteria for inclusion in the PSURs principal line listings for the relevant time period are discussed in the PSUR. All reports received during a PSUR period are taken into considerations when making a cumulative evaluation (presented in Section 9 of the PSUR), although not included in the principal line listings. The types of case reports included in the PSUR listings are detailed in Appendix C of the PSUR. Non-medically confirmed case reports are presented in separate listings. Case reports without AEs and non-serious reports from Health Authorities are not included in any PSUR line listings.

Case reports in the AstraZeneca global safety database are updated when follow-up information becomes available. The PSUR may contain follow-up information on individual case reports presented in a previous PSUR. If significant follow-up data has been obtained which is relevant to the interpretation of the case e.g., information with significant impact on the case description, adverse

events (PTs) or analysis, the updated case report (including the correction or clarification) will be presented in this PSUR.

For completeness, the number of events reported in children for metoprolol tartrate (Seloken) is presented cumulatively in Appendix C of this response document. Cases reported regarding treatment with metoprolol, without specification of salt, are assigned to metoprolol tartrate.

Conclusion
In the opinion of AstraZeneca the updated search in the AstraZeneca global safety database did not identify any safety data changing the benefit-risk profile of metoprolol succinate. The safety profile in children is considered to be comparable to the safety profile in adults.

Assessor's comment:
From tables 5-7, it is concluded that the adverse events that were reported for children are in line with the known safety profile of metoprolol use in adults. The events that were reported are either listed in the SmPC, or are isolated cases that do not warrant further action.
The conclusion of the MAH is agreed with, the currently available data do not indicate a different safety profile for adults and children using metoprolol.

Question 5
The MAH is requested to give a text proposal for the package leaflet regarding information on paediatric use based on the SmPC.

Summary of company response
Proposed additions to package leaflets of Metoprolol CR/ ZOK guiding its use in children aged 6-18.

1. WHAT METOPROLOL CR/ZOK IS AND WHAT IT IS USED FOR
Children and adolescents from 6-18 years:
For treating high blood pressure (hypertension)

3. HOW TO TAKE METOPROLOL CR/ZOK
Children and adolescents:

High blood pressure: For children aged 6 years and older, the dose depends on the child's weight. The doctor will work out the correct dose for your child.

The usual start dose is 1 mg/kg once a day but not exceeding 50 mg. The dose will be adjusted to the nearest tablet strength. Your doctor may increase the dose to 2.0 mg/kg depending on blood pressure response. Doses above 200 mg once daily have not been studied in children and adolescents.

Metoprolol CR/ZOK tablets are not recommended for children under 6 years.

Assessor's comment:
This information is supported.

Question 6
The MAH is requested to give an overview of medicinal products involved.

Summary of company response
Seloken ZOK 25 mg, 50 mg, 100 mg and 200 mg, i.e. prolonged release tablets containing 23.75 mg, 47.5 mg, 95 mg and 190 mg metoprolol succinate respectively.

Assessor's comment:
Agree.

Question 7

The primary statistical analysis in the study 307A was based on the intention-to-treat (ITT) population which included all patients who received at least 1 dose of study medication and had baseline and at least 1 post-baseline measurement. The missing data were imputed using LOCF. It should be clarified if also an analysis using per-protocol population has been made. In such case the results should be submitted. The possible impact of ITT-analysis on the statistical power should be discussed.

Summary of company response
The Per-protocol population was defined as the subset of patients in the ITT population who completed the study without any major protocol deviations. This analysis was supportive to the main analysis.

Definitions of major protocol violations and deviations are given in the Statistical Analysis Plan (Study 307A Appendix 12.1.9) and summarized below:

- Ineligible baseline BP defined as both SBP and DBP less than the 95th percentile for age, gender-, and height-adjusted charts at Visits 2 and 3 for newly diagnosed patients or at Visit 3 for previously diagnosed patients. The average BP from each visit was rounded to the nearest integer before comparison to the 95th percentile.
- No on-treatment sitting BP at Week 4 defined as no on-treatment sitting BP data at the Week 4 visit, where on-treatment is defined as taking study medication within 50 hours prior to the Week 4 visit and the same arm was used for BP measurement at baseline and Week 4.

Table 8 **Study 307A Per-protocol population SBP tables presented in Appendix 11**

Table	Title
Table 11.1.4	Inclusions and Exclusions from Intention-to-Treat (ITT), Per-Protocol (PP), and Safety Analysis Sets
Table 11.1.7	Patient Demography
Table 11.1.10	Descriptive Statistics for Age, Weight, and Height
Table 11.2.2.9	Mean and SD for Sitting SBP Over Time
Table 11.2.2.10	Median and Range for Sitting SBP Over Time
Table 11.2.2.11	Mean and SD for Baseline and Changes from Baseline in Sitting SBP Over Time
Table 11.2.2.12	Median and Range for Baseline and Changes from Baseline in Sitting SBP Over Time
Table 11.2.2.13	Dose Response for Placebo-Corrected Change from Baseline to Week 4 for Sitting SBP

Twenty-two patients were excluded from the PP population, mainly for no Week 4 on-treatment sitting BP values. The proportion of patients who discontinued study drug early was comparable in the 3 TOPROL XL groups (4% to 6%) and lower than that in the placebo group (17%).

Table 9 **Study 307A populations for analysis by treatment group (all randomized patients)**

Population/ Protocol deviation[a]	Placebo (N=24) n	(%)	TOPROL-XL treatment groups 0.2 mg/kg (N=47) n	(%)	1.0 mg/kg (N=23) n	(%)	2.0 mg/kg (N=50) n	(%)	All patients (N=144) n	(%)
ITT population										
Included in ITT population	23	(95.8)	45	(95.7)	23	(100.0)	49	(98.0)	140	(97.2)
Excluded from ITT population	1	(4.2)	2	(4.3)	0		1	(2.0)	4	(2.8)

Population/ Protocol deviation[a]	Placebo (N=24) n	(%)	TOPROL-XL treatment groups 0.2 mg/kg (N=47) n	(%)	1.0 mg/kg (N=23) n	(%)	2.0 mg/kg (N=50) n	(%)	All patients (N=144) n	(%)
PP population										
Included in PP population	19	(79.2)	39	(83.0)	21	(91.3)	43	(86.0)	122	(84.7)
Excluded from PP population	5	(20.8)	8	(17.0)	2	(8.7)	7	(14.0)	22	(15.3)
SBP and DBP <95th percentile	0		2	(4.3)	1	(4.3)	1	(2.0)	4	(2.8)
No Week 4 on-treatment sitting BP values	5	(20.8)	6	(12.8)	1	(4.3)	6	(12.0)	18	(12.5)

[a] Patients could meet more than 1 criterion for exclusion.
[b] Patient No. 003-015 in the 0.2 mg/kg group was excluded because he was lost to follow-up after randomization and had no post randomization data, while Patient No. 031-004 in the 2.0 mg/kg group was discontinued after randomization for taking a prohibited medication and never received study drug.

BP blood pressure; DBP diastolic blood pressure; ITT intention-to-treat; PP per-protocol; SBP systolic blood pressure.

Data derived from Table 11.1.4, Section 11.1.

The demographic and baseline characteristics of the PP populations were similar to those described for the ITT population (Section 11.1, Tables 11.1.7 and 11.1.10).

The dose-response conclusions from the ITT analysis and the PP analysis for SBP (which required Week 4 values collected within 50 hours of last dose) are similar (Table 10).

Table 10 Dose response for placebo-corrected change from baseline to Week 4 for sitting SBP

Trough sitting SBP	Estimate	Standard error	95% CI
ITT Predicted values (LOCF)			
Dose ratio = 1	-3.7554	1.1840	-6.1006, -1.4102
Dose ratio = 5	-4.1950	0.7929	-5.7655, -2.6245
Dose ratio = 10	-4.7445	1.1679	-7.0578, -2.4311
PP Predicted values (Observed)			
Dose ratio = 1	-2.4460	1.2915	-5.0080, 0.1160
Dose ratio = 5	-2.8583	0.8614	-4.5672, -1.1495
Dose ratio = 10	-3.3738	1.2685	-5.8901, -0.8575

The reduction in overall study population by approximately 15% will likely reduce the power of the analysis. However it is often theorized that a PP population reduces variability by increasing adherence to the protocol. In this case, most exclusions are based on missing data. This, in combination with smaller changes and somewhat larger variability, indicates that the study most likely has a loss of power while analyzing the PP analyses.

Assessor's comment:
A substantial and accepted proportion of the included patients was included in the PP population. Both ITT analyses and PP analyses seem to demonstrate a similar effect. However, an additional dose response for the highest dose has not been demonstrated for the SBP, only for DBP.

Question 8

In the study 307A the patient population was inhomogeneous, comprising of untreated and currently treated patients, i.e. patients with concomitant treatment at the time of entry. The applicant should provide details about the concomitant medications and the number of these patients and clarify, if a subgroup analysis was performed for these patients.

Summary of company response
AstraZeneca asks to refer to Question 1 for coverage of this topic, where a detailed presentation of the patients, split by previous antihypertensive treatment or not, is given.

Conclusion
It is the opinion of AstraZeneca that previous antihypertensive treatment has not impacted on the characteristics of the patients. Furthermore the therapeutic responses in the two sub-groups do not deviate from the overall outcome of the study. Thus, a subgroup analysis is not warranted.

Assessor's comment:
The data requested have been provided. For further assessment see question 1.

Question 9
Study 307A, efficacy: from Figure 2 of the results, it seems that metoprolol moderately reduces SBD and DBP in the 1.0 and 2.0 mg/kg doses, however the statistical significance is very marginal (P= 0.049 & 0.027). It is also not clear if the blood pressure reductions are of clinical importance. The applicant is requested to supply a summary table of placebo corrected results that clearly displays blood pressure reductions with the level of

significance (P value), before the question of paediatric indication and the wording of the 4.2 can be considered.

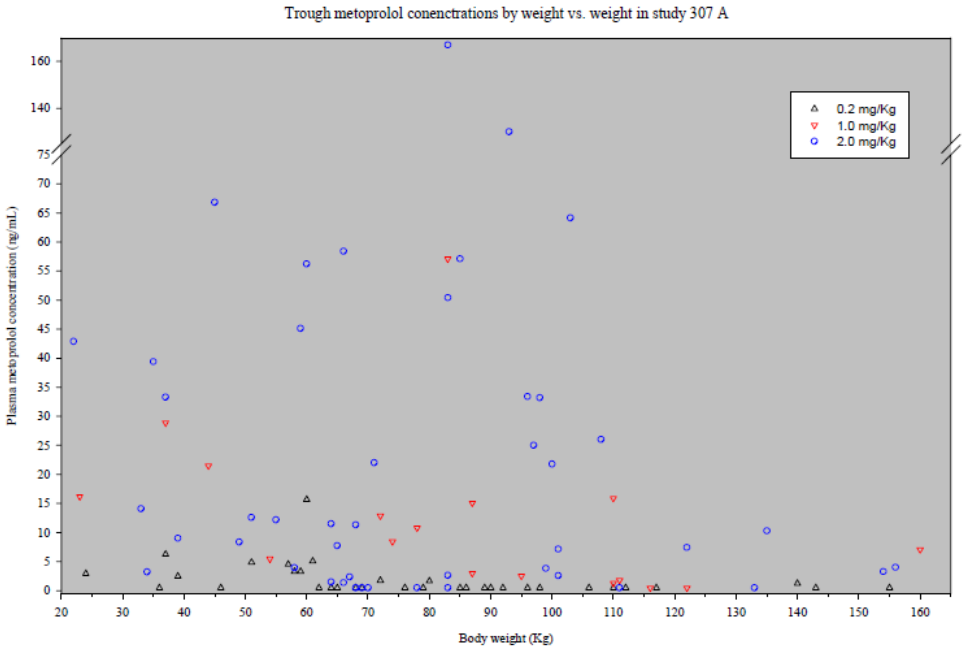
Summary of company response
Table 11.2.2.8 from the clinical study report of study 307A (presented as Table 11 below), details placebo adjusted estimates by metoprolol succinate dose group in its terminal 3 rows.

Table 11 **Treatment Group Effects and Pairwise Comparisons for Change from Baseline to Week 4/LOCF based on ANOVA for sitting SBP Intention to treat patients (n=140)**

Trough sitting SBP	Least square mean	p-value	95% CI	
			Lower bound	Upper bound
Placebo	-1.85507	0.3133	-5.4802	1.7700
Toprol-XL 0.2 mg/kg	-5.15556	0.0001	-7.7472	-2.5639
Toprol-XL 1.0 mg/kg	-7.65217	0.0001	-11.2773	-4.0271
Toprol-XL 2.0 mg/kg	-6.26531	0.0001	-8.7489	-3.7817
Toprol-XL 0.2 mg/kg vs. Placebo	-3.3005	0.1453	-7.7567	1.1558
Toprol-XL 1.0 mg/kg vs. Placebo	-5.7971	0.0270	-10.9238	-0.6704
Toprol-XL 2.0 mg/kg vs. Placebo	-4.4102	0.0492	-8.8045	-0.0159

The apparent absence of a dose- response relationship is most likely due to the impact form body mass on plasma concentrations, as can be seen from Figure 1, together with the maximal allowed dose in study 30A dose was 200 mg o.d. It would thus seem central that dosing of metoprolol succinate in children is done by body mass.

Figure 1 **Trough concentrations by weight**



Assessor's comment:
A substantial proportion of patients in the highest dose level have similar plasma levels or even lower than patient in the mid-dose group. However, according to the boxplot, median levels for the highest dose were higher than for the mid-dose. So, this does not explain the lack of dose response across the dose levels for the SBP, in contrast to DBP (See also page 12 Table 2).

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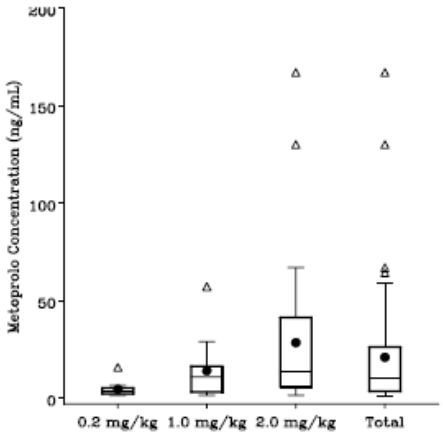
Figure 11.1.22 Boxplots for Trough Metoprolol Concentrations (ng/mL) All Randomized Patients



Question 10

The frequency of adverse events was comparable between placebo and treatment in children, however no comparison of frequency of adverse events between children and adults was discussed. The applicant is requested to provide a summary table of frequency of adverse events in children (pooled across all studies) and the available adult data.

Summary of company response
The studies 307A and 307B conducted in children 6-16 years old with hypertension have previously been presented by AstraZeneca. There are no additional studies conducted by AstraZeneca in this population.

A total of 153 unique patients were exposed to Toprol XL (metoprolol succinate) in Study 307A and/or Study 307B. Pooling of adverse events (AEs) from studies 307A and 307B is not considered appropriate from a methodological perspective, since 137 of the 138 patients in study 307B had participated in study 307A. Additionally, study 307A was double-blind and study 307B open-label and there were differences in treatment duration between the studies (4 weeks and up to 52 weeks, respectively).

There are no appropriate AstraZeneca studies for pooling of AEs in adults with hypertension treated with metoprolol succinate.

Providing a table with a quantitative comparison between the AEs reported in children in the studies on hypertension and the established safety profile of the product as presented in the Company Core Data Sheet (CDS) is not feasible. The adverse drug reaction (ADR) profile as described in the CDS is based on data from multiple sources and not directly comparable to study data. Furthermore, the ADR data are reported in the adult population with a wide range of cardiovascular indications, also including other indications than hypertension.

For AEs among the children participating in studies 307A and 307B, see Table 12. Headache is a common AE in studies in general, but it is also a listed ADR for metoprolol succinate. Infections, e.g. upper respiratory tract infection, nasopharyngitis and otitis media, are frequent seasonal co-morbidities in children. The AEs fatigue, diarrhoea, dizziness, abdominal pain, oedema and vomiting, may occur due to temporary co-morbidity, but are also listed ADRs for metoprolol succinate. No

unexpected drug reactions were seen among the patients in studies 307A and 307B. For information on Postmarketing Surveillance Data for metoprolol in children, see Response to Question 4.

Conclusion
The quantitative comparison requested is not possible to perform. Based on a qualitative review of the AEs in studies 307A and 307B AstraZeneca considers that the safety profile of metoprolol succinate in children is comparable to the established safety profile in adult patients. This is also supported by Postmarketing Surveillance data.

Table 12 Number (%) of patients who had at least 1 AE by preferred term, occurring with an incidence of at least 5% in the 52-week study (safety populations)

	307A (4 weeks)[a]		307B	
	Placebo (N=24)	All Toprol-XL groups (N=118)	Toprol-XL 16 weeks (N=52)	Toprol-XL 52 weeks (N=100)
Preferred term	n (%)	n (%)	n (%)	n (%)
Headache	4 (16.7%)	15 (12.7%)	9 (17.3%)	30 (30.0%)
Upper respiratory tract infection	1 (4.2%)	8 (6.8%)	0	20 (20.0%)
Cough	2 (8.3%)	3 (2.5%)	2 (3.8%)	19 (19.0%)
Nasopharyngitis	0	3 (2.5%)	7 (13.5%)	13 (13.0%)
Pharyngolaryngeal pain	0	3 (2.5%)	3 (5.8%)	12 (12.0%)
Influenza	0	0	2 (3.8%)	10 (10.0%)
Pyrexia	0	5 (4.2%)	4 (7.7%)	10 (10.0%)
Fatigue	0	3 (2.5%)	2 (3.8%)	9 (9.0%)
Back pain	0	1 (0.8%)	0	8 (8.0%)
Diarrhoea	1 (4.2%)	3 (2.5%)	3 (5.8%)	7 (7.0%)
Nasal congestion	0	2 (1.7%)	1 (1.9%)	7 (7.0%)
Otitis media	1 (4.2%)	2 (1.7%)	1 (1.9%)	7 (7.0%)
Dizziness	1 (4.2%)	5 (4.2%)	3 (5.8%)	6 (6.0%)
Abdominal pain upper	0	3 (2.5%)	2 (3.8%)	5 (5.0%)
Dysmenorrhoea	0	0	2 (3.8%)	5 (5.0%)
Gastroenteritis viral	0	2 (1.7%)	0	5 (5.0%)
Oedema peripheral	0	1 (0.8%)	0	5 (5.0%)
Vomiting	0	2 (1.7%)	1 (1.9%)	5 (5.0%)

[a] For Study 307A, only treatment-emergent adverse events (AEs), defined as AEs that began after the first dose of double-blind study medication, are shown.

Assessor's comment:
The position of the company is concurred that it is very difficult to compare the exact frequencies between this paediatric study and the information provided in the SmPC based on trial data for several indications and based on post-marketing data. The qualitative comparison shows a similar safety profile, although some AEs of upper respiratory tract infection and pyrexia are not typical AEs for metoprolol but could be typical children co-morbidities.

Question 11
In the view of a probable paediatric indication, the applicant is requested to commit to submission of a consolidated version of Risk Management Plan (RMP) for metoprolol including the identified risks for the paediatric population. The paediatric exposure in clinical trials and in post marketing use by age group, indication (including off label use), dose, duration of use, gender and ethnicity should be specifically discussed and followed. The Risk Management Plan may be submitted through a suitable variation procedure.

Summary of company response
Metoprolol has been on the market since 1975, with generic products available since 1991. The Paediatric indication has been approved in 26 countries (including 14 European countries) from 2007 to 2011. There is extensive experience with the use of metoprolol in adults and increasing experience of use in children. The studies 307A and 307B on metoprolol for hypertension in children provided indications that the risks from paediatric use are recognizable, few and manageable, and comparable to the established profile in adult patients reflected in the Core Data Sheet (CDS). This is supported by the post-marketing experience in children, as reviewed on an annual basis at internal Safety Evaluation Review Meetings (SERM) and also reported in PSURs.

It is the opinion of AstraZeneca that the safety profile of the product is well established, and that the identified risks are adequately managed through the routine pharmacovigilance and risk minimization activities already in place. These include product information (SmPC and PIL, including updates), the primary tool to communicate information about the benefits and risks associated with the use of metoprolol, control of promotional material and sales representative training. AstraZeneca has a comprehensive system and processes for signal detection, regular safety reviews, identifying and evaluating issues potentially affecting patient safety, and developing safety recommendations (including changes to the CDS, when warranted, which are submitted for implementation in the SmPC and PIL).

It is therefore the opinion of AstraZeneca that no risk minimization activities in addition to the routine pharmacovigilance activities already in place are warranted.

Assessor's comment:
The reasoning of the MAH is supported. Based on the currently submitted data, the safety profile in children appears to be comparable to that in the adult population. There are no specific safety issues identified related to the use of this product in children, and therefore we consider a Risk Management Plan not necessary.

Question 12
a. In France, the metoprolol succinate controlled release tablets, SELOZOK, are only indicated in the *treatment of chronic heart failure*. The indication in *essential hypertension* in adults is authorized for the other salt of metoprolol (i.e. tartrate of metoprolol), consequently, the SPC and the PL of SELOZOK are not suitable as they do not contain information regarding such indication. If an indication will be granted for the hypertensive paediatric population, the SPC should be revised at the national level to include the appropriated information particularly in sections 4.1 Therapeutic indication, 4.4 Special warning and 4.8 adverse events. The MAH should comment.

b. Moreover, only 3 of 4 dosages of SELOZOK are authorized in France (23.75 mg, 95 mg and 190 mg), thus patients who need dosages between 23.75 mg and 95 mg, should take several tablets. The MAH should comment.

The conclusions of the Article 45 should only concern the metoprolol succinate release tablets.

Summary of company response
The following information is proposed to be added to the national SmPC including France:

4.1 Therapeutic indications:
Children>6 and adolescents (aged 6-18 years): Hypertension

4.2 Posology and method of administration
Children and adolescents:
The recommended initial dosage in hypertensive patients >6 years is 1.0 mg/kg metoprolol CR/ZOK, not exceeding 50 mg, once daily given approximated by dose strength. In patients not responding to 1.0 mg/kg, the dose can be increased to a maximum daily dose of 2.0 mg/kg. Doses above 200 mg once daily have not been studied in children and adolescents.

Efficacy and safety of use in children < 6 years have not been studied. Therefore, metoprolol CR/ZOK is not recommended in this age group.

5.1 Pharmacodynamic properties
In 144 paediatric patients (6 to 16 years of age) with essential hypertension, metoprolol CR/ZOK has been shown in a 4-week study to reduce placebo-corrected systolic blood pressure for the 1.0 and 2.0 mg/kg doses (4 to 6 mmHg). For diastolic blood pressure, there was a placebo-corrected reduction for the 2.0 mg/kg dose (5 mmHg) and a dose-dependent reduction for the dose range 0.2, 1.0 and 2.0 mg/kg. No apparent differences in blood pressure reduction were observed based on age, Tanner stage, or race.

5.2 Pharmacokinetic properties
The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

Response to Question 12 b
Children requiring dosages between 23.75 mg and 95 mg may take multiples of the 23.75 mg tablet.
The 23.5 mg tablet is smaller than the higher strength tablets. Furthermore, it can be divided to adjust dosage or for ease of swallowing.

AstraZeneca agrees that the conclusions of the Article 45 should only concern the metoprolol succinate prolonged release tablets.

Assessor's comment:
The proposed text for the SmPC would be acceptable if an indication would be granted.
Flexibility in terms of dose strengths have been justified.
~~That t~~The conclusions of the procedure should only concern the metoprolol ~~succinate~~ prolonged release tablets~~is supported~~, ~~,~~regardless of the salt form of the tablets.

Question 13

a. We particularly sustain the RMS question 1, the MAH should provide the detail of the other hypertensive treatments at the inclusion and during clinical trials. Moreover, the renal status of all treated children should be submitted.

b. Regarding the 3 cases of medication error and 4 cases of accidental exposure the MAH should commit to provide details (narrative: age/sex, effect, dose, time to onset, outcome and for medication error the action taken) on these cases.

Summary of company response
Astra Zeneca provides a composite response consisting of:

- Comparison of results for treatment naïve patients vs. patients with previous antihypertensive pharmacologic therapy
- Medical history and clinical chemical laboratory values with relevance for renal Function

Comparison of results for treatment naïve patients vs. patients with previous antihypertensive pharmacologic treatment
Details on patient with pharmacologic treatment for hypertension, prior to enrolment in study 307A, are provided in the Response to Question 1.

Medical history and clinical chemical laboratory values with relevance for renal function
Additional past and present medical conditions for the 144 randomised patients are presented in Q1, Appendix A, where medical history over patients with past or present renal conditions is laid out as well.

Individual medical histories for patients with pharmacologic antihypertensive treatment prior to enrolment is given in Appendix A.

Clinical chemical laboratory results for patients with, and without, prior pharmacologic antihypertensive treatment are given in Appendix B. Laboratory data are missing for subject E0101001.

Narratives for case reports concerning patients with out-of-range clinical chemical laboratory values are provided below.

Patient E0008007 (male Caucasian, 13 years, weight 57 Kg, randomised to 0.2 mg/Kg*day-1) gave a history of current persistent proteinuria (MedDRA low level term: proteinuria). No conditions, other than hypertension and proteinuria, were recorded. Clinical chemical analyses – including urine protein – were negative at enrolment and upon completion of the study at visit 7. The patient completed study 307A.

Patient E0043012 (male Caucasian, 11 years, weight 35 kg, randomised to 0.2 mg/Kg*day-1) suffered from "mild renal insufficiency" (MedDRA low level term: renal insufficiency) secondary to complications at birth. Creatinine was elevated to 124 µmol/L at enrolment as well at end of study. Blood urea nitrogen was marginally increased at enrolment 9.5 mmol/L (upper reference value 9.0 mmol/L) and increased further to 12.0 mmol/L by end of study. The patient completed study 307A (27 days of treatment) and received 12.5 mg of metoprolol succinate as maximal dose.

Patients E0001002, E0003021, E0004010, E0009003, and E0012001 showed urinary dipstick tests with >1+ for urinary protein or haemoglobin. Individual data are given in Appendix B and summary results for treatment naïve and previously treated patients are presented in Table 13 and Table 14, respectively.

Table 13 **Urine protein and haemoglobin by visit in previously untreated patients of study 307A**

		Lab parameter									
		Occult blood					Protein, Qual.				
		Neg.	Trace	1+	2+	3+	Neg.	Trace	1+	2+	3+
Visit	1	96	4	1	1	1	92	7	2	2	0
	1.1	4	0	0	0	0	3	0	0	1	0
	7	86	1	1	1	1	76	8	4	1	1
	7.1	1	0	0	0	0	0	0	1	0	0
	8	1	0	0	0	0	1	0	0	0	0
	99	4	0	0	0	0	3	0	1	0	0

Table 14 **Urine protein and haemoglobin by visit in patients with previously treated hypertension in study 307A**

		Lab parameter									
		Occult Blood					Protein, Qual.				
		Neg.	Trace	1+	2+	3+	Neg.	Trace	1+	2+	3+
Visit	1	31	1	0	0	0	28	3	1	0	0
	7	27	1	0	0	1	23	4	1	1	0

Conclusion
It is the opinion of AstraZeneca, that neither previous antihypertensive treatment, nor renal function has impacted on the results of study 307A.

Response to Question 13 b
Narratives for the three case reports (2005UW14661, 2003UW11764 and 2004UW01410) concerning medication error and the four case reports (2001UW16611, 2002UW15679, 2000UW05023 and 1999AU12815) concerning accidental exposure are provided below:

Case report 2005UW14661 was a serious spontaneous report from a consumer in the US that concerned a 12-year-old female who was dispensed Toprol-XL (metoprolol succinate) 25 mg instead of Topamax (topiramate) 25 mg daily due to a drug dispensing error by the pharmacy. Over the next 3 months, dosage was increased to 75 mg daily. The child experienced chest pain, headache, dizziness, difficulty breathing, and hands and feet turning blue. The chest pain, headache, and hands and feet turning blue had not resolved at the time of the report. (PTs: Drug name confusion, Dyspnoea, Cyanosis, Chest pain, Dizziness, Headache)

Case number 2003UW11764 was a serious spontaneous report from the USP Practitioner's Reporting Network concerning an 11-year-old female who was prescribed Tegretol XR (carbamazepine) 200 mg for seizures. The pharmacist incorrectly filled the prescription with Toprol-XL (metoprolol succinate) 200 mg. The patient did not receive any Toprol-XL because her mother recognized that the wrong medication was in the bottle. According to the report, the patient had a seizure as a result of not receiving her antiepileptic medication. No further information is available. (PTs: Convulsion, Drug name confusion)

Case number 2004UW01410 was a spontaneous report from a consumer in the US concerning his son, who may or may not have ingested his father's metoprolol succinate 50 mg. No adverse event (AE) was reported and no further information is available. (PT: Medication error)

Case number 2001UW16611 was a serious spontaneous report from a Poison Control Center in the US concerning a 2-year-old male who was hospitalized after he accidentally ingested "approximately" one half of a 100 mg metoprolol succinate tablet. The outcome was not provided. No further information is available. (PT: Accidental exposure)

Case number 2002UW15679 was a spontaneous report from a pharmacist in the US concerning a 4-year-old patient who possibly ingested a 100 mg tablet of metoprolol succinate. The patient was observed in the emergency room for less than 24 hours. No symptoms were observed. (PT: Accidental overdose)

Case number 2000UW05023 was a spontaneous report from a physician in the US concerning a child who accidentally took "one dose" of metoprolol succinate. No symptoms were reported and no further information is available. (PT: Accidental exposure)

Case 1999AU12815 was a spontaneous report from a physician in the US that concerned an 18-month old child who accidentally ingested an unspecified number of the grandmother's metoprolol succinate 50 mg tablets. The outcome was not reported. No further information is available. (PT: Accidental exposure)

Time period 02 December 2005 to 15 November 2012
The updated search for the time period 02 December 2005 to 15 November 2012 identified 9 case reports on accidental exposure (2007UW19820 (also including PT Medication error), 2008UW17290, 2008UW28129, 2009UW10571, 2010SE17391, 2011SE08010, 2011SE29934, 2011SE48305, 2012SE27365) and 6 case reports of medication errors (2005UW11150, 2007AC02486, 2007UW06629, 2008UW05904, 2008UW05916, 2008UW05921). The narratives are provided below:

Case 2007UW19820 was a serious spontaneous report from a physician in Brazil regarding a 2-year old female child, weight 12 kg. The child accidentally ingested one tablet of metoprolol succinate 100 mg. Activated charcoal was administered. No symptoms were reported. No further information is available. (PTs: Accidental drug intake by child; Medication error)

Case 2008UW17290 was a non-serious spontaneous report from a physician in Brazil concerning a 2-year old male child, weight 15 kg. The child had ingested one single dose of metoprolol succinate 50 mg. The accidental ingestion was reported to be asymptomatic. No further information is available. (PT: Accidental exposure)

Case 2008UW28129 was a non-serious spontaneous report from a consumer in the US concerning a 2-year old male child. The reporter stated that her grandson had ingested her metoprolol succinate. The child was reported to have recovered. There is no additional information available. (PT: Accidental drug intake by child)

Case 2009UW10571 was a non-serious spontaneous report from a consumer in Brazil on a 1- year old female child, weight 9 kg. The child had accidentally ingested metoprolol succinate. No symptoms were reported. There is no further information available. (PT: Accidental drug intake by child)

Case 2010SE17391 was a non-serious spontaneous report from a pharmacist in Germany concerning a 3-year old male child. On an unknown date the child had swallowed a single dose of 95 mg metoprolol succinate without any side effects. No further information is available. (PT: Accidental drug intake by child)

Case 2011SE08010 was a spontaneous non-serious report from a consumer in the US concerning a 3-year old male child, who had accidentally ingested metoprolol succinate 50 mg. No symptoms were reported. The outcome of the event is unknown. (PT: Accidental drug intake by child).

Case 2011SE29934 was a spontaneous non-serious report from a consumer in China on a 1- year old male child, who accidentally ingested 23.75 mg of metoprolol succinate without symptoms. No further information is available. (PT: Accidental drug intake by child)

Case 2011SE48305 was a spontaneous report from a consumer in China concerning a 16- month old child of unknown gender, weight 10 kg. The child accidentally ingested 'half a tablet' of metoprolol succinate. It was reported that the child was taken to hospital for examination and no abnormalities were found. The child experienced no discomfort. The child was reported to have recovered. (PT: Accidental drug intake by child)

Case 2012SE27365 was a spontaneous non-serious report from a physician in Brazil on a 1- year old female child, weight 12 kg. She had accidentally ingested metoprolol succinate without any symptoms. The outcome of the event is unknown. (PT: Accidental drug intake by child)

Case 2005UW11150 was a spontaneous non-serious report from the father of a 1-year old male patient in the US. The patient used Topamax (topiramate) for treatment of seizures and received Toprol XL (metoprolol succinate) from the pharmacy (PT: Medication error). The patient did not take the metoprolol succinate. The drug dispensing error was reported to the pharmacy.

Case 2007AC02486 was a serious spontaneous report (literature case reported by physician) on a 17-year old female patient with epilepsy. She did well on Tegretol (carbamazepine) and her seizures were mild and infrequent. In June 2001, she had been seizure-free for 30 months when her Tegretol prescription was filled at the local pharmacy and she received Toprol XL (metoprolol succinate) instead of Tegretol. The patient noted that the medication was a different shape and colour, but assumed that she had been given a generic version. After four days without Tegretol, the patient had two seizures that were more complex than the others she had previously experienced. The seizures continued with increased frequency and intensity, and she was forced to drop out of college. In February 2004, brain surgery was performed that significantly resolved her symptoms. Eventually, the medication error was discovered, and the pharmacy admitted their involvement. (PTs: Convulsion; Drug dispensing error)

Case 2007UW06629 was a non-serious spontaneous report concerning a 16-year old male. His brother reported that the patient by mistake took one tablet of Toprol XL (metoprolol succinate) 50 mg instead of Tegretol (carbamazepine). The pharmacy had according to the reporter given the patient the wrong product. The patient had chewed the Toprol XL tablet. He complained of headache and dizziness. No further information is available. (PTs: Drug dispensing error; Drug administration error; Headache; Dizziness)

Case 2008UW05904 was a serious spontaneous report from a consumer in the US concerning a 15-year old male patient. The patient received Toprol XL (metoprolol succinate) instead of Celexa (citalopram) 20 mg due to a pharmacy drug dispensing error (PT: Medication error). It was unclear whether the adolescent ingested any of the Toprol XL. The patient's condition was unknown. No further information is available.

Case 2008UW05916 was a serious spontaneous, non-medically confirmed report from the US concerning a 7-year old female patient. The patient received metoprolol succinate. Concomitant medication included sertraline. Medication error (PT: Medication error) was reported, but no details were provided. No symptoms were reported. The patient's condition was unknown. No further information is available.

Case 2008UW05921 was a serious spontaneous report from a health professional in the US on a medication error concerning a 14-month old male child, who ingested unknown doses of metoprolol succinate, morphine, hydrocodone with APAP, antihyperlipidemic, benzodiazepine derivative and trazodone hydrochloride. The patient was hospitalized the same day. The adverse events lethargy, somnolence, bradyarrhytmia/cardiac arrhythmia, firstdegree atrioventricular block/conduction disorder, opiates, dementia, delirium, non-infectious encephalitis and meningitis were reported. The patient was treated in the Paediatric Intensive Care Unit with naloxone and intravenous fluids. He recovered without sequelae and was discharged two days later. (PTs: Medication error; Atrioventricular block first degree; Lethargy; Opiates; Somnolence; Bradyarrhythmia; Arrhythmia; Conduction disorder; Dementia; Encephalitis; Delirium; Meningitis)

Assessor's comment:
The company has provided the request to question 13a in question 1. For further discussion see question 1.

In two cases, the wrong drug was dispensed (topiramate instead of metoprolol and vise versa). One of these patients experienced a seizure which is due to the missed administration of topiramate (and not taken the mistakenly dispensed metoprolol) . In the other case, which was reported by a consumer, the patient experienced chest pain, headache, dizziness, difficulty breathing, and hands and feet turning blue. These adverse events are in line with the known safety profile of metoprolol and do not provide new safety information.

In three cases, no adverse events were reported following accidental exposure to metoprolol. In two cases, no information was provided on whether or not any adverse events were reported, nor was the outcome reported in these cases.

In the majority of the 15 cases that were reported regarding accidental exposure/medication errors in the period 02 December 2005 to 15 November 2012, no adverse events were reported (9/15). For three cases, no information has been provided on the adverse events or the outcome. In one case, the events that were reported are known for metoprolol. Two cases concerned dispensing errors, in which metoprolol has been dispensed instead of carbamazepine. In the remaining case, the child took overdose of multiple drugs.

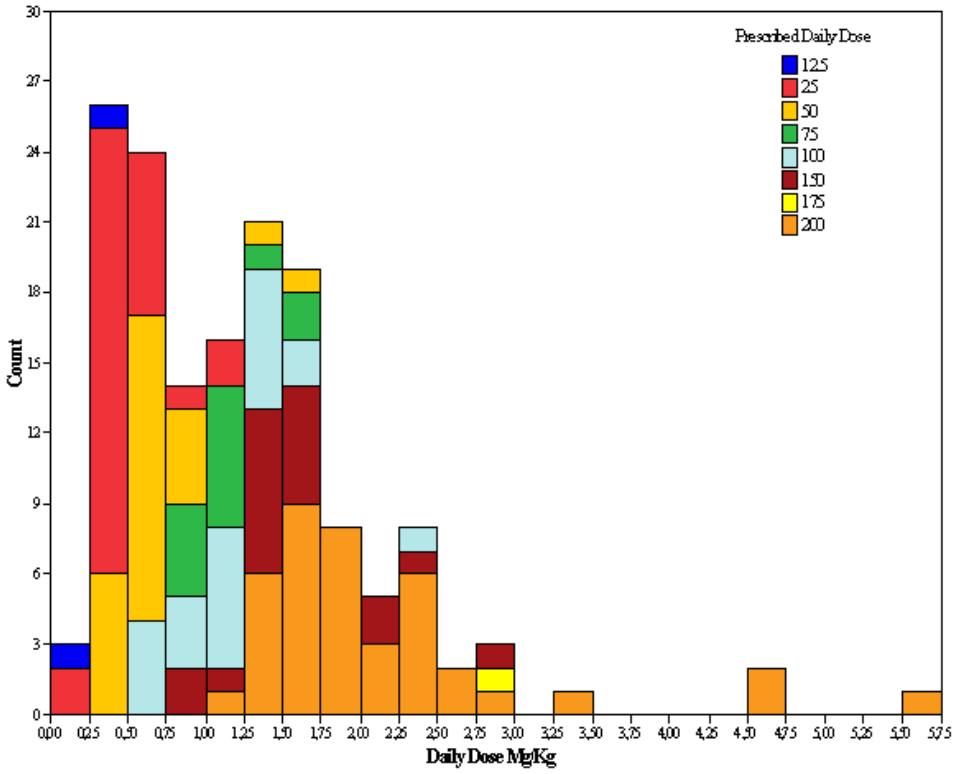
Overall, these cases do not provide new safety information and no measures are deemed necessary.

Additional comment:

In Sweden, the currently approved recommended starting dose in children is 0.5 mg/kg. The approval was based on the same studies that are submitted in the current pdWS procedure: 4-week dose ranging study (study 307A) and a 52 week open label extension study (307B).

The study 307A showed that the lowest starting dose distinguishable from placebo was 1.0 mg/kg. In the open-label study 307B, the starting dose was set at 12.5-25 mg and the dose was then titrated up. In order to better understand the data and to be able to correlate the data with the results from study 307A where dosing was done per kg bodyweight the MAH was asked to present as a histogram showing the number of patients per dose per bodyweight given as dose intervals in the study 307B as a part of the Swedish national procedure:

Fig 1. Daily dose of metoprolol by patient weight at the end of follow-up, week 16 or week 52



At the end of follow-up, about 35 % of the subjects were receiving doses below 0.75 mg/kg. Since the instructions were that the dose should be titrated up in case of an inadequate effect on blood pressure it could be assumed that this group includes a number of responders (responder rates being 46 % at week 16 and 65 % at week 52).
It is acknowledged that the lowest dose shown to be efficient in study 307A was 1.0 mg/kg. However, the lowest dose tested (0.2 mg/kg) was only about one third of the recommended starting dose in adults, which is 50 mg (which would correspond to approximately 0.65 mg/kg in a person weighing 75 kg).
Adverse effects of metoprolol such as bradycardia may occur at lower doses than 1.0 mg/kg and a more precautious starting dose corresponding to the dose recommended in adults is advocated, especially since nothing in the data suggest that the response in children is different to that in adults and no significant correlation with age 7-17 years in AUCt or Cmax in PK study patients. Since recommendations are given in the posology to titrate up the dose in case of insufficient response, lower starting dose would not withhold efficient treatment but may minimise the risk for premature discontinuation.

In summary, the data indicate that there appears to be subjects that respond to lower doses than 1.0 mg/kg. It is therefore proposed that lower starting dose more in correspondence with the adult dose is recommended. To simplify dosing a starting dose of 0.5 mg/kg is proposed.

Assessor's comment:
The data presented by SE are from study 307B (the open-label extension study). All but one of these 138 patients were included in study 307A as well. Therefore, all patients were already pretreated with

metoprolol, and dosing in study 307B cannot be considered a real starting dose, rather a follow-up dose. However, based on the data presented it seems that a substantial proportion of the patients achieve their blood pressure goal based on lower doses than the currently advised 1.0 mg/kg dose. This could also implicate that a substantial proportion may still achieve their treatment goal with a starting dose of 0.5 mg/kg, but possibly after longer follow up. Such a starting dose would also be more in line with the adult starting dose (0.65 mg/kg based on 50 mg dose in a 75 kg person). Based on these assumptions, and with the aim of minimizing the risk of adverse effects we would support a starting dose of 0.5 mg/kg.

VI. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

Overall conclusion
In line with the national assessment of the similar data, it can be concluded that a blood pressure effect can be observed with metoprolol succinate controlled release across the dose range investigated with an acceptable safety profile. The blood pressure effect was most obvious for the DBP. Therefore, the data are considered sufficiently compelling to approve an indication for treatment of hypertension. Consequently, information should be included in section 4.1, 4.2, 5.1 and 5.2 of the SmPC. for prolonged release metoprolol tablets.

Recommendation
A Type IB variation to be requested from the MAH by 3 months after finalisation of the procedure should include information based on the conclusions of the current procedure as outlined below:

4.1 Indication

Children and adolescents 6-18 years of age
Treatment of hypertension

4.2 Posology and method of administration
Children and adolescents

The recommended initial dosage in hypertensive patients ≥6 years is 0.5 mg/kg Seloken ZOK (0.48 mg/kg metoprolol succinate) once daily. The final dose administered in milligrams should be the closest approximation of the calculated dose in mg/kg. In patients not responding to 0.5 mg/kg, the dose can be increased to 1.0 mg/kg (0.95 mg/kg metoprolol succinate), not exceeding 50mg (47.5 mg metoprolol succinate). In patients not responding to 1.0 mg/kg, the dose can be increased to a maximum daily dose of 2.0 mg/kg (1.9 mg/kg metoprolol succinate). Doses above 200 mg (190 mg metoprolol succinate) once daily have not been studied in children and adolescents.
Efficacy and safety of use in children < 6 years have not been studied. Therefore, Seloken ZOK is not recommended in this age group.

*Appropriate amendments to the posology should be made for tartrate prolonged release products.

5.1 Pharmacodynamic properties
In 144 paediatric patients (6 to 16 years of age) with primarily essential hypertension, Seloken ZOK has been shown in a 4-week study to reduce systolic blood pressure with 5.2 mmHg with 0.2 mg/kg (p=0.145), 7.7 mmHg for 1.0 mg/kg (p=0.027) and 6.3mmHg for 2.0 mg/kg doses (p=0.049) with a maximum of 200mg/day compared to 1.9 mmHg on placebo. For diastolic blood pressure, this reduction was 3.1 (p=0.655), 4.9 (p=0.280), 7.5 (p=0.017) and 2.1 mmHg, respectively. No apparent differences in blood pressure reduction were observed based on age, Tanner stage, or race.

5.2 Pharmacokinetic properties
The pharmacokinetic profile of metoprolol in paediatric hypertensive patients aged 6-17 years is similar to the pharmacokinetics described previously in adults. Metoprolol apparent oral clearance (CL/F) increased linearly with body weight.

VII. LIST OF MEDICINCAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

Astra Zeneca's Metoprolol Succinate