PHARMACOMETRICS REVIEW

ADDENDUM 2

NDA Number:	N19962 SE5 #033
Generic Name:	Metoprolol succinate
Brand Name:	TOPROL-XL
Proposed Indication:	Hypertension
Sponsor:	Astrazeneca
Type of submission:	Pediatric supplement
Pharmacometrics (PM) reviewer:	Pravin Jadhav Ph.D.
Primary reviewer:	Robert Kumi Ph.D.
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This report serves as an addendum to the original pharmacometrics review (dated November 7, 2006) and a supplement review (dated November 29, 2007). An approval letter was issued on November 14, 2006 identifying the following deficiencies and potential alternatives to resolve such deficiencies:

"In addition to the trend (p=0.135) in dose-response for the prospectively defined primary end point, slope among non-zero doses for sitting systolic blood pressure, there are favorable trends for other analyses—sitting diastolic pressure, standing systolic and diastolic pressure, slope with or without inclusion of placebo, and high doses compared to placebo—some of which are nominally statistically significant. It is likely that the doses were chosen too closely spaced (and certainly the distribution of trough plasma levels of metoprolol overlap greatly across dose groups), so that the ability of the study to demonstrate a dose-response was impaired. An analysis of exposure-response performed as part of our review is also fairly supportive of a treatment effect on systolic pressure.

There are several potentially acceptable alternatives to provide sufficient evidence of an effect of metoprolol in children.

The most straightforward would be to do a successful study similar in design to 307A, but with dose levels chosen better to separate exposure in each arm. You might also reasonably engineer a formulation to allow better targeting of mg/kg doses. If one were sure there were a dose-response (or an exposure-response), then one could use available pharmacokinetic data to predict the effect throughout the interdosing interval; thus, demonstration of a statistically significant effect on peak systolic or diastolic pressure would be sufficient for this confirmatory study.

The less-certain alternative is to do some further exposure-response modeling. As noted previously, some exposure-response analyses have been undertaken with the available data. Some further analyses of the available data might be adequately persuasive. You are encouraged

to meet with the Agency to discuss that possibility, but a complete set of analyses would include systolic and diastolic pressures, sitting and standing, and a careful assessment of the false-positive error rate for these analyses. The goal would be to define the incremental evidence from exposure that was not a consequence of trend in dose-response."

The sponsor chose the later alternative to submit further exposure-response analysis (submission date- January 18, 2007) to pursue the approval. In addition, the sponsor was given a table covering 5 different analysis methods, such as, linear regression, ANOVA and mixed model repeated measures (MMRM), to support evidence of effectiveness. The sitting and standing blood pressures (systolic and diastolic) at week 3 and/or 4 were recommended as efficacy endpoints.

The major aim of this report is to summarize evidence of effectiveness for metoprolol from analyses conducted at the agency and review supportive evidence provided by the sponsor in the January 18, 2007 submission.

1. Key points from the reviewer's analysis:

1. Significant relationship between plasma trough concentration and effect on sitting systolic blood pressure (sSBP) as exhibited by slope (-0.091 ± 0.03) with a p-value =0.0064.
2. Significant difference between the randomized dose groups and placebo using a mixed model repeated measures (MMRM) approach (p-values: 0.009 (2 mg/kg), 0.023 (1 mg/kg) and 0.056 (0.2 mg/kg)).
3. Observed relationship between Toprol-XL dose (p-value= 0.0155) as well as plasma trough concentration and sitting diastolic blood pressure (sDBP).
4. Observed relationship between Toprol-XL dose as well as plasma trough concentration and heart rate.
5. Consistent effects on BP and HR across trials; the model predicted dose-response from 307B study reasonably matched with observed effects in 307A study.
6. Reasonable control over type-1 error rate for concentration response analysis (conditional type-1 error rate calculated by 2 different methods)

2. Key points from the sponsor's January 18th submission:

1. Reasonable evidence that TOPROL-XL lowers DBP and that the reduction is dose related.

   Substantial evidence (p=0.015) for dose-sDBP, the principle secondary measure of interest remains even after applying a conservative multiple comparison adjustment to the significance level for slope of change in sDBP, eg, 0.05/2 = 0.025.
2. Nominally significant evidence of superiority of doses over placebo even though the study was not powered to detect these differences (see Table 2)

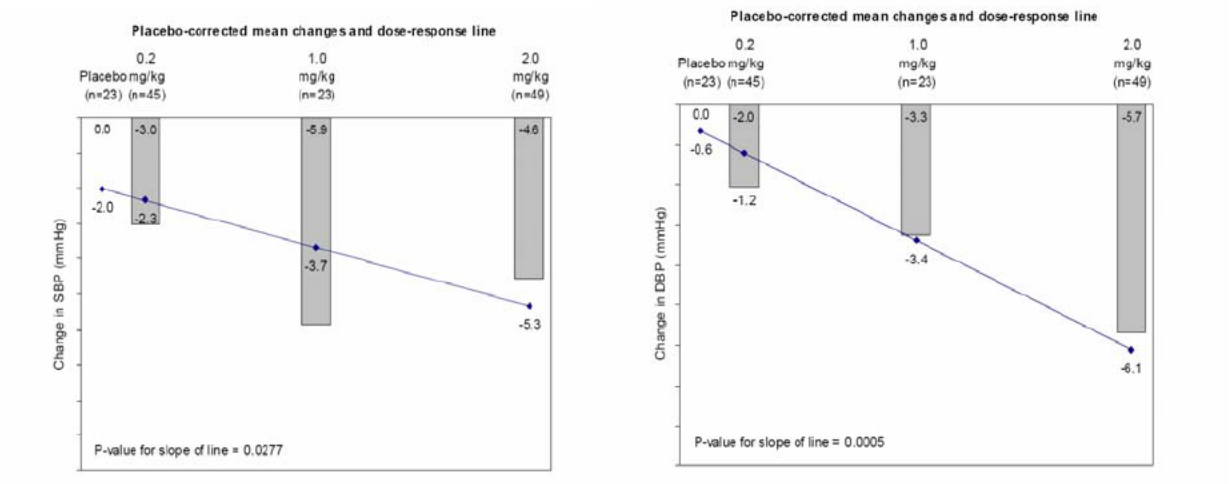
   Of specific note, the high (2.0 mg/kg) dose effect on sSBP proved superior to placebo (difference of 4.4 mmHg; p=0.049), as did the mid-dose (1.0 mg/kg; difference of 5.8 mmHg; p=0.027), and all doses pooled (p=0.035). For sDBP the high dose group also proved superior to placebo (difference of 5.4 mmHg; p=0.017).

3. Significant dose response relationship based new analysis method.

   Due to high visit-to-visit variability in blood pressure measurement and possible regression to the mean, new dose response analyses was conducted. In the new dose response analyses, the baseline BP value as a term to the regression model and by changing the dependent variable to the change from baseline to the mean of the last 2 BP values. The last 2 BP values represent the 2 values collected on the highest randomized dose assigned to the patient (ie, post-titration) for those patients who completed the study. These new analyses were conducted both with and without the placebo group.

   The slope for change in sSBP as a function of dose ratio was significant with placebo included in the model (p=0.028- Figure 1). (With placebo excluded, the test for slope = 0 p-value was 0.232.) The slope for sDBP remained significantly different from 0 in both models (with or without placebo).

Figure 1: Placebo-corrected dose response line and mean changes from baseline to the mean of the last 2 visits for sitting SBP (left) and sitting DBP (right), all treatment groups (Study 307A, ITT population)



4. Alleviated need for additional antihypertensive medications through week 16 for patients (N=20) randomized to placebo treatment during the double blind period (307A) but continued on TOPROL-XL in 307B study.

   Further, additional reduction in blood pressure was achieved in 307B study for these 20 patients. The blood pressure declined 2.3/0.6 mmHg for these 20 patients during Study 307A; then, following the introduction of TOPROL-XL, blood pressure declined by an additional 6.3/5.8 mmHg (95% CI: –10.3,–2.2/–9.6, –2.0) at Week 16/LOCF (Table 8).

5. 62% overall response rate at week 16 in 307B study.

   The confidence intervals (CI) for this rate, as well as for all time periods, clearly exclude 0, including that for the entire study period (52 weeks) where the response rate was 64% (95% CI: 55%, 74%); only 11 patients (11%) were taking

an additional antihypertensive drug. Importantly, the equivalent response rate on placebo at week 4 was 30% (95% CI: 10%, 50%). (Table 1)

Table 1: Response rates, concurrent antihypertensive medications, and mean dose at selected time points during the 52-week study (Study 307B)

	Entry into Study 307B	Week 16	Week 32	Week 52/ LOCF
Number (%) of responders (95% CI in %)	41 (41) (32, 51)	62 (62) (53, 72)	70 (70) (61, 79)	63 (64) (55, 74)
Number (%) of patients receiving at least 1 antihypertensive	NA	7 (7.2)	12 (12.4)	11 (11.0)
Mean TOPROL-XL dose, mg (mg/kg)	37.0 (0.5)	96.6 (1.2)	108.2 (1.3)	112.3 (1.3)

Note: A responder was defined as any patient whose sitting systolic and diastolic blood pressure was less than the 95th percentile at the specified timepoint.
CI confidence interval. LOCF Last observation carried forward. NA Not available.

6. Effect on heart rate complements effect on blood pressure thus establishing beta-blockade potential, an expected pharmacodynamic effect, of TOPROL-XL.

   The dose response of changes from baseline to Week 4/LOCF in ECG heart rate had a p-value for the slope of 0.06.

7. Reasonable exposure response relationship for various endpoints of blood pressure and heart rate.

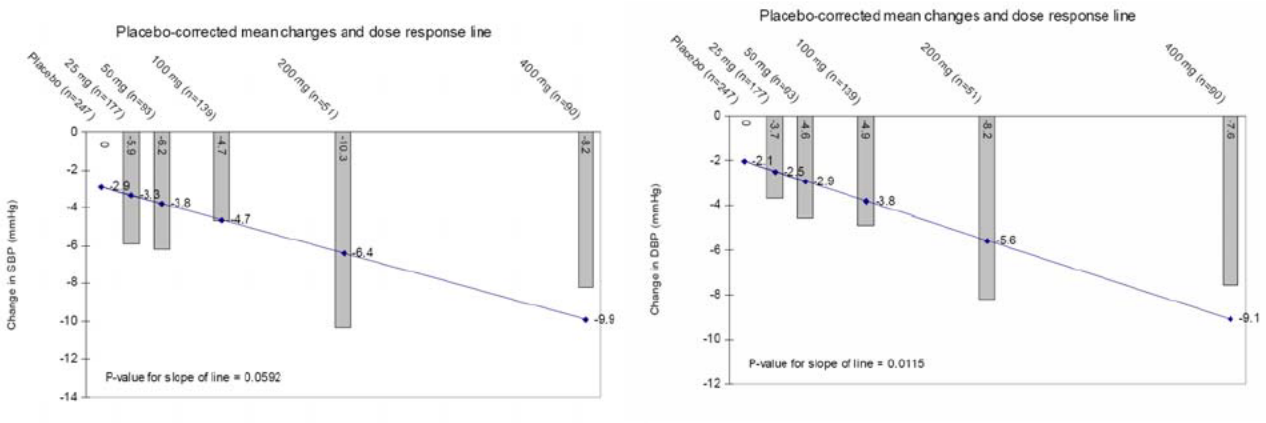
8. Consistent effects in pediatric and adult population based on the ATTACH[†] and the M-FACT[‡] studies.

   All the doses studied in these trials were significantly superior to placebo. DBP). The slope for change in sSBP was not significantly different from 0 (p=0.06) (Figure 2). The slope was, however, significant for sDBP (p=0.01) and the slope of –0.44 (SE=0.13) was consistent with that observed in the pediatric 307A study (slope= –0.55, SE=0.15).

[†] A phase III, multi-center, randomized, double-blind, placebo-controlled, parallel group factorial study of metoprolol succinate extended-release tablets (TOPROL-XL), hydrochlorothiazide and their combination in patients with essential hypertension.

[‡] Metoprolol Succinate-Felodipine Antihypertension Combination Trial: A multicenter, randomized, double-blind, placebo-controlled, factorial efficacy trial of combination therapy of metoprolol succinate plus felodipine once daily dosing

Figure 2: TOPROL-XL dose response for sSBP (left) and sDBP (right) - in hypertensive adults, Studies ATTACH and M-FACT pooled, N=797



The sponsor concludes that the data from Studies 307A and 307B, and the population PK analyses, support the conclusion that TOPROL-XL lowers BP in hypertensive children 6 years of age and older. The magnitude of antihypertensive response is dose-related and is consistent with the available adult information. Furthermore, the data are sufficient to support labeling recommendations for use of TOPROL- XL in this pediatric population, which will provide clinicians with a suggested starting dose, guidelines for dose adjustment, and a recommended maximum dose.

3. Table 2: Tabular listing of p-values covering most relevant statistical analyses (completed by the sponsor based on the template provided by the agency)

Method	Endpoint	Analysis specifics	Week 4	Week 3
Linear regression (Slope of dose response curve)	sSBP	Baseline and placebo correction	0.5731	0.2020
		Baseline correction	0.13	0.0230
	sDBP	Baseline and placebo correction	0.015	0.0573
		Baseline correction	0.0043	0.0105
	StSBP	Baseline and placebo correction	0.1409	0.2385
		Baseline correction	0.0112	0.0172
	StDBP	Baseline and placebo correction	0.1443	0.4781
		Baseline correction	0.0152	0.1064
Analysis of variance (ANOVA)	sSBP	Pooled dose versus placebo	0.0351	0.0108
	sDBP		0.1189	0.0374
	StSBP		0.0065	0.0031
	StDBP		0.0135	0.0338
Linear regression (Slope of weight adjusted dose response curve)	sSBP	Baseline and placebo correction	0.3862	0.2381
		Baseline correction	0.0843	0.0298
	sDBP	Baseline and placebo correction	0.0089	0.0373
		Baseline correction	0.0025	0.0070
	StSBP	Baseline and placebo correction	0.0494	0.0871
		Baseline correction	0.0035	0.0052
	StDBP	Baseline and placebo correction	0.1141	0.2771
		Baseline correction	0.0122	0.0559
Analysis of variance (ANOVA)	sSBP	2 mg/kg versus placebo	0.029	0.0023
	sDBP		0.004	<0.0001
	StSBP		0.0021	0.0011
	StDBP		0.0003	0.0017
	sSBP	1 mg/kg versus placebo	0.038	0.0183
	sDBP		0.204	0.3337
	StSBP		0.0129	0.0222
	StDBP		0.022	0.1069
	sSBP	0.2 mg/kg versus placebo	0.112	0.0631
	sDBP		0.114	0.0058
	StSBP		0.0623	0.0200
	StDBP		0.016	0.0112
Mixed model repeated measures (MMRM) analysis	sSBP	2 mg/kg versus placebo	0.009	
	sDBP		0.0002	
	StSBP		0.0005	
	StDBP		0.0006	
	sSBP	1 mg/kg versus placebo	0.023	
	sDBP		0.23	
	StSBP		0.0087	
	StDBP		0.029	
	sSBP	0.2 mg/kg versus placebo	0.056	
	sDBP		0.022	
	StSBP		0.0116	
	StDBP		0.007	

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