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Study center(s)
Protocol 307B was initiated at 36 centers in the United States and 1 center in the Dominican Republic. Nine centers in the United States were shipped drug but did not enroll any patients. Thus, a total of 27 centers in the United States and 1 center in the Dominican Republic enrolled patients into this study.

Publications
No publications at the time of writing this report.

Study dates
<table>
<thead>
<tr>
<th>First patient enrolled</th>
<th>16 week: 03 July 2002</th>
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<tr>
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<td>52-week: 27 December 2002</td>
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<tr>
<td>Last patient completed</td>
<td>16 week: 22 March 2004</td>
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<td>52-week: 25 March 2005</td>
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Objectives
The purpose of this study was to evaluate the pharmacokinetics and long-term safety and tolerability of TOPROL-XL in hypertensive pediatric patients.
Study design
Protocol 307B was designed as an open-label extension to a previously conducted, 4-week, double-blind, placebo-controlled study of TOPROL-XL (Protocol 307A). Protocol 307B was initially designed as a 16-week study. In accordance with revisions to the Written Request from the Food and Drug Administration (FDA) regarding the use of TOPROL-XL in pediatric hypertensive patients, the protocol was amended to increase the duration of the open-label treatment period to 52 weeks to more accurately assess the long-term safety and tolerability of TOPROL-XL in pediatric patients aged 6 to 16 years with hypertension. Following the protocol amendment, enrollment into the original 16-week protocol was terminated and patients were offered the opportunity to transfer to the amended 52-week protocol. Patients who had completed the original 16-week protocol were also contacted and offered enrollment in the amended 52-week protocol. All patients were to begin the 52-week study at Visit 1, regardless of how they were enrolled. Throughout this report, the original protocol is referred to as either 307B (16 week) or the 16-week study, while the amended protocol is referred to as either 307B (52 week) or the 52-week study.

The suggested starting dose of TOPROL-XL for all patients was 25 mg. Investigators were instructed that the starting dose of TOPROL-XL could be as low as 12.5 mg. The TOPROL-XL dose was to be increased every 2 weeks in increments of 25 mg or 50 mg based on tolerability until blood pressure (BP) was controlled or the maximum daily dose of 200 mg was attained. 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.

Target patient population and sample size
Consented male and female patients, aged 6 to 16 years of age, with a history of, or presenting with, reproducible sitting systolic blood pressure (SBP) or diastolic blood pressure (DBP) ≥95th percentile using height-adjusted charts for age and gender. Patients were eligible to enroll into Protocol 307B if they met 1 of the following criteria: 1) successfully completed Protocol 307A; 2) discontinued from Protocol 307A (for any reason other than a drug-related AE); 3) failed screening for Protocol 307A (had sitting SBP >20 mmHg or DBP >10 mmHg above the 95th percentile using height-adjusted charts for age or gender); or 4) had not previously been enrolled in Protocol 307A but met all screening criteria for Protocol 307B and were eligible for enrollment at a site that randomized at least 6 patients into Protocol 307A.

Investigational product and comparator(s): dosage, mode of administration and batch numbers
TOPROL-XL (metoprolol CR/XL), 25 mg or 50 mg tablets, administered orally once daily, batch numbers H0960-10-01-01, H0960-10-01-02, and H0638-09-03-09.

Duration of treatment
16 weeks (16-week study); 52 weeks (52-week study)
Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

The percentage of patients having a response to treatment, defined as SBP or DBP <95th percentile, was determined, as were changes in sitting and standing trough SBP and DBP over time.

Serial pharmacokinetic (PK) samples were obtained following a 48-hour washout period from a subset of patients after administration of a single 25 mg dose of TOPROL-XL at anytime between Visits 1 and 18 and the following parameters were to be estimated: area under the concentration-time curve from hour 0 to the last measurable plasma 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 half-life (T1/2). In addition, trough plasma metoprolol concentrations were determined for all patients at the Final Visit, except for those who completed the serial PK portion of the study at Visit 18.

Safety

Number and percentage of patients with adverse events (AEs); changes in clinical laboratory tests, pulse rate, body weight, height, body mass index (BMI), z-scores for weight, height, and BMI, and electrocardiographic (ECG) parameters; and the incidence of clinically significant abnormal laboratory values and physical examination findings.

Statistical methods

All analyses were performed on patients who received at least 1 dose of study medication (ie, the all treated patients population). Data were analyzed using observed data although in some instances, additional analyses impute for missing values by using the last value carried forward (LOCF) method. The percentage of responders was analyzed at study entry into 307B and using an LOCF approach at Weeks 16, 32, and 52 and was summarized by frequency counts, percentages, and 95% confidence intervals. Mean changes in sitting and standing SBP and DBP from randomization into Protocol 307A to study entry into 307B, at Weeks 16, 32, 52, and at the Final Visit were examined only for patients who were randomized to double-blind treatment in Protocol 307A. For patients without prior randomization in Protocol 307A, mean sitting and standing SBP and DBP values are reported for each timepoint.

Descriptive statistics were used to summarize trough plasma metoprolol concentrations and the serial PK parameters. Safety data were summarized for all treated patients. No formal statistical analyses were performed on the safety data in this study.

The results of the 52-week study are considered of primary importance and therefore the focus of this Clinical Study Report is on data obtained under the amended 52-week protocol.
Patient population

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 (No. 042-002) 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.

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/m² and 64% of patients were overweight (BMI ≥95th percentile adjusted for age and gender). Three-quarters of patients in the 52-week study had been diagnosed with hypertension within 2 years prior to study entry. The majority of patients entered with a diagnosis of isolated systolic hypertension (61%) or both systolic and diastolic hypertension (27%). Among patients who had been randomized in Protocol 307A, sitting SBP and DBP averaged 127 mmHg and 75 mmHg, respectively, upon entry in the 52-week study. Mean sitting SBP and DBP at study entry among the 12 patients without prior randomization in Protocol 307A were 138 mmHg and 82 mmHg, respectively.

Efficacy and pharmacokinetic results

Among all treated patients in the 52-week study, 64% of treated patients in the 52-week study had a response to treatment at the Final Visit (Week 52/LOCF), defined as sitting SBP and DBP <95th percentile. Similar response rates at Week 52/LOCF were also evident among patients who were receiving a concomitant antihypertensive agent at the Final Visit (6 of 11, 55%) and among those receiving TOPROL-XL monotherapy (57 of 87, 66%).

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 C_{max} or AUC{\textsubscript{t}} 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 AUC{\textsubscript{t}} 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 C_{max} and AUC{\textsubscript{t}} were within the ranges observed in healthy young adult subjects. In addition, T_{\text{max}} (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.
Safety results

The 100 patients who were included in the main analysis set for the 52-week study were treated for an average of 354 days. The mean daily prescribed dose at the Final Visit was 112.3 mg, with approximately 60% of patients receiving TOPROL-XL doses of 12.5 mg to 100 mg. Few patients (n=10) required down titration of study medication during the study. Overall, long-term administration of TOPROL-XL for up to 52 weeks in pediatric and adolescent hypertensive patients was generally well tolerated (Table S1). The most common individual AEs reported in the 52-week study were headache (30%), upper respiratory tract infection (20%), cough (19%), nasopharyngitis (13%), and pharyngolaryngeal pain (12%). The majority of events in the 52-week study were mild to moderate in intensity, with only 5 patients having an event that was assessed as severe in intensity. No patient died and neither of the 2 SAEs (pneumonia and menometrorrhagia) was considered causally related to study medication.

Table S1 Number (%) of patients who had an adverse event in any category (all treated patients)

<table>
<thead>
<tr>
<th>Category of adverse event</th>
<th>52-week study (N=100)</th>
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<tr>
<td>At least 1 adverse event</td>
<td>83 (83.0)</td>
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<tr>
<td>At least 1 drug-related adverse event</td>
<td>18 (18.0)</td>
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<tr>
<td>Serious adverse events leading to death</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Serious adverse events not leading to death</td>
<td>2 (2.0)</td>
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<tr>
<td>Discontinued study due to an adverse event</td>
<td>4 (4.0)</td>
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* One additional patient (No. 004-006) was reported to have study drug stopped on Day 378 due to an AE (bradycardia) on the Adverse Event page of the case report form. This adverse event was noted on the ECG performed at the Final Visit. The patient’s last dose was on Day 377 and he was noted as having completed the study on the Study Completion/Withdrawal page of the case report form.

There was no apparent effect of gender, age, race, Tanner stage, BMI percentile, maximum dose, or final mg/kg dose on AE incidence in this study, and examination of individual AEs did not reveal any clearly discernible pattern in the distribution of AEs across these subgroups. There was no evidence that increased duration of treatment had any effect on AE incidence rates. Treatment with TOPROL-XL for up to 52 weeks was not associated with clinically significant changes in clinical laboratory tests, pulse rate, or physical examination findings. Based on weight, height, and BMI z-scores, TOPROL-XL had no apparent effect on the normal growth of pediatric and adolescent patients in this study. Bradycardia was reported for 3 (3%) patients in the 52-week study and 1 (1%) patient in the 16-week study, the latter of whom was discontinued from the study due to this event. No patient experienced clinical sequelae of bradycardia, with all cases identified at the time of assessment of vital signs or by ECG. No specific findings of concern related to rate, rhythm, conduction or repolarization were apparent in ECGs performed at the Final Visit.
Conclusion(s)

The results of this study indicate that long-term treatment with TOPROL-XL at daily doses of 12.5 mg to 200 mg in pediatric and adolescent patients with hypertension was safe and generally well tolerated. The tolerability profile of TOPROL-XL was comparable to that reported for adult hypertensives and there were no unexpected adverse drug reactions compared with the known product profile. The effect on blood pressure reduction persisted through to the end of the 52-week treatment period. The PK profile of metoprolol following a 25 mg dose of TOPROL-XL was generally comparable between younger (Tanner Stage ≤3) and older (Tanner Stage >3) patients, and no correlations between systemic exposure of metoprolol and age and body weight were observed. No differences in PK estimates between males and females were noted. The PK profile of metoprolol among pediatric and adolescent hypertensive patients is comparable to that in adults.

Date of the report

20 February 2006