1 EXECUTIVE SUMMARY

Astra Zeneca submitted NDA 19-962 SE5 #033 (pediatric supplement) to fulfill a FDA pediatric written request for TOPROL-XL, metoprolol succinate extended release tablets. Metoprolol, a beta blocker, is approved for hypertension, angina and heart failure in adults. In adults with hypertension the usual initial dosage is 25 to 100 mg daily (single dose) as monotherapy or in combination with a diuretic; this dosage is titrated at weekly intervals until optimum blood pressure reduction or control is achieved. The current application focuses on Toprol-XL use in pediatric patients six years and older. The initial proposed dosing in children six and older is 1.0 mg/kg; subsequently the dose is titrated based on clinical response.

Two clinical trials, Studies 307A (dose-response) and 307B (safety extension of 307A), were conducted in pediatric patients with hypertension to support the proposed labeling changes. The applicant conducted dose-response (n = 140 patients), population PK (n = 120 patients) and PK/PD (n = 65 patients) analyses using data from pediatric hypertensive patients receiving Toprol-XL in the mentioned studies. PK and PD measures estimated in the analyses or determined during the trials included: Ctrough, Cmax, AUC0–24, CL/F, Tlag (lag time), ka (first order absorption rate constant), V2/F (volume of distribution in central compartment), Q/F (inter-compartmental clearance), .DBP (change in diastolic blood pressure, .SBP (change in systolic blood pressure), and .HR (change in heart rate). Selected covariates including age, body weight, gender, race, and Toprol-XL dose were evaluated for their potential impact upon PK parameters.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information submitted to NDA 19-962 SE5 #033. The clinical pharmacology and biopharmaceutics information provided in the current submission is acceptable. However, the sponsor should note the following.

Comments to sponsor

A. In future studies with pharmacometric components you should consider the following:
   1. Collect sufficient (multiple) samples from individual subjects to allow assessment of inter-occasion variability and estimation of inter-individual variability (eta) for all relevant parameters.
   2. Placebo groups should be identically matched across all dose groups (e.g. same titration schedule and number of tablets) to minimize potential bias or apparent differences in the placebo effect.

B. Please address labeling changes and comments in the attached revised label.

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

1. **Dose-Response**: A statistically significant dose-response did not exist for placebo (pooled)–corrected .SBP from baseline; however, the relationship was evident when placebo (specific-group) –corrected data were used.

2. **Proposed Pediatric Dosage**: Overall, information from the dose-response study suggests that Toprol XL is effective in the pediatric population. The optimal initial dose in mg/kg or the maximum safe and effective dose cannot be determined from the information provided. However, the 1.0 mg/kg (proposed by applicant) appears to be a reasonable initial dose; subsequent titration based on clinical response is acceptable. Relative to adults (assuming average adult weighs 70 kg), the proposed initial pediatric dose is in the range but closer to the high end of the usual initial adult dose: 0.36 – 1.43 (25 to 100 mg).

3. **Metoprolol Pharmacokinetics in Pediatric Patients**: Metoprolol PK in children (6 – 16 years old) were adequately characterized by a 2-compartment model with flip-flop, first-order absorption, and an absorption lag time using a population PK approach. The population PK model yielded precise parameter estimates. Estimated PK Measures (median values) were CL/F = 227.5 L/hr; V2/F = 96.1 L; Q/F = 675 L/hr; V3/F = 620 L; ka = 0.0467 hr–1; and Tlag = 0.853 hr. Overall, the PK measures in children are of a similar magnitude as that in adults reported in the literature.

4. **Metoprolol Exposure in Children**: At the proposed pediatric initial dose, 1.0 mg/kg, average Cmin was ~ 12.2 ng/ml and average Cmin was ~ 24.6 ng/mL at the 2.0 mg/kg dose; however data were highly variable with CV > 100 %. The majority of samples were below the lower limit of quantitation at the lowest studied dose, 0.2 mg/kg. In adults (literature reports), average Cmin following 50 mg (~0.71 mg/kg) was ~ 8.5 ng/mL and ~ 22.6 ng/mL following 100 mg (~1.43 mg/kg).

5. **Covariates**: Sex, age, race, body weight, and Toprol-XL dose did not have a clinically significant effect on metoprolol PK.

6. **Population PK/PD Model**: Using a log-linear model or linear model, there were statistically significant relationships ($p < 0.005$) between the changes in SBP and DBP from baseline and measures of metoprolol plasma exposure (Ctrough, $AUC_{(0–24)}$ and Cmax). However, the goodness-of-fit of the PK/PD models were generally poor and parameters were not precisely estimated in most models due to a high degree of variability in the blood pressure data. Based on the PK/PD analysis, plasma exposure (AUC) explains < 10 % of the variability in response (reduction in systolic blood pressure). However, the PK/PD relationship suggests that there is a trend for increased response with increased exposure (dose driven), thus supporting dose titration.

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Concurrence

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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