**MEMORANDUM** DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** January 16, 2008

**TO:** Lisa L. Mathis, M.D., Associate Director
Pediatric and Maternal Health Staff (PMHS)
Office of New Drugs (OND), CDER
and
M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OC

**FROM:** Mary Ross Southworth PharmD, Postmarketing Safety Evaluator
Division of Drug Risk Evaluation

**THROUGH:** Ann McMahon, MD, Deputy Director
Division of Drug Risk Evaluation

**SUBJECT:** Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Carvedilol (Coreg; NDA 20-297)
Pediatric Exclusivity Approval Date: 11/06/2006

**RCM#:** 2007-255

## Executive Summary

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of carvedilol in pediatric patients. Up to the "data lock" date of November 29, 2007, AERS contained 4576 reports for carvedilol (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.5% of the total (21/4576).

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity (granted November 6, 2006). We used an AERS data lock of November 29, 2007 to allow time for reports received up to November 6, 2007 to be entered into AERS. During the first year after pediatric exclusivity was granted, AERS received a total of 1206 reports (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.2% of the total number of cases (2/1206).

There were 10 pediatric cases (8 foreign, 2 domestic) identified in AERS for review during the entire marketing period (9/14/1995- 11/29/2007). The events in these cases were hypoglycemia, sudden death, hypotension, “disturbed consciousness”, and congenital anomaly. The majority of these events are labeled (hypoglycemia,

hypotension, disturbed consciousness), disease related (sudden death), or an association could not be made between the event and carvedilol use (congenital anomaly).

In conclusion, this review did not identify any serious unexpected events associated with carvedilol use in pediatric patients. We will continue to monitor reports of adverse events associated with carvedilol use.

## 1.0 Background

Carvedilol, a nonselective beta adrenergic blocker (marketed as COREG by GlaxoSmithKlein) with alpha-1 blocking activity, was approved by the FDA on September 14, 1995. It is approved for the following indications: hypertension, left ventricular dysfunction following myocardial infarction, and mild to severe heart failure. Pediatric exclusivity was granted on November 6, 2006; the Agency approved a supplemental NDA which added information to the label regarding the results of a placebo controlled trial and an open label extension study in pediatric congestive heart failure patients on February 23, 2007 (see section 2.3). The data submitted in the NDA were insufficient to recommend a new indication for pediatric use of carvedilol, as the primary endpoint was not achieved (change in CHF composite outcome response[1]). Adverse reactions noted in the medical review[1] of the supplement included worsening heart failure, arrhythmias, viral infection, pneumonia, syncope, dehydration, dizziness, dyspnea, chest pain, and headache. No unexpected safety events were reported.

An OSE safety review of post-marketing skin adverse events associated with carvedilol[2] resulted in the addition of serious skin events (TEN, SJS) to the post-marketing adverse events section of labeling. Two other reviews[3,4] analyzed the post-marketing events, renal failure and hyperglycemia, but did not support changes to the label for carvedilol.

The AERS database was searched for reports of adverse events (serious and non-serious) occurring with the use of carvedilol in pediatric patients. Up to the "data lock" date of November 29, 2007, AERS contained 4576 reports for carvedilol (raw counts, all ages, foreign and domestic, as well as those with no information on age and country of origin). Pediatric reports represent approximately 0.5% of the total (21/4576).

The Office of Pediatric Therapeutics requested a review of all serious adverse events reported in pediatric patients from the AERS database since time of marketing. Events of interest included hypoglycemia, hypotension, severe skin reactions, and behavioral changes based on the pharmacologic properties of carvedilol, known safety issues, and a preliminary review of the pediatric events in AERS. It was also requested to include events reported in patients up to and including 17 years of age.

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[1] Improved (e.g. decreased NYHA class); Worsened (death, hospitalization, drop out, increased NYHA class); or Unchanged. See Medical Review (NDA 20297-S022) by Maryann Gordon for complete explanation.
[2] Southworth MR. OSE review "Serious skin reactions with carvedilol", PID#D040841, 4/13/05
[3] Johnston MF. ODS review "Renal failure with carvedilol", PID#D020316, 10/25/02
[4] Southworth MR. OSE review "Hyperglycemia with Toprol XL and Coreg" RCM# 2006-525, 12/21/06

## 2. Product, Indications, and Pediatric Labeling

### 2.1 Coreg Product

Coreg (carvedilol), which is sponsored by GlaxoSmithKlein and approved in the US on September 14, 1995, is formulated in:

Tablets: 3.125 mg, 6.25 mg, 12.5 mg, 25 mg

### 2.2 Coreg approved indications

Coreg is indicated for the treatment of hypertension, left ventricular dysfunction following a myocardial infarction, and mild to severe heart failure.

### 2.3 Coreg Pediatric labeling

Pertinent pediatric labeling:

USE IN SPECIAL POPULATIONS

#### *Pediatric Use*

*Effectiveness of COREG in patients younger than 18 years of age has not been established.*

*In a double-blind trial, 161 children (mean age 6 years, range 2 months to 17 years; 45% less than 2 years old) with chronic heart failure [NYHA class II-IV, left ventricular ejection fraction <40% for children with a systemic left ventricle (LV), and moderate-severe ventricular dysfunction qualitatively by echo for those with a systemic ventricle that was not an LV] 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 4-6 heart beats per minute, indicative of beta-blockade activity. Exposure appeared to be lower in pediatric subjects than adults. After 8 months of follow-up, there was no significant effect of treatment on clinical outcomes. Adverse reactions in this trial 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%).*

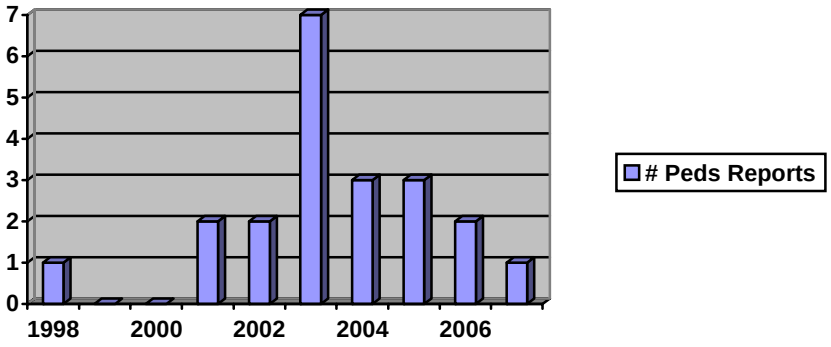
## 3. AERS Search Results: Carvedilol (Coreg)

### 3.1 Count of Reports: AERS Search including all sources - U.S. & foreign from marketing approval date (Table 1)

| Table 1: Crude counts[1] of AERS Reports for All Sources from Marketing Approval Date (09/14/1995 – 11/29/2007) (US counts in parentheses) | | | |
|---|---|---|---|
| | All reports (US) | Serious[2] (US) | Death (US) |
| Adults (≥ 17 yrs.) | 3272 (2096) | 2185 (1029) | 345 (138) |
| Pediatrics (0-16 yrs.) | 21 (6) | 19 (4) | 3 (1) |
| Age unknown (Null values) | 1283 (1192) | 434 (347) | 49 (30) |
| Total | 4576 (3294) | 2638 (1380) | 397 (169) |

[1] May include duplicates; miscoded cases
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life-threatening, hospitalization (initial or prolonged), disability, and congenital anomaly.

**Figure 1: Reporting trend for pediatric reports (Age 0 to 16) from approval date (9/15/95) to 11/29/07:**




### 3.2 Count of Reports: AERS Search including all sources - U.S. & foreign from Pediatric Exclusivity approval date (Table 2)

| Table 2: Crude counts[1] of AERS Reports for All Sources from date Pediatric Exclusivity was Granted (11/06/06-11/29/07) (US counts in parentheses) | | | |
|---|---|---|---|
| | All reports (US) | Serious[2] (US) | Death (US) |
| Adults (≥ 17 yrs.) | 1206 (1062) | 375 (292) | 53 (40) |
| Pediatrics (0-16 yrs) | 2 (1) | 1 (0) | 0 |
| Age unknown (Null Values) | 679 (665) | 147 (133) | 10 (9) |
| Total | 1887 (1728) | 523 (425) | 63 (49) |

[1] May include duplicates; miscoded cases
[2] Serious adverse drug experience per regulatory definition (CFR 314.80), which includes death, life threatening, hospitalization, disability, and congenital anomaly.

### 4. Postmarketing Review of All Serious Pediatric Adverse Event Reports associated with Carvedilol use.

A search of AERS was performed on November 29, 2007 to identify ***all serious case***s since marketing approval (September 14, 1995) reported in those ≤17 years of age in

association with carvedilol use; 21 cases were retrieved. There were 4 duplicates. Four cases were excluded because they involved patients >17 years of age (included in search results due to coding error). One was excluded because the event was not serious. Two additional reports were excluded because they reported events which occurred during the pediatric clinical trials and have been reported in the Medical Officer's review of the supplemental NDA. The remaining 10 cases are summarized below:

Hypoglycemia

*ISR 4383653 (Death) Japan:* A 6 month old male was started on 0.02 mg/kg/d carvedilol[5] for heart failure (history of congenital heart disease [CHD]) and titrated up to 0.4 mg/kg/d over an unreported period of time. Concomitant medications included furosemide, hydrochlorothiazide, spironolactone, digoxin, and enalapril. Five months after starting carvedilol, the patient experienced sweating, cyanosis, and tachypnea; his blood glucose was 18 mg/dL. He was admitted to the hospital and intubated due to respiratory insufficiency; carvedilol was discontinued on an unknown date. The hypoglycemic symptoms improved about 10 days later. Carvedilol was restarted and titrated up to 0.15 mg/kg/d over about 1 month. About three months later, the patient experienced bronchitis, poor oral intake, spasm, and hypoglycemia (glucose 56 mg/dL) and was readmitted. It was unknown if the patient was still receiving carvedilol at this time. The patient developed shock requiring IV hydration and glucose injections, but died the day after admission without responding to treatment.

*ISR 5056161 (Hosp) Japan:* A 4 year old male (weight unreported) was started on 3 mg/d of carvedilol for heart failure prophylaxis (history of CHD). Concomitant medications included enalapril and furosemide. Three months after starting carvedilol he developed flu symptoms, sore throat, cough, and diarrhea. The next day he reportedly experienced "indistinct conciousness". After taking his carvedilol, he collapsed and was not arousable. He was hospitalized. On admission, his blood glucose was 21 mg/dL. Carvedilol was discontinued. An unknown time later his blood glucose was 90 mg/dL. Carvedilol was restarted at 1 mg daily and no further hypoglycemia was reported.

*ISR 4383652 (Hosp) Japan:* A 4 year old 13 kg male was started on carvedilol 0.05 mg/kg/day and titrated up over 2 weeks to 1 mg/kg/d for the treatment of heart failure (history of CHD and bradycardia/tachycardia syndrome). Concomitant medications included furosemide, digoxin, and cilazapril. Two weeks after starting carvedilol, the patient experienced loss of consciousness twice. EEG and CT scan of the head revealed no abnormalities. Sixteen months after starting carvedilol, the patient experienced convulsions. When he arrived at the clinic he developed respiratory arrest and was intubated. Blood glucose was 11 mg/dL and he was acidotic. He was transferred to another hospital and experienced another convulsion and was treated with anticonvulsants. The hypoglycemia resolved, but neurologic abnormalities persisted. Therapy with carvedilol continued.

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[5] Although pediatric dosing is not FDA approved, the dosing scheme used in the pediatric study titrated to a maximum dose of 0.2 mg/kg (under 62.5 kg) or 12.5 mg/d BID in the low dose group and 0.4 mg/kg (under 62.5 kg) or 25 mg BID in the high dose group

*ISR 4198044 (Hosp) Japan:* A 7 year old male started carvedilol 5 mg BID (weight unreported) for the treatment of heart failure (history of CHD). Concomitant medications included furosemide, spironolactone, and digoxin. At an unreported time after starting carvedilol, he experienced two episodes of loss of consciousness. EEG, brain CT and MRI, ECG, and Holter were normal. Three and ½ years after starting carvedilol, the patient was to undergo scintigraphy (indication unreported) and was NPO. That afternoon he developed "disturbed consciousness"; blood glucose was 68mg /dL. He was treated with glucose and hydration. Nine weeks later, he again experienced disturbed consciousness, sweating, and coldness. He was taken to the hospital and found to have a blood glucose of 24 mg/dL. He had had very little lunch that day. He was treated with glucose and his blood sugar normalized (107 mg/dL). Treatment with carvedilol was continued.

Sudden death

*ISR 4519302 (Death) US:* A 17 year old male (270 lbs) received carvedilol 50 mg BID (duration unreported) for the treatment of heart failure (history of CHD, CVA, and GERD) and died suddenly (cause unknown). Patient had been on carvedilol for at least 6 months. Autopsy was not performed.

*ISR 5142333 (Death) US*: A 17 year old male (case reported by father) was taking carvedilol (dose, indication unreported) for three months and "gained no benefit", was nauseous, vomiting, and experienced bradycardia, hypotension, and pulmonary edema and died. Cause of death is unknown; it is unknown if an autopsy was performed. No details of the death were reported other than, "[carvedilol] interfered with all standard resuscitation techniques". No further information is available.

Hypotension

*ISR 4251126 (Hosp) Japan:* A 4 year old 7 kg female received enalapril 1.5 mg daily, losartan 8 mg daily, and carvedilol 2.5 mg daily for the treatment of congestive heart failure (history of CHD). Concomitant medications included digoxin, spironolactone, and torsemide. After approximately 3 years of therapy with enalapril and 1 year of therapy with losartan and carvedilol, she experienced exhaustion, pyrexia, and cyanosis. BUN and Creatinine were 61mg/dL and 0.74 mg/dL respectively (no baseline reported). The symptoms were considered to be consistent with hypotension (no BP reported) and renal failure. All medications were discontinued. Ten days later she was improved; BUN and Creatinine were 36 mg/dL and 0.43 mg/dL, respectively. Losartan, digoxin, and carvedilol were re-initiated. No further follow up is available.

Disturbed Consciousness

*ISR 5315819 (Hosp) Japan:* A 36 month old female (weight unreported) was started on 0.15 mg BID of carvedilol and titrated up to 0.9 mg BID over an 8 month period for the

treatment of heart failure (history of CHD). Concomitant medications included enalapril and torsemide. She experienced sleepiness with each uptitration of dose. The day after the 0.9 mg dose was initiated, she experienced "disturbed consciousness", general malaise, sleepiness, and cold sweats. She was hospitalized; her BP was 100/62; HR 136; Blood glucose 101. EEG and CT scan showed no abnormalities. Carvedilol was decreased to 0.9 mg QD for one day only. The next day she recovered. Carvedilol was restarted at 0.75 mg BID.

Congenital Abnormalities

*ISR 3945460 Germany:* A male neonate (GA 34 weeks) experienced hypoglycemia and respiratory failure one hour after birth. The mother had taken carvedilol 25 mg BID for hypertension (HELLP syndrome) throughout her pregnancy. He was intubated and ventilated for 6 hours after birth. The hypoglycemia resolved at an unknown time.

*ISR 4045045 Belgium* A female neonate (GA unreported) was born with complete cleft palate. The mother had taken carvedilol 0.5 (sic-units unreported) throughout the pregnancy for an unknown indication; the mother also smoked 10 cigarettes per day during pregnancy and had a history of cerebral hemorrhage. No further information is available.

## 5. Discussion

Ten unique cases (8 foreign, 2 domestic) reporting serious adverse events in pediatric (≤17 years old) patients were found in AERS.

Hypoglycemia was reported in 4 cases (3 hospitalization, 1 death-all Japanese). In two cases, decreased oral intake or flu symptoms preceded the hypoglycemic event. In all hospitalization cases, the hypoglycemia resolved with treatment and therapy with carvedilol continued . One of the cases reported convulsions in association with the hypoglycemia; the patient was treated with anticonvulsants. The hypoglycemia resolved, but persistent neurologic abnormalities were reported. In the case reporting death, the patient experienced two episodes of hypoglycemia. The second event resulted in shock and death, however, it was unclear whether the patient was taking carvedilol at the time of this event. None of the cases reported a medical history of diabetes or hypoglycemia nor were hypoglycemic agents listed as concomitant medications.

Beta blockers (particularly non selective beta blockers, like carvedilol) are well known to have effects on lipolysis, glycogenolysis, and gluconeogenesis which may predispose patients to hypoglycemia. In fact, several published case reports[6,7,8,9,10] describe the

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[6] Artman M et al. Propranolol in children: safety-toxicology. Pediatrics 1982; 70:30-2.
[7] Kallen RJ et al. Hypoglycemia: a complication of treatment of hypertension with propranolol. Clinc Pediatr 1980; 19:567-8.
[8] McBride et al. Hypoglycemia associated with propranolol. Pediatrics 1973; 51:1085-7.

occurrence of hypoglycemia in children taking *propranolol* who have experienced decreased oral intake. The label for propranolol contains the following warning: *"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."* This statement does not appear in the label for other commonly used beta blockers (atenolol, labetalol, metoprolol, pindolol, carvedilol).

The WARNINGS section of the label for carvedilol contains the following warning:

*"Nonselective β-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."*

Hypoglycemia is also listed as an adverse event (incidence 1% to 3 %) that was observed in the clinical trials of carvedilol for heart failure in adults. Hypoglycemic adverse events were not mentioned in the medical officer's review of the pediatric trials with carvedilol[1]. A literature search for case reports of hypoglycemia in association with pediatric use of carvedilol did not reveal any publications.

Two cases of sudden death were identified; both involved 17 year old males-one reporting a history of congenital heart disease. Sudden death is a frequent occurrence in patients suffering from cardiac abnormalities and/or heart failure. Neither of the cases suggests that the event was related to carvedilol use.

One case reported "disturbed consciousness", sleepiness, and malaise with each uptitration of carvedilol. Due to the lack of information (foreign case), it is not possible to assess the appropriateness of the dose that the patient received. The label lists asthenia, fatigue, and somnolence as adverse events observed during the adult clinical trials with carvedilol.

The case of "hypotension" contains little data to suggest an association between carvedilol use and the event. In this case, therapy with carvedilol was continued.

Two cases of congenital abnormalites in children born to mothers who had taken carvedilol were identified. It is impossible to ascertain from these cases whether carvedilol played a contributory role.

None of the serious cases involving pediatric patients in AERS reported severe skin reactions or changes in behavior.

## 6. Conclusions/Recommendations

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[9] Zeligs MA, et al. Perioperative hypoglycemia in a child treated with propranolol. Anesth Analg 1983;62:1035-7.
[10] Feller JM et al. Danger of hypoglycemia with use of propranolol. Med J Aust 1973; 2:92.

This review did not identify any serious unexpected events associated with carvedilol use in pediatric patients. Of the 4 hypoglycemia cases (all Japanese), 2 report decreased oral intake prior to the hypoglycemic event (which may have contributed to the event); the remaining 2 do not contain information regarding this or other risk factors for hypoglycemia. Because hypoglycemia was not identified as a safety signal in the pediatric clinical trial, there are no US cases reporting such an event, and the WARNING section of labeling contains information regarding hypoglycemia, no regulatory action is recommended at this time. We will continue to closely monitor for this event.

None of the cases reviewed reported severe skin reactions or changes in behavior.

We will continue to monitor reports of adverse events associated with carvedilol and will notify you of any potential safety signals in the pediatric population.

Mary Ross Southworth, PharmD
*concur:*

Cindy Kortepeter, PharmD
Safety Evaluator Team Leader

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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.**

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/s/
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DRUG SAFETY OFFICE REVIEWER

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