

CLINICAL PHARMACOLOGY REVIEW

Division of Pharmaceutical Evaluation I

NDA 20297 N (#022)

SUBMISSION DATE: September 1, 2006

Type: Pediatric Exclusivity Submission of Supplement #22 to NDA 20297

Brand Name: Coreg® Tablets and Coreg® CR Capsules

Dosage Strength: 3.125, 6.25, 12.5 and 25 mg IR tablets

10, 20,40, 80 mg CR capsules

Indication: Treatment of mild to severe heart failure of ischemic or cardiomyopathic origin, left ventricular dysfunction following myocardial infarction or hypertension

Sponsor: GlaxoSmithKline

Research Triangle Park, NC

Reviewing Division: Division of Cardiovascular and Renal Products, HFD-110

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Reference is made to the approved NDA 20297 for Coreg Immediate release Tablets of 3.125, 6.25, 12.5 and 25 mg strengths tablets. Except for the 3.125mg tablet the Coreg tablets are scored. Coreg® is a non-selective β -adrenergic blocking agent, devoid of intrinsic sympathomimetic activity with α 1-blocking activity and indicated in adults for the treatment of:

- Mild to severe heart failure of ischemic or cardiomyopathic origin, usually in addition to diuretics, ACE inhibitors, and digitalis, to increase survival and, also, to reduce the risk of hospitalization
- Left ventricular dysfunction following myocardial infarction: to reduce cardiovascular mortality in clinically stable patients who survive the acute phase of a myocardial infarction and have a left ventricular ejection fraction of $\leq 40\%$
- Hypertension alone or in combination with other anti-hypertensives

In adults the maximum tolerated dose of carvedilol is 50 mg bid in patients with essential hypertension and mild to moderate heart failure and 25 mg bid in patients with left ventricular dysfunction resulting from myocardial infarction. The carvedilol tablets are to be taken with food to slow the absorption of the drug to minimize orthostatic side effects.

Supplement Type SE-5 to NDA 20297 dated September 1, 2006 includes the reports of:

1. Study SK&F-105517/321: A multi-center, placebo controlled, 8 month study of the effect of twice daily carvedilol in children with congestive heart failure due to systemic ventricular systolic dysfunction
2. Study SK&F-105517/396: A multi-center, open-label extension study to evaluate the safety of twice daily oral carvedilol in pediatric subjects with chronic heart failure.
3. Study COG103639: A multi-center, observational study of oral carvedilol in pediatric subjects with dilated cardiomyopathy: A report from the North American Pediatric Cardiomyopathy registry (PCMR)
4. The population pharmacokinetic analysis for Study SK&F-105517/321
5. Study SK&F CCRV104257: A randomized, open-label, two period, period balanced, crossover study to estimate the relative bioavailability of a liquid suspension formulation of carvedilol compared to the tablet formulation in healthy adult volunteers.
6. Preparation of the Pediatric Suspension Formulation

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1. Executive Summary

Stipulations of the Written Request

The Witten Request (WR) stipulated the performance of an outcome/safety trial in which carvedilol and placebo are added to standard therapy in pediatric patients with congestive heart failure (CHF) due to systemic left ventricular dysfunction. The outcome trial must be a randomized, double-blind, parallel comparison of carvedilol and placebo of at least 6 month duration in a population judged to be of adequate size. A 1-year (nominal) open treatment phase should follow the controlled trial phase. The study is to be analyzed by looking for a treatment-related reduction in endpoint events (e.g. death or cause specific hospitalizations) or other indications of clinical benefit (e.g. NYHA class or growth) in the entire randomized population.

The subjects enrolled should be diagnosed with heart failure according to the standards of local practice.

The subjects to be enrolled in the trial were to be in Tanner stage 3 to < 18 years (up to 50%) with the remainder less than Tanner Stage 3. The enrollment strategy should ensure a mixture of black and non-black subjects. The study should enroll at least 150 subjects with 75 patients having >1 year of exposure.

The pharmacokinetics of carvedilol should be determined in pediatric patients either in a separate study or in a sub-study of the outcome trial. The PK data must be obtained over the dose range studied for effectiveness and the patients should have grossly normal metabolic function. AUC, half life, oral apparent clearance, volume of distribution, C_{max} and t_{max} should be determined for S(-) and R(+) carvedilol. The WR also recommended an in vivo characterization of the suspension formulation relative to the tablet in adults.

Studies Performed by the Sponsor

Pivotal Trial

The sponsor performed an efficacy and safety study using a randomized, placebo controlled, double-blind, parallel group design in 161 children with congestive heart failure due to systemic ventricular systolic dysfunction with a one year open label extension. The primary endpoint was a composite measure of heart failure outcomes of “worsened”, “unchanged” or “improved”. The composite outcome included death, hospitalization or discontinuation for worsening heart failure, NYHA or Ross’ heart failure classification and/or global assessment. The children received a low or high dose of carvedilol or placebo bid for 8 months. The study used a suspension formulation allowing body weight adjusted dosing of 0.025, 0.05, 0.1, 0.2 mg/kg (low dose) or 0.05, 0.1, 0.2, 0.4 mg/kg (high dose) in subjects weighing <62.5 kg and the immediate release tablets 3.125, 6.25, 12.5 (low dose) or 3.125, 6.25, 12.5, 25 mg (high dose) for children weighing ≥ 62.5 kg. Children weighing ≥ 62.5 kg randomized to the low dose 1.563 mg treatment received a suspension, because there is no equivalent strength tablet available. The study medications were administered with a small amount of food to slow the absorption of carvedilol. Following a screening phase the pediatric patients were randomized in a blinded fashion to receive placebo, low-dose or high-dose carvedilol in a 1:1:1 randomized schedule. In a 2 month up-titration phase the doses of carvedilol were titrated every 2 weeks, as tolerated, through four dose levels. The subjects continued on the dose level achieved during the up-titration phase during the 6 months maintenance phase. During this period, if the subject was unable to reach the target dose during the up-titration phase, the investigator had the option to intermittently continue to increase the dose level to achieve dose level 4, i.e. for children weighing < 62.5 kg 0.2 mg/kg (low dose level) or 0.4 mg/kg (high dose level) and for children weighing ≥ 62.5 kg 12.5 mg (low dose level) and 25 mg (high dose level)

Patients were stratified at the time of randomization as having a left ventricle or non-left ventricle according to the anatomic substrate of the patients’ ventricular dysfunction.

As shown below the efficacy of carvedilol in the pediatric target population could not be demonstrated:

Outcome	Treatment Group			
	Placebo (N=54)	Low-Dose Carvedilol (N=51)	High-Dose Carvedilol (N=52)	Combined Carvedilol (N=103)
	n (%)	n (%)	n (%)	n (%)
Improved	30 (55.6)	27 (52.9)	31 (59.6)	58 (56.3)
Unchanged	8 (14.8)	11 (21.6)	9 (17.3)	20 (19.4)
Worsened	16 (29.6)	13 (25.5)	12 (23.1)	25 (24.3)

The pre-specified primary analysis of the CHF composite outcome showed no statistically significant difference in the distributions or proportions of the outcomes between placebo and the combined active treatments ($p= 0.740$, Wilcoxon rank-sum test). Possible reasons for the negative result include high placebo effect, too small sample size or ineffectiveness of carvedilol.

Clinical Pharmacology Studies

PK Sub-Study

The pediatric data from 80 children were pooled with data rich information obtained earlier in 162 adults with CHF or post-MI left ventricular dysfunction. A total of 3 blood samples were collected in the children during the first 3 months (1, 2, 3 month visits). If feasible an additional blood sample was drawn during months 4 to 5. The adults received placebo or the immediate release tablets of strength 3.125, 6.25, 12.5 or 25 mg bid together with food. As in the children, both enantiomers, R(+) carvedilol and S(-) carvedilol, were measured in the adult patients. The plasma concentrations from study 369 in 162 adult patients were used to define the structural model for the carvedilol enantiomers in the population-PK analysis of the pediatric data and to compare the adult and pediatric exposure data.

The major findings of the POPPK analysis of the combined data were that for R(+) carvedilol age was a significant covariate for CL/F. No significant covariate was discernable for S(-) carvedilol. In the pediatric patients weight had a significant impact on both R(+) carvedilol and S(-) carvedilol. CL/F for the typical pediatric patient (median age 4 years, median weight 16.5 kg) was 1.25 L/h/kg for R(+) carvedilol and 2.30 L/h/kg for S(-) carvedilol. The typical values for the adults (median age 60.5 years, median weight 87 kg) was 0.62 L/h/kg for R(+) carvedilol and 1.52 L/h/kg for S(-) carvedilol. Due to this difference in CL/F the exposure to the carvedilol enantiomers is smaller in children than in adults. Post-hoc estimates of exposure (AUC) in pediatric patients were lower (on average 37% d for R(+) carvedilol and 26% for S(-) carvedilol in pediatric patients compared to adults.

Relative Bioavailability Study

The sponsor performed the relative bioavailability study comparing the suspension with the tablet in healthy adults of both sexes. Poor metabolizers of carvedilol were excluded from the

study. Two doses of carvedilol separated by 12 hours were administered to the subjects. Both carvedilol enantiomers were measured. The results showed that AUC and C_{max} of the suspension and tablet were comparable. T_{max} was smaller with the suspension than with the tablet.

Compliance with Stipulations of Written Request

A comparison of the Clinical Pharmacology methods used by the sponsor in performing the studies with the stipulations of the Written Request (WR) shows the following:

The POPPK analysis used data from 80 children, who constituted the large majority of the subjects on active treatment. They included 43 males and 37 females, with median age 4 (0.33-18) years and median weight 16.5 (5-127) kg. There were 47 Caucasians, 18 blacks and 15 of other origin. Fifteen, 54 and 11 had Class I, Class II, and Class III heart failure, respectively. The demographics of the children were in accordance with the WR which requested that up to 50 % of the children were to be in Tanner Stage 3 to up to 18 years and at least 50% of the population should be younger, and there should be a mixture of black and non-black subjects.

The plasma concentrations of the active enantiomers S(-) carvedilol with nonselective β blocking activity and α 1-blocking activity, and R(+) carvedilol with α 1- blocking activity were measured. The sponsor did not measure the plasma concentrations of 4-hydroxyphenyl-carvedilol, an active metabolite whose contributions to the overall β -blocking activity equals that of the parent drug. This was in accordance with the revised WR which did not stipulate any longer that “ carvedilol and any metabolite that makes substantial contributions to its efficacy and/or toxicity should be measured”. In agreement with the WR the protocol excluded subjects with abnormal metabolic function. As requested by the WR the plasma concentrations of the carvedilol enantiomers were measured over the range of doses tested for efficacy. The PK parameters CL/F and AUC were reported. The WR requested additional reporting of V/F, C_{max}, t_{max} and t_{1/2}. However, these latter parameters were to be obtained if a data rich approach was applied.

In accordance with the WR the tablet and suspension formulations used were appropriate to the age of the patients and the clinical setting. The Coreg tablets have been characterized earlier and the submitted relative bioavailability study comparing the suspension with the tablet characterized the new suspension formulation adequately. The carvedilol suspension can be prepared by local pharmacists. The WR indicated specifically that a suspension would be acceptable. There is no need for a marketed formulation for the younger children.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation I (OCP/DPE1) has reviewed the study reports of the population pharmacokinetic analysis of the clinical trial data in the target pediatric population (study 321), the relative bioavailability study in adults comparing the suspension containing 25 mg carvedilol with the Coreg tablet formulation (study 257), the corresponding assay validation reports, and the compounding procedure to generate the suspension.

A comparison of the Clinical Pharmacology studies and methods used by the sponsor with the stipulations of the Written Request (WR) shows agreement. The Clinical Pharmacology database compiled by the sponsor is acceptable. Therefore, from a Clinical Pharmacology view point the sponsor should be granted 6 month pediatric exclusivity. The PK results of the study should not be described in the label.

Peter H. Hinderling, MD

DPE 1

OCP

RD Initialed by Patrick Marroum, Ph.D. _____

Briefing held on January 23, 2007 (Drs. Jadhav, Marroum, K. Kumi, Rahman, Tornoe, Uppoor, Bashaw, Reynolds, Gobburu, Madabushi, Stockbridge, Mehta, Sahajwalla, Huang, Hinderling)

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