EXECUTIVE SUMMARY

This submission consists of two studies in support of the use of Toprol-XL in pediatric patients. The data, as submitted, are insufficient to recommend a new indication for pediatric use for metoprolol.

Study 307A was an unbalanced, double-blind, placebo-controlled, dose-ranging study. Pediatric patients (aged 6-16 years), with either systolic or diastolic hypertension were randomized to treatment with either placebo or metoprolol, at approximate doses (based on 12.5 mg increments, the size of the scored portion of the Toprol-XL tablet) of 0.2, 1.0 and 2.0 mg/kg. The randomization to placebo: Toprol-XL 0.2 mg/kg: Toprol-XL 1 mg/kg: Toprol-XL 2.0 mg/kg was in a ratio of 1:2:1:2. The administered dose for the two highest randomized doses was titrated after one week (1 mg/kg Toprol-XL) or 2 weeks (2 mg/kg Toprol-XL). The primary metric of the study was the slope of placebo-subtracted sitting systolic blood pressure at trough at the end of the study. The sponsor's analysis did not include the placebo point in defining the slope. The primary analytic plan did not demonstrate a significant slope effect. The inclusion of the placebo-group to anchor the analysis of slope also did not produce a significant value ($p= 0.135$).

The sponsor performed several additional analyses including comparison of the high dose and mid dose to placebo. Both these analyses were nominally marginally significant.

Additional analyses were performed by Dr. Freidlin (biostatistics) and Dr. Kumi (biopharmaceutics). Although some, but not all, of these analyses were nominally statistically significant, demonstrating a blood pressure effect of Toprol-XL in children, the primary metric of the study was not statistically significant. Modeling of the data resulted in some model-based analyses, but not all, which indicate a significant effect of Toprol-XL in children. No modeling of blood pressure response to either concentrations or dose in adults is available to define the most appropriate analysis to be performed in children. There is, therefore, insufficient data to recommend that Toprol-XL be approved in children for the treatment of hypertension.

The concentrations of racemic metoprolol at the 0.2 mg/kg were largely below the LLQ. The median values of metoprolol (consisting of the active and inactive enantiomers) suggest that the 0.2 mg/kg dose might be considered as a pseudo-placebo. The trough concentrations for adults for a 50 mg, culled from the literature, are approximately 35 nmol/L (23 ng/ml). If one assumes linearity for the 25 g dose, the resultant value for the lowest approved antihypertensive dose in adults would be approximately12 ng/ml or an order of magnitude greater than that observed in the pediatric study. There was approximately twice the number of subjects in the 0.2 mg/kg dose group than in placebo, to assess blood pressure effects, suggesting a better estimate for the effect of the 0.2 mg/kg dose than placebo effect. The 0.2 mg/kg dose could reasonably be treated as a pseudo-placebo. Consequently, the proposed analytic plan that

excluded the placebo in the analysis should not be dismissed as totally illogical, since the lowest dose (0.2 mg/kg) may adequately serve as the placebo.

Study 307B was a 52-week open-label extension study. Subjects could enter this study by any one of several routes. The vast majority of subjects were enrolled after participating in study 307A. The initial protocol only planned to maintain follow-up for 16 weeks. The protocol was subsequently amended that follow up would be for 52 weeks. There were 138 patients who enrolled either into the 16 or 52 week extension. Of those enrolled, there were 27 who prematurely discontinued either the 16 week or 52 week extension. There were 45 patients who completed the 16 week extension (not re-enrolling to complete 52 weeks) and 81 who completed the 52-week extension.

Adverse events did suggest either unusual or drug-related concerns. The most frequent events were headache and URI. Most of the adverse events are common events in a pediatric population.

There were no laboratory events or shift from baseline in laboratory measurements of concern.

Heart rates at values below 50 BPM were measured in 3 patients during the double-blind phase of the study (measured at trough). During the open-label phase there were 5 subjects with heart rate values measured under 50 BPM. The decrease in heart rate likely reflects an extension of the β-blockade effect.

There were small but clear changes in measures of ECG repolarization. These changes are of uncertain accuracy, due to the uncertainties of the correction when heart rate is substantially decreased. In addition, given, the long-history of use of Metoprolol (as an IR or XL formulation), there does not appear to be a significant risk of proarrhythmic events with its use in adults.

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