

NDA #20297

Supplement amendment: 022 dated September 1, 2006

Sponsor: GlaxoSmithKline

Name of Finished Product: Coreg®

Name of Active Ingredient: carvedilol

Proposed indication: pediatric patients with symptomatic systemic ventricular systolic dysfunction

Conclusion:

There is no indication that the use of carvedilol in doses up to 25 mg bid is efficacious in children with heart failure. There were no unexpected safety events reported in this NDA supplement. No labeling changes regarding the use of this agent in children are recommended.

Summary:

The data base for the use of carvedilol in children consists of one efficacy study (105517/321) and the extension study (105517/396), a report from the North American Pediatric Cardiomyopathy Registry (COG103639), and a review of the published literature.

Background

Study 105517/321 was a multicenter, placebo-controlled, 8-month study of the effect of twice daily carvedilol in children with congestive heart failure due to systemic ventricular systolic dysfunction. The primary objective of this protocol was to compare the efficacy of placebo and carvedilol administered twice daily for 8 months as assessed by a composite measure of clinical congestive heart failure (CHF) outcomes in children with symptomatic systemic ventricular systolic dysfunction and CHF.

The screening phase was up to 14 days. Those subjects meeting the entry criteria were randomized, in a blinded fashion, to placebo, low-dose carvedilol, or high dose carvedilol in a 1: 1: 1 randomization schedule. At the time of randomization, subjects were stratified according to the anatomic substrate of the subject's ventricular dysfunction¹. Subjects received the first dose of double-blind study medication (Level 1) at the Randomization Visit.

Doses of study medication were titrated every 2 weeks, as tolerated, through four dose levels. Within the low-dose² and high-dose carvedilol groups³, the mg/kg administered for each of these four levels was assigned according to weight (above or below 62.5 kg). Suspensions or tablets were supplied.

Subjects continued taking the dose level achieved during up-titration and returned to the clinic at 1, 2, 3, 4.5, and 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 Level 4. Subjects who completed the study and did not enter open-label studies and those who were prematurely withdrawn entered into the 4 week Down-Titration

¹ the investigator determined whether the patient would be stratified as left ventricle (LV) or non left ventricle (NLV) according to the anatomic substrate of the subject's ventricular dysfunction, i.e., those with systemic left ventricular dysfunction or those with right ventricular or single ventricular physiology. Patients with tricuspid atresia and a single left ventricle were to be randomized as LV if a left ventricular morphology was present and left ventricular systolic function could be analyzed using normal echocardiographic analyses.

² Target dose 0.2 mg/kg bid if weight was < 62.5 kg or 12.5 mg bid if weight was ≥ 62.5 kg

³ Target dose 0.4 mg/kg bid if weight was < 62.5 kg or 25 mg bid if weight was ≥ 62.5 kg

Phase and returned 2 weeks later for final safety assessments. Premature withdrawals were followed for the duration of the study period (randomization to one day after the planned last maximum dose of study medication, approximately eight months) for the collection and documentation of study endpoints.

Diagnosis and main criteria for inclusion

Subjects who

- were male or female children from birth through 17 years,
- had chronic symptomatic CHF (NYHA Class II-IV, if > 5 years-of-age or Ross' Classification of CHF Class II-IV if <5 years-of-age),
- had left ventricular ejection fraction (LVEF) <40%,
- had systemic left ventricular dysfunction or qualitative evidence of a dilated ventricle with moderate systemic ventricular systolic dysfunction in subjects with right ventricular or single ventricular physiology (i.e., NL V),
- were receiving standard heart failure therapy.

Excluded subjects included those with protocol defined medical conditions, were actively listed for transplantation or corrective heart surgery during the eight month period of the study, required protocol defined prior or concomitant medications, or were unwilling to practice acceptable contraceptive measures.

The primary efficacy variable was a CHF composite outcome response. Subjects were determined to have a CHF composite outcome response⁴ of "Worsened", "Improved", or "Unchanged" determined 12 hours after the last dose of study medication. The definitions of the categories were:

Worsened

- subject died,
- was hospitalized for at least 24 hours for worsening heart failure requiring intravenous heart failure medication;
- permanently discontinued double-blind treatment due to worsening heart failure, treatment failure or lack of/insufficient therapeutic response;
- permanently discontinued double-blind treatment due to withdrawal of consent or other administrative reason and had worsening heart failure at the time of study discontinuation;
- demonstrated worsening in NYHA Class or Ross' Classification for CHF in children at last observation carried forward (LOCF) or moderate-marked worsening of physician or subject/parent global assessment score at LOCF.

Improved

- subject did not worsen (as defined above), and
- demonstrated improvement in NYHA Class or Ross' Classification for CHF in children at LOCF and/or moderate-marked improvement in physician or subject/parent global assessment score at LOCF.

Unchanged

- subject was neither improved nor worsened.

⁴ An Endpoint Committee, consisting of six participating investigators, adjudicated independently before unblinding, all deaths, hospitalizations, and permanent withdrawals to determine which events were associated with worsening heart failure.

Statistical methods

Sample size calculations were based on the primary endpoint of composite CHF composite outcome response of Worsened, Improved, or Unchanged. The primary comparison of interest was between the placebo group and the combined carvedilol group.

Results

A total of 161 subjects were randomized: 55 to placebo, 53 to low-dose carvedilol, and 53 to high-dose carvedilol.

The treatment groups were similar for the percentages of subjects who completed or withdrew from the study (including the specific reasons for withdrawal).

Demographics

A small majority of subjects were male. Mean age was lower for the placebo group (56 months) compared to the active treatment groups (83 and 71 months for low dose and high dose carvedilol, respectively). Over 80% of all subjects were birth to Tanner Stage 2. About one quarter of subjects were black and most were less than 62.5 kg in weight. The majority of subjects were NYHA/Ross CHF classification II and the mean LV ejection fractions were around 27%. The groups were similar in the type of patient population.

As expected, all subjects had heart failure. The next most common cardiovascular conditions were cardiomegaly, primary cardiomyopathy, and cardiac murmurs. Commonly taken cardiac medications included digoxin, diuretics and ACE inhibitors/angiotensin receptor blockers. Commonly taken non cardiac medications included analgesics and antibiotics. Anti-asthmatic medication was taken by more than 20% of the study population.

Efficacy Results

Primary Efficacy Variable

The results of the primary endpoint (the CHF composite response being improved, unchanged, or worsened) for placebo and the combined as well as individual dose groups of carvedilol are shown below.

Number and (percent) of subjects

	Placebo	Low-Dose Carv	High-Dose Carv	Combined Car
Outcome	n=54	n=51	n=52	n=103
Improved	30 (56)	27 (53)	31 (60)	58 (56)
Unchanged	8 (15)	11 (22)	9 (17)	20 (19)
Worsened	16 (30)	13 (26)	12 (23)	25 (24)

There were small, irrelevant differences between placebo and the combined carvedilol group for the protocol specified primary endpoint of the CHF composite response ($p=0.740$, Wilcoxon rank sum).

There is no evidence from the hazard ratios for mortality rate and hospitalization rate that the use of carvedilol in this patient population is harmful.

Safety Results

Deaths

There were 14 reported deaths during the trial period (6 placebo, 5 low dose carvedilol, and 3 high-

dose carvedilol). Of the 14 deaths, 5 occurred during the treatment phase and 9 occurred post treatment.

There were 38 subjects (36%) randomized to carvedilol who reported a serious adverse events compared to 24 (44%) of subjects randomized to placebo. The most commonly reported event was worsening heart failure followed by viral infection and dehydration. Nothing seems to indicate an association with carvedilol.

There were 22 subjects who withdrew from the study because of adverse events (7 placebo, 7 low dose carvedilol, 8 low dose carvedilol). The most frequent adverse event resulting in withdrawal was worsening heart failure (cardiac failure and cardiac failure congestive combined) with 6 subjects in each group.

Adverse Events: The placebo subtracted rates for dizziness and dyspnea were 11%. The rates for chest pain and headache were 9% and 7%, respectively. All the other events were 5% or less.

There is no evidence for a dose relationship for any of the adverse events.

Clinical laboratory

There were no reported study drug withdrawals because of abnormal laboratory values in any of the drug groups.

There is no evidence that carvedilol is associated with life-threatening changes in clinical laboratory parameters. There could be a minor effect of carvedilol on decreasing hemoglobin.

There are minor differences among the treatment groups regarding the numbers of subjects who underwent transplantation.

There were no study withdrawals because of abnormal ECG. There were 2 reports of serious safety: atrioventricular block (low dose carvedilol) and nodal arrhythmia (high dose carvedilol).

Protocol number 396

This was a multicenter, open label extension study to evaluate the safety of twice daily oral carvedilol in pediatric subjects with chronic heart failure.

Objectives: The primary objective of this protocol was to evaluate the long term safety of carvedilol in pediatric subjects with heart failure who completed the study 321.

The safety review includes 102 subjects, 66 subjects who were enrolled in study 396 and 36 subjects who participated in the 321 OL phase but did not enter study 396.

Demographics: the 102 subjects who received open label carvedilol (66 from study 396 and 36 from open label use of carvedilol) were primarily white (49%), male (55%), and were in the age category of birth to Tanner stage 2 (86%). The mean age was 66.7 month and 36% were NYHA/Ross Class I.

Duration of treatment: there were 84 subjects (82%) who received carvedilol for \geq 366 days. The mean duration of exposure was 719 days (range 12 to 1812 days).

Deaths

There were 7 reported deaths.

It appears unlikely that carvedilol contributed to the death of any of these subjects. All had complex medical histories that included severe (congenital) cardiac abnormalities and seemed to be able to tolerate long term use of carvedilol.

Worsening heart failure, cardiomyopathy, pneumonia, and syncope were the most often reported serious adverse events.

Overall, there were 7 withdrawals for worsening heart failure. In addition, there was one withdrawal for ventricular fibrillation and one arrhythmia.

Conclusions: there is no indication from this review that the use of carvedilol in this patient population is different from the safety conclusion derived from the sponsor supported clinical trials (321 and 396)

Summary

The literature review⁵ included 55 citations (14 manuscripts, 23 unique abstracts, 5 partial data reviews and 13 case reports). The approximate number of patients included in the review was 273 patients. The patients' ages were between 2 weeks and 20 years and they were treated with carvedilol for indications of heart failure (53 citations) or hypertension (2 citations). The duration of the studies ranged from 6 months to 5 years. Most of the trials included patients with diagnoses of cardiomyopathy, including chemotherapy-induced cardiomyopathy and idiopathic dilated cardiomyopathy, as well as non-specified diagnoses of heart failure. In addition, there were 10 trials that included patients with heart failure based on congenital heart disease, and a small number of patients with Duchenne's muscular dystrophy.

Despite a paucity of details, the deaths appear to be expected in this patient population and not dissimilar to those reported in the sponsor studies.

REGISTRY REVIEW

Conclusions

There is no evidence from this study that the use of carvedilol is harmful in pediatric patients with dilated cardiomyopathy enrolled in the North American Pediatric Cardiomyopathy Registry (PCMR).

Introduction

Study Number: COG103639

Title: A Multicenter Observational Study of Oral Carvedilol in Pediatric Subjects with Dilated Cardiomyopathy: A Report from the North American Pediatric Cardiomyopathy Registry.

12 centers in the United States contributed subjects to Study COG103639. These 12 sites represent 50.5% of the total PCMR.

Objectives: The objective of this study was to assess the experience of pediatric subjects with dilated cardiomyopathy in the PCMR receiving carvedilol.

⁵ through June 2006

Methodology: This was an open-label, uncontrolled, registry designed to assess the long-term experience of pediatric subjects with dilated cardiomyopathy enrolled in the PCMR who were receiving carvedilol. Carvedilol was prescribed by, and doses were determined by, patients' physicians. All relevant data were extracted from patient charts dating from June, 1997 (the date of availability of carvedilol for prescription in the US) through September 20, 2005.

There were four deaths on-therapy (congestive cardiomyopathy, 2 patients; cardiac arrest, 1 patient; and respiratory distress, 1 patient) and 1 post-therapy death (cardiac failure). The mean age at death was 9.76 years, and the mean carvedilol dose at death was 7.05 mg. There is no evidence of an unsafe effect of carvedilol on these patients.

There were no hospital admissions for hypotension or bradycardia. Twenty-six patients received heart transplants; 24 while on carvedilol.

Clinical laboratory evaluation

Less than half of patients had any laboratory assessment during the Registry. There were 7 subjects who developed hematocrit $\leq 30\%$ at the first post drug initiation visit and 6 patients who were still anemic at the last on-drug assessment. There were no patients who had an elevated LFT or serum creatinine during carvedilol treatment but did not have the elevation at baseline.

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