

# **One Year Post-Exclusivity Adverse Event Review: Carvedilol**

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# Background Drug Information

**Drug:** Coreg<sup>®</sup> (carvedilol)

**Therapeutic Category:**  $\beta$ -adrenergic blocking agent

**Sponsor:** GlaxoSmithKline

**Original Market Approval:** September 14, 1995

**Pediatric Exclusivity Granted:** November 8, 2006

# Background Drug Information

## Indications

- For the treatment of mild-to-severe chronic heart failure of ischemic or cardiomyopathic origin to increase survival and to reduce the risk of hospitalization (usually in addition to diuretics, ACE inhibitors, and digitalis)
- To reduce cardiovascular mortality in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of  $\leq 40\%$  (with or without symptomatic heart failure)
- For the management of essential hypertension

# Drug Use Trends in Outpatient Settings

- 12.4 million dispensed prescriptions for all age groups during the 12 month post-exclusivity period
  - 14,000 (0.1%) were dispensed for pediatric patients 0 to 16 years old
- 20% increase in prescriptions for all age groups between the 12 month pre- and post-exclusivity periods
  - 9% increase for the pediatric population

# Drug Use Trends in Outpatient Settings

- Cardiology was the most frequent prescriber specialty during the 12 month post-exclusivity period.
  - Cardiology: 35% (4,324,000)
  - Pediatrics: 0.8% (100,000)
- Use among pediatric patients was too low to evaluate for office-based physician carvedilol visits stratified by visit diagnosis codes.

# Pediatric Exclusivity Studies: Overview

- **Indication**  
Heart failure in pediatric patients
- **Studies**
  - **Efficacy and Safety Study**  
161 pediatric patients, 2 months to 17 years old, with congestive heart failure (CHF) due to systemic ventricular systolic dysfunction
  - **PK Study** (sub-study of the Efficacy and Safety Study)  
80 pediatric patients, 4 months to 18 years old
  - **Safety Study** (extension of the Efficacy and Safety Study)  
102 pediatric patients with chronic heart failure

# **Pediatric Exclusivity Studies: Efficacy and Safety Study (n=161)**

## **Design**

Multi-center, randomized, placebo-controlled, double-blind, parallel-group, 8 month study of low and high dose carvedilol added to standard treatment (8 week titration phase and 6 month maintenance phase)

## **Dosing Regimen**

- Placebo (n=55)
- Target low dose (n=53)
  - < 62.5 kg: 0.2 mg/kg BID or  $\geq$  62.5 kg: 12.5 mg BID
- Target high dose (n=53)
  - < 62.5 kg: 0.4 mg/kg BID or  $\geq$  62.5 kg: 25 mg BID

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Primary Efficacy Endpoint

CHF composite outcome response determined 12 hours after the last dose of study medication

- **Worsened**
  - 1) Death;
  - 2) Hospitalization for worsening heart failure;
  - 3) Study discontinuation due to or occurring temporally with worsening heart failure; or
  - 4) Demonstrated worsening of the New York Heart Association (NYHA) Class or Ross' Classification for CHF or demonstrated moderate-marked worsening of physician or subject/parent global assessment score
- **Improved**
  - Patient did not worsen (as defined above); and
  - Demonstrated improvement in the NYHA Class or Ross' Classification for CHF and/or demonstrated moderate-marked improvement in physician or subject/parent global assessment score
- **Unchanged**

# **Pediatric Exclusivity Studies: Efficacy and Safety Study**

## **Efficacy Results and Conclusions**

- There were small, irrelevant differences between placebo and the combined carvedilol group for the primary endpoint of CHF composite response.
- There is no evidence that carvedilol is efficacious in children with heart failure in doses up to 25 mg BID.

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Safety Results and Conclusions

- No unexpected safety events were reported.
- Numbers of patient deaths, non-fatal serious adverse events, and withdrawals were similar across placebo and carvedilol groups.
  - 14 patient deaths
    - Placebo (6), low dose carvedilol (5), high dose carvedilol (3)
  - 62 patients with non-fatal serious adverse events
    - Placebo (24), low dose carvedilol (19), high dose carvedilol (19)
  - 22 patients withdrawing from the study due to an adverse event
    - Placebo (7), low dose carvedilol (7), high dose carvedilol (8)

# **Pediatric Exclusivity Studies: Efficacy and Safety Study**

## **Deaths** (n=14 patients)

- Relationship of deaths to carvedilol treatment
  - 5 deaths during treatment
  - 9 deaths after treatment
- Each case is confounded by a complex cardiac condition(s).

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Placebo (n=6 patient deaths)

- 1) 12 y.o. male had a sudden collapse, was found to be in ventricular fibrillation, and was unable to be resuscitated.
- 2) 11 y.o. male had a cardiac arrest during insertion of a pacemaker and recovered. Was awaiting cardiac transplantation when he became asystolic and expired.
- 3) 16 y.o. male was hospitalized for worsening heart failure, was withdrawn from the study, and died 11 days post cardiac transplantation.
- 4) 13 m.o. female died due to respiratory distress caused by an acute viral syndrome.
- 5) 24 m.o. male had syncope resulting from “torsades de pointes,” received open-label carvedilol, had an episode of acute hypotension, ventricular tachycardia, and ventricular fibrillation, and died of cardiac failure.
- 6) 7 y.o. male with worsening heart failure died due to a ventricular arrhythmia.

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Low Dose Carvedilol (n=5 patient deaths)

- 1) 12 m.o. female with a complex medical history died of pneumonia on study day 108.
- 2) 7 y.o. female with dyspnea 4 hours after starting carvedilol. Treated for heart failure, withdrawn from the study on day 7, and underwent cardiac transplantation on day 8. Developed positive blood cultures for candida, acute respiratory distress syndrome, renal failure, thrombocytopenia, and subarachnoid hemorrhage post-op and died about 5 weeks after carvedilol was discontinued.
- 3) 15 y.o. female with myocarditis and dilated cardiomyopathy. 44 days after starting carvedilol, collapsed with ventricular fibrillation and was unable to be resuscitated.
- 4) 16 y.o. male with cardiomegaly and dilated cardiomyopathy. Was hospitalized for worsening heart failure about 2 months after starting carvedilol and had his dose reduced. Had an episode of sepsis, had sudden cardiac arrest on day 106, and died on day 107.
- 5) 22 m.o. female with a history of dilated cardiomyopathy and pansystolic murmur. Developed resistant otitis media with positive blood cultures for strep viridans and staph about 7 months after starting carvedilol. Was positive for influenza B infection, was diagnosed with bone marrow failure, discontinued carvedilol, and died about 2 months later.

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## High Dose Carvedilol (n=3 patient deaths)

- 1) 28 m.o. female with a history of sinus bradycardia. Had a loss of consciousness and sinus bradycardia and discontinued carvedilol on day 1. On day 106, she had decreased oral intake, respiratory distress, bradycardia, **hypoglycemia\***, and chest x-ray abnormalities and died later that day due to congestive heart failure and dilated cardiomyopathy associated with neonatal myocarditis and possibly due to a viral infection.
- 2) 8 y.o. female with tetralogy of Fallot. Developed worsening heart failure 102 days after starting carvedilol, was withdrawn from carvedilol, and died of congestive heart failure about 1 month later.
- 3) 13 y.o. female with congenital heart disease. Had edema, vomiting and shortness of breath 8 days after starting carvedilol. Diagnosed with worsening heart failure, discontinued carvedilol on day 29, and died due to an arrhythmia 19 days after the last carvedilol dose.

\*Cases involving hypoglycemia will be discussed further in subsequent slides.

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Serious Adverse Events (SAEs) (n=62 patients)

- There was no evidence of a clear association of any SAE with carvedilol.
- SAE distribution across study groups
  - Placebo (24 patients)
  - Low dose carvedilol (19 patients)
  - High dose carvedilol (19 patients)
- Most common SAEs were reported by all groups
  - Worsening heart failure
  - Viral infection
  - Dehydration

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Serious Adverse Events (n=109 SAEs)

(SAEs reported by 2 or more carvedilol-treated patients are listed in detail)

- Placebo (33 SAEs)
  - *Worsening heart failure* (10)
  - Bronchiolitis (2), *viral infection* (2), *dehydration* (1), bradycardia (1), pyrexia (1), failure to thrive (1)
  - Other (15)
- Low dose carvedilol (42 SAEs)
  - *Worsening heart failure* (7)
  - Upper respiratory tract infection (2), *dehydration* (2), septic shock (2), failure to thrive (2), anemia (2), bronchiolitis (1), pneumonia (1), *viral infection* (1), bradycardia (1), pyrexia (1)
  - Other (20)
- High dose carvedilol (34 SAEs)
  - *Worsening heart failure* (7)
  - *Viral infection* (4), *dehydration* (3)
  - Vomiting (2), bronchiolitis (1), pneumonia (1), bradycardia (1), pyrexia (1)
  - Other (14)

# Pediatric Exclusivity Studies: Efficacy and Safety Study

## Withdrawals (n=22 patient withdrawals)

- Worsening heart failure was the adverse event most frequently reported
- Reasons for Patient Withdrawals
  - Placebo (7 patient withdrawals)
    - Reported by 6 patients: cardiac failure
    - Reported by 1 patient: decreased ejection fraction
  - Low dose carvedilol (7 patient withdrawals)
    - Reported by 6 patients: cardiac failure
    - Reported by 1 patient each: congenital coronary artery malformation, respiratory tract infection
  - High dose carvedilol (8 patient withdrawals)
    - Reported by 6 patients: cardiac failure
    - Reported by 1 patient each: bradycardia, chest pain, fatigue, viral infection, muscle cramp, loss of consciousness, exertional dyspnea

# **Pediatric Exclusivity Studies: PK Study (n=80)**

## **Design**

- Population PK sampling was employed in the Efficacy and Safety Study.

## **Results and Conclusions**

- In pediatric and adult patients, age is a significant covariate for oral clearance (CL/F) for the R(+) carvedilol enantiomer.
- In pediatric patients, weight has a significant impact on CL/F for both the R(+) and S(-) carvedilol enantiomers.
- **Pediatric patients have greater oral clearance and less exposure to carvedilol enantiomers than adults.**

# Pediatric Exclusivity Studies: Safety Study (n=102)

## Design

- Multi-center, open-label extension study of carvedilol BID (8 week titration period and 6 month maintenance period)

## Dosing Regimen

- Target dose
  - $< 62.5$  kg: 0.4 mg/kg BID or  $\geq 62.5$  kg: 25 mg BID

# **Pediatric Exclusivity Studies: Safety Study (n=102)**

## **Safety Results**

- 7 patient deaths
- 30 patients with non-fatal serious adverse events
- 11 patients withdrawing from the study due to an adverse event

# Pediatric Exclusivity Studies: Safety Study

## Deaths (n=7 patients)

- It appears unlikely that carvedilol contributed to the deaths, as each patient:
  - Had complex medical histories including severe congenital cardiac abnormalities; and
  - Seemed to be able to tolerate long-term use of carvedilol.

# Pediatric Exclusivity Studies: Safety Study

## Deaths

- 1) 6 y.o. female with dilated cardiomyopathy died suddenly after 4 years of treatment with carvedilol and other cardiac medications. Preliminary autopsy results included thrombus, pulmonary embolism or infarct, biventricular dilation, left ventricular hypertrophy, and left ventricular endocardial fibroelastosis.
- 2) 10 m.o. male with mitochondrial abnormalities, including dilated cardiomyopathy. Had a cardiac arrest 40 days after starting blind medication and died. Autopsy showed severe cardiomegaly.
- 3) 7 y.o. male with numerous cardiac abnormalities including T wave abnormalities, cardiomegaly, and dilated cardiomyopathy. Died suddenly after taking carvedilol for about 2 years. Had an episode of syncope and was hospitalized for a viral infection and worsening cardiac function 2 months prior to death.
- 4) 3 y.o. male with complex congenital heart disease experienced asystole shortly after a follow-up cardiac catheterization and could not be resuscitated. Had received his last dose of carvedilol 2 weeks prior.

# Pediatric Exclusivity Studies: Safety Study

## Deaths (continued)

- 5) 14 y.o. male developed ventricular tachycardia/ventricular fibrillation, was hospitalized and withdrawn from the study, had multi-organ failure, and died about 1 week later.
- 6) 10 y.o. female with a history of severe congenital heart disease underwent heart transplantation after 19 months of treatment with carvedilol. The study drug was discontinued, and she experienced a cardiac arrest about 27 days post transplantation.
- 7) 9 y.o. female with multiple congenital heart abnormalities including aortic coarctation, cardiomegaly, right ventricular dysfunction, and diffuse ST and T wave changes. Collapsed and then died 2 days later. Had been taking carvedilol for about 19 months with several serious adverse events.

# Pediatric Exclusivity Studies: Safety Study

## Serious Adverse Events (SAEs) (n=30 patients)

- 59 total SAEs
- Most frequent SAEs
  - Worsening heart failure (13), cardiomyopathy (3), pneumonia (3), syncope (3)
- Other SAEs
  - Reported by 2 patients for each
    - Vomiting, pyrexia, gastroenteritis, dehydration, hypotension
  - Reported by 1 patient for each
    - Anemia, atrial fibrillation, atrial flutter, bradycardia, ventricular fibrillation, ventricular tachycardia, electromechanical dissociation, hypothermia, anaphylactic reaction, bacteremia, croup infection, lobar pneumonia, otitis media, viral respiratory tract infection, shigella infection, upper respiratory tract infection, viral infection, bronchiolitis, respiratory syncytial virus infection, viral upper respiratory tract infection, head injury, therapeutic agent toxicity, decreased INR, **hypoglycemia\***, complex partial seizures, asthma, pharyngeal hemorrhage

# Pediatric Exclusivity Studies: Safety Study

## Withdrawals (n=11 patients)

- 12 total adverse events (AEs)
- Worsening heart failure was the AE most frequently reported.
  - Reported by 7 patients
- Other AEs reported by 1 patient each
  - Ventricular fibrillation, arrhythmia, cardiomyopathy, fatigue, nausea

# Pediatric Exclusivity Studies: Labeling Changes

## Pediatric Use

- Effectiveness of COREG in patients younger than 18 years of age has not been established.
  - In a double-blind trial, 161 children with chronic heart failure who were receiving standard background treatment were randomized to placebo or to two dose levels of carvedilol.
  - These dose levels produced placebo-corrected heart rate reduction of 4 to 6 heart beats per minute, indicative of beta-blockade activity. After 8 months of follow-up, there was no significant effect of treatment on clinical outcomes.
  - Exposure appeared to be lower in pediatric subjects than adults.
  - Adverse reactions that occurred in greater than 10% of patients treated with COREG and at twice the rate of placebo-treated patients included chest pain (17% vs. 6%), dizziness (13% vs. 2%), and dyspnea (11% vs. 0%).

# Adverse Event Reports During the Post-Exclusivity Period

11/6/2006 – 11/29/2007

<b>Raw Counts*</b>	<b>All Reports (US)</b>	<b>Serious (US)</b>	<b>Death (US)</b>
<b>Adults (≥ 17)</b>	1206 (1062)	375 (292)	53 (40)
<b>Pediatrics (0 to 16)</b>	2 (1)	1 (0)	0 (0)
<b>Age unknown</b>	679 (665)	147 (133)	10 (9)
<b>All ages</b>	1887 (1728)	523 (425)	63 (49)

\*May include duplicate cases

Source: Adverse Event Reporting System, FDA

# Adverse Event Reports Since Marketing Approval

9/14/1995 – 11/29/2007

<b>Raw Counts*</b>	<b>All Reports (US)</b>	<b>Serious (US)</b>	<b>Death (US)</b>
<b>Adults (≥ 17)</b>	3272 (2096)	2185 (1029)	345 (138)
<b>Pediatrics (0 to 16)</b>	21 (6)	19 (4)	3 (1)
<b>Age unknown</b>	1283 (1192)	434 (347)	49 (30)
<b>All ages</b>	4576 (3294)	2638 (1380)	397 (169)

\*May include duplicate cases

Source: Adverse Event Reporting System, FDA

# Pediatric Adverse Events Since Marketing Approval

- 21 raw count cases
- 11 cases excluded
  - Duplicate cases (4)
  - Miscoded cases involving patients  $\geq 17$  years old (4)
  - Not a serious adverse event (1)
  - Occurred during the pediatric clinical trials (2)
- 10 remaining cases
  - Deaths (3)
  - Other serious adverse events (7)

# Pediatric Deaths Since Marketing Approval

The 3 death cases were notable for complicated underlying medical conditions and/or insufficient details.

- (Japan) 16 m.o. male with h/o congenital heart disease, open heart surgery, and heart failure on carvedilol titrated to 0.4 mg/kg/d since the age of 6 months (concomitant meds: furosemide, hydrochlorothiazide, spironolactone, digoxin, enalapril). Eight months after starting carvedilol, he had bronchitis, poor oral intake, spasm, **hypoglycemia\***, and shock not responsive to IV hydration and glucose. Unclear if he still was receiving carvedilol at that time.
- (US) 17 y.o. male (270 lbs) with h/o CHF, a cerebrovascular accident, and reflux. Had been on carvedilol 50 mg BID for at least 6 months. Died suddenly of unknown causes (unknown if there were concomitant medications).
- (US) 17 y.o. male on carvedilol for 3 months who experienced vomiting, bradycardia, hypotension, pulmonary edema, and death of unknown cause (unknown past medical history, carvedilol dose and duration, and concomitant medications).

\*Cases involving hypoglycemia will be discussed further in subsequent slides. 30

# Serious Adverse Events

## Since Marketing Approval (n=7, 0 US)

- **Hypoglycemia (3)** – all from Japan
  - Cases described on the next 3 slides
- **Congenital anomalies and maternal exposure (2)**
  - 34 week infant with hypoglycemia and respiratory failure
  - Neonate with cleft plate
- **Hypotension/renal failure (1)**
  - BUN 36 mg/dL, creatinine 0.43 mg/dL, no blood pressure reported
- **Disturbed consciousness (1)**
  - General malaise, sleepiness

# Hypoglycemia Cases: Postmarketing Serious Adverse Events

- 1) (Japan) 4 y.o. male with congenital heart disease (tetralogy of Fallot) and heart failure started on carvedilol 3 mg/d for heart failure prophylaxis (concurrent meds: enalapril, dipyridamole, potassium, furosemide, and spironolactone).

Three months later, he developed flu symptoms with sore throat, coughing, and diarrhea followed on the next day by an unarousable state. On admission, his **blood glucose was 21 mg/dL**. Carvedilol was discontinued. **His blood glucose increased to 90 mg/dL**. Approximately 1 week after admission, he was restarted on carvedilol at 1 mg/d, and there were **no further episodes of hypoglycemia**. He was discharged 3 weeks later on carvedilol 2 mg/d.

# Hypoglycemia Cases:

## Postmarketing Serious Adverse Events (continued)

2) (Japan) 4 y.o. male with congenital heart disease (heart surgery at 9 months old for transposition of the great arteries and cleft mitral valve), bradycardia/tachycardia syndrome, increased clotting time, and growth retardation on carvedilol 1 mg/kg/d for heart failure (concurrent meds: furosemide, cilazapril, digoxin, spironolactone).

Approximately 16 months after starting carvedilol, he experienced convulsions and developed respiratory arrest requiring intubation. **Hypoglycemia (blood glucose of 11 mg/dL)** and acidosis were detected. He was transferred to another hospital and experienced another convulsion and was treated with anticonvulsants and an unspecified drug for brain edema. **Hypoglycemia resolved** but neurological symptoms persisted. Treatment with carvedilol continued.

# Hypoglycemia Cases:

## Postmarketing Serious Adverse Events (continued)

3) (Japan) 7 y.o. male with congenital heart disease (prior heart surgery for tetralogy of Fallot), bigeminy, bradycardia, and pulmonary artery stenosis on carvedilol 5 mg BID for heart failure (concurrent meds: furosemide, spironolactone, digoxin, captopril).

Either 3.5 years or 8 months later (inconsistency in report), the patient experienced disturbed consciousness, coldness, and a **blood glucose of 68 mg/dL when NPO** prior to undergoing scintigraphy. Nine weeks later, he experienced disturbed consciousness, sweating, coldness, and a **blood glucose of 24 mg/dL** after having little for lunch that day. Both episodes required 20% glucose infusions. Treatment with carvedilol continued.

# Hypoglycemia Cases: Postmarketing Death

(Japan) 16 m.o. male with h/o congenital heart disease, open heart surgery, heart failure, and poor weight gain on carvedilol continuously (titrated to 0.4 mg/kg/d) since the age of 6 months (concomitant meds: furosemide, hydrochlorothiazide, spironolactone, digoxin, enalapril).

Five months after starting carvedilol, he experienced sweating, cyanosis, tachypnea, and **hypoglycemia (blood glucose of 18 mg/dL)**. He was hospitalized and intubated, carvedilol was discontinued, and the hypoglycemia improved. Carvedilol was restarted and titrated to 0.15 mg/kg/d.

Three months later, he experienced bronchitis, poor oral intake, spasm, **hypoglycemia (blood glucose of 56 mg/dL)**, and shock not responsive to IV hydration and glucose. Unclear if he still was receiving carvedilol at that time.

# Hypoglycemia Cases: Pediatric Exclusivity Studies (from the Efficacy and Safety Study)

28 m.o. female with a history of sinus bradycardia. Had a loss of consciousness and sinus bradycardia and discontinued carvedilol on day 1.

On day 106, she had decreased oral intake, respiratory distress, bradycardia, hypoglycemia (blood glucose of 20 mg/dL), and chest x-ray abnormalities and died later that day due to congestive heart failure and dilated cardiomyopathy associated with neonatal myocarditis and possibly due to a viral infection.

# Hypoglycemia Cases: Pediatric Exclusivity Studies (from the Safety Study)

27 m.o. male with chronic heart failure (specific etiology not described).

Approximately 225 days after his first carvedilol dose, he had lethargy, hypothermia (93.2 F), hypoglycemia (blood glucose of 29 mg/dL), hypotension, and hyponatremia (124 mmol/L). Treated with IV fluids, glucose, antibiotics, sodium bicarbonate, potassium chloride and dopamine drip. Symptoms resolved without further episodes of hypoglycemia. Final diagnosis was presumed sepsis.

# Warnings and Precautions: Carvedilol Labeling

## Glycemic Control in Type 2 Diabetes

In general,  $\beta$ -blockers may mask some of the manifestations of hypoglycemia, particularly tachycardia. Nonselective  $\beta$ -blockers may potentiate insulin-induced hypoglycemia and delay recovery of serum glucose levels.

Patients subject to spontaneous hypoglycemia, or diabetic patients receiving insulin or oral hypoglycemic agents, should be cautioned about these possibilities.

# Warnings and Precautions: Propranolol Labeling

## Diabetes and Hypoglycemia

$\beta$ -adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia, especially in labile insulin dependent diabetics. In these patients, it may be more difficult to adjust the dosage of insulin.

Propranolol therapy, particularly when given to infants and children, diabetic or not, has been associated with hypoglycemia, especially during fasting as in preparation for surgery.

Hypoglycemia has been reported in patients taking propranolol after prolonged physical exertion and in patients with renal insufficiency.

# Summary: Carvedilol

- This completes the 1 year post-exclusivity AE reporting.
- The safety review identified 4 cases of young children with hypoglycemia which coincided with their carvedilol therapy.
- Does the present carvedilol labeling adequately address the possible hypoglycemia risk for the pediatric population or is additional wording needed?
- FDA recommends routine monitoring of carvedilol for adverse events in all populations.

Does the Advisory Committee agree?

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