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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20297/S004

Trade Name: Coreg 3.125, 6.25, 12.5 and 25 mg Tablets

Generic Name: (carvedilol)

Sponsor: SmithKline Beecham Pharmaceuticals

Approval Date: September 8, 1999

INDICATION: Provides for final printed labeling revised under the Precautions/Drug Interactions section to describe the effects of carvedilol on cyclosporin concentrations in renal transplant patients.
NDA 20-297/S-004

SmithKline Beecham Pharmaceuticals
Attention: Ms. Catherine K. Clark
1250 S. Collegeville Road, UP4455
P.O. Box 5089
Collegeville, PA 19426-0989

Dear Ms. Clark:

Please refer to your supplemental new drug application dated May 6, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Coreg (carvedilol) 3.125, 6.25, 12.5 and 25 mg Tablets.

We note that this supplement was submitted as a 'Special Supplement - Changes Being Effected' under 21 CFR 314.70(c).

This supplemental new drug application provides for final printed labeling revised under the Precautions/Drug Interactions section to describe the effects of carvedilol on cyclosporin concentrations in renal transplant patients. The following section was added:

**Cyclosporin:** Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Also added to the **How Supplied** section was the statement, “Rx only” as well as minor editorial changes.

Your submission stated May 4, 1999 as the implementation date for this change.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included with your May 6, 1999 submission. Accordingly, the supplemental application is approved effective on the date of this.
We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Zelda McDonald  
Regulatory Health Project Manager  
(301)594-5300

Sincerely,

[Signature]

Raymond J. Lipicky, M.D.  
Director  
Division of Cardio-Renal Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20297/S004

FINAL PRINTED LABELING
**PRESCRIBING INFORMATION**

**COREG® Tablets**

**DESCRIPTION**

Carvedilol is a non-selective β-adrenergic blocking agent with α-blocking activity. It is a racemic mixture with the following structure:

![Chemical Structure of Carvedilol]

Carvedilol Tablets for Oral Administration: Carvedilol is a white, oral, film-coated tablet containing 2.5 mg, 5 mg, 10 mg, or 25 mg of carvedilol. The 2.5 mg, 5 mg, and 10 mg strength tablets are light yellow to orange in color. The 25 mg strength tablets are light brown in color. When administered orally, carvedilol is 90% absorbed with an absolute bioavailability of approximately 90%.

**PHARMACOKINETICS**

Carvedilol is rapidly and extensively absorbed following oral administration, with absolute bioavailability of approximately 90% and Cmax of 25% to 35% at a single dose. Following the administration of a single 50 mg dose, carvedilol is extensively metabolized. Following oral administration of radioactively labeled carvedilol to healthy volunteers, carvedilol accounted for about 7% of the total radioactivity in plasma as measured by area under the curve (AUC). Less than 2% of the dose was excreted unchanged in the urine. Carvedilol is metabolized primarily by aromatic ring oxidation and glucuronidation. Oxidized metabolites are further metabolized by conjugation via glucuronidation and sulfation. The metabolites of carvedilol are excreted primarily via the bile into the feces. Demethylation and hydroxylation at the phenyl ring produce three active metabolites with a 2:1:1 ratio of 8-OH:4-OH:4-OH metabolites in plasma.
Following oral administration, when postural hypotension has occurred it has been transient and is uncommon. In some patients, the dose may be increased as needed, and the lowest effective dose is usually reached by 2 days. In general, as is true for other β-blockers, responses are not age- or gender-related in normotensive patients. The peak antihypertensive effect occurs 1 to 2 hours after a dose. The dose-related blood pressure response was accompanied by a dose-related increase in adverse effects (see ADVERSE REACTIONS).

INDICATIONS AND USAGE

Congestive Heart Failure

Corgar is indicated for the treatment of mild or moderate hypotension in congestive heart failure (NYHA class II or III) heart failure of ischaemic or cardiomyopathic origin, in combination with digitalis, diuretics, and ACE inhibitor, to reduce the progression of disease as assessed by the investigator. Corgar should only be used if continuous cardiac monitoring is required. The response to digitalis therapy must be adequate.

Corgar may be used in patients unable to tolerate an ACE inhibitor and may be used in patients who are or are not receiving digitalis and diuretic therapy.

Hypertension

Corgar is also indicated for the management of essential hypertension. It can be used alone or in combination with diuretics (see PRECAUTIONS). Drug interaction

CONTRAINDICATIONS

Corgar is contraindicated in patients with NYHA class IV decompensated congestive heart failure requiring intravenous inotropic therapy, bronchial asthma (there have been reports of death in patients receiving single dose or multiple dose CAV block), sick sinus syndrome (serious arrhythmias may be precipitated), and cardiacogenic shock or severe bradycardia.

Use in pregnant patients or patients with a history of malignancy who may have an increased risk of cardiac arrhythmia.

Pregnancy

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Use in pregnant patients or patients with a history of malignancy who may have an increased risk of cardiac arrhythmia.
recommended that cannnal be used with caution. The dos- sages should be closely observed, and if evidence of bronchodism is observed during use, it may be necessary to discontinue use.

Hypertensive Patients with Left Ventricular Failure: In hypertensive patients who have severe congestive heart failure, hypertension may be reduced by digitalis or diuretics. In such patients, digoxin or diuretics should be started and adjusted according to patient response. The beneficial effects of diuretics are felt within 1 to 2 days, whereas the beneficial effects of digoxin may be delayed for weeks. When the diuretics are started or increased, the digitalis dosage should be decreased, if possible.

Information for Patients

In patients taking digitalis, they should:

- Not eat foods with high potassium content, such as bananas, prunes, or apricots.
- Avoid caffeine-containing beverages.
- Avoid aspirin, aspirin-containing drugs, or nonprescription pain relievers.
- Notify their physician immediately if they develop symptoms such as:
  - Dizziness or vertigo
  - Nausea or vomiting
  - Abnormal heartbeat

Drug Interactions

(See also CLINICAL PHARMACOLOGY: Pharmacokinetics and Pharmacodynamics)

Inhibitors of CYP450: Poor metabolizers of digoxin or digoxin-conjugated metabolites may be at increased risk of digitalis toxicity. Patients should be monitored closely for evidence of digitalis intoxication.

Cardiovascular Disease: In patients with advanced cardiovascular disease, the effects of digitalis may be less pronounced, and the dosage may need to be reduced. Patients should be monitored closely for evidence of digitalis toxicity.

Nursing Mothers

It is not known whether this drug is excreted in human milk. When human milk is given to a nursing woman, the drug should be withdrawn.

Pediatric Use

Safety and efficacy in patients younger than 16 years of age have not been established.

Geriatric Use

Of the 556 patients with congestive heart failure randomized to digoxin in U.S. clinical trials, 31% (175) were 65 years of age or older. The safety and efficacy of digoxin in patients with congestive heart failure was similar in all age groups. The dosage of digoxin should be reduced in patients with renal insufficiency.

Dipstick: Digoxin concentrations are increased by approximately 10% in patients with renal insufficiency. Therefore, digoxin concentrations should be measured at regular intervals to ensure that the dosage is appropriate.

ADVERSE REACTIONS

Cardiac Toxicity

Digoxin has been associated with an increased risk of angina attack in patients with coronary artery disease. The risk of cardiac toxicity is increased in patients with concomitant use of other drugs that can cause digitalis toxicity, such as beta blockers, calcium channel blockers, or potassium-sparing diuretics.

Nausea and Vomiting

Nausea and vomiting are common side effects of digoxin. They usually occur within the first few weeks of therapy and are often dose-related. In some cases, the symptoms can be alleviated by administering a smaller dose of digoxin or by switching to a different formulation of the drug.

Other Side Effects

Other side effects of digoxin include dizziness, flushing, and ATPase activity. In some cases, these symptoms can be alleviated by administering a smaller dose of digoxin or by switching to a different formulation of the drug.


table 1

Adverse Events

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<th>Category</th>
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table 2

Clinical Trials of Contraceptive Failure

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<td>Anticonvulsants</td>
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</tbody>
</table>
Incidence <2%, Regardless of Causality; Withdrawal Rates due to Adverse Events

In addition to the new events in Table 1, asthenia, cardiac failure, influenza, anorexia, dyspepsia, palpitation, edema, hyperglycemia, arthralgia, angina pectoris, insomnia, depression, ataxia, viral infection, dyspnea, coughing, and chest pain were also reported, but rates were equal to or less than 1%.

The following adverse events were reported more frequently with Coreg in U.S. placebo-controlled trials in patients with concomitant psychiatric disease.

Incidence >1% to <2%

Body as a Whole: Peripheral edema, allergy, sudden death, malaise, hypothyroidism.

Cardiovascular: Fluid overload, postural hypotension.

Central and Peripheral Nervous System: Hypersomnia, vertigo.

Gastrointestinal: Meiosis, paresthesias.

Liver and Biliary System: SGPT increased, SGOT increased.

Metabolic and Nutritional: Hypokalemia, hyperglycemia, hypomagnesemia, increased alkaline phosphatase.

Platelet, Bleeding and Clotting: Prothrombin decreased, purpura.

Psychiatric: Somnolence.

Reproductive, male: Impotence.

Urinary System: Abnormal renal function, aluminuria.

POSTMARKETING EXPERIENCE

The following adverse reactions have been reported in postmarketing experience; reports of asymptomatic have been excluded and only when cardiovascular was mentioned concurrently with other medications associated with the above adverse events in U.S. placebo-controlled trials directly comparing Coreg monotherapy in doses up to 50 mg (n=1,142) and 4.9% of Coreg patients discontinued for adverse events vs. 2.2% of placebo patients. Although there were no apparent differences in discontinuation rates, discontinuations were more common in the control group than in the placebo group (1% vs. 0%).

The incidence of adverse events in U.S. placebo-controlled trials for hypertension was found to increase with increasing doses of Coreg. For Coreg, there were no significant differences in discontinuation rates between the two groups, although worsening of symptoms of hypertension was more frequent in drug-treated patients than placebo-treated patients.

Table 2

Adverse Events in U.S. Placebo-Controlled Hypertension Trials

Incidence >1% to <2%.

Body as a Whole: Peripheral edema, allergy, sudden death, malaise, hypothyroidism.

Cardiovascular: Fluid overload, postural hypotension.

Central and Peripheral Nervous System: Hypersomnia, vertigo.

Gastrointestinal: Meiosis, paresthesias.

Liver and Biliary System: SGPT increased, SGOT increased.

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Psychiatric: Somnolence.

Reproductive, male: Impotence.

Urinary System: Abnormal renal function, aluminuria.

DOSEAGE AND ADMINISTRATION

Congentive Heart Failure

DOSEAGE MUST BE INDIVIDUALIZED AND CAREFULLY MONITORED BY A PHYSICIAN DURING INITIATION, SEQUENTIAL DOSE INCREASES, AND ACE INHIBITION (if used) should be started at a reduced level. The recommended starting dose of Coreg is 6.25 mg twice daily for two weeks. If this dose is tolerated, it may be increased to 12.5 mg twice daily if needed.

In the event of new onset of hypotensive symptoms or symptoms of congestive heart failure, BP should be controlled to the lowest effective dose. The patient should be observed for signs of dizziness or lightheadedness and may be decerebrate with progression to hypotension.BP should be controlled to the lowest effective dose. The patient may be decerebrate with progression to hypotension. BP should be controlled to the lowest effective dose. The patient should be observed for signs of dizziness or lightheadedness and may be decerebrate with progression to hypotension.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20297/S004

ADMINISTRATIVE DOCUMENTS
In a letter dated December 8, 1998, FDA requested that the firm add a discussion of the interaction between carvedilol and cyclosporin to the CLINICAL PHARMACOLOGY/Pharmacokinetic Drug-Drug Interactions subsection of the labeling for Coreg. This request was based on an abstract of a study that the firm submitted in their November 13, 1998 annual report. The study was entitled, “Elevation of cyclosporin A blood levels during carvedilol treatment in renal transplant patients” by Kaijser, M., et al, Clin Transplant Dec 1997, 11(6) p577-81.

In response to this request the firm submitted this Special Supplement – Changes Being Effected. The supplemental application provides for final printed labeling revised by adding a new section to the Precautions/Drug Interactions section immediately prior to the section on Digoxin. The new section follows:

Cyclosporin: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

Also added to the How Supplied section was the statement, “Rx only” as well as minor editorial changes.

The medical officer, Dr. Norman Stockbridge, stated that this change is acceptable. Further review of the labeling indicates that except for the new section above, the “Rx only” statement and minor editorial changes, no other changes have been made since the last labeling was approved on July 28, 1998. This supplemental application can be approved. An approval letter will be prepared for Dr. Lipicky’s signature.

/ Signature
Natalia Morgenstern
Chief, Project Management Staff

Cc: Orig NDA
HFD-110/ZMcdonald
HFD-110/Blount
HF-2/MedWatch
NDA 20-297
COREG® (carvedilol) Tablets

Raymond J. Lipicky, M.D., Director
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
Document Control Room
Food and Drug Administration
1451 Rockville Pike
Rockville, Maryland 20857

Special Supplement – Changes Being Effect

Dear Dr. Lipicky:

Reference is made to our approved New Drug Application for Coreg® (carvedilol) Tablets.

Additional reference is also made to a request from the Division to include a section in the approved Prescribing Information regarding a potential for increased cyclosporin levels in renal transplant patients receiving carvedilol. In a recent conversation, the following wording regarding cyclosporin was judged satisfactory: "Cyclosporin: Modest increases in mean trough cyclosporin concentrations were observed following initiation of carvedilol treatment in 21 renal transplant patients suffering from chronic vascular rejection. In about 30% of patients, the dose of cyclosporin had to be reduced in order to maintain cyclosporin concentrations within the therapeutic range, while in the remainder no adjustment was needed. On the average for the group, the dose of cyclosporin was reduced about 20% in these patients. Due to wide interindividual variability in the dose adjustment required, it is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate." The new section appears in the Precautions/Drug Interactions section of the labeling immediately prior to the section on Digoxin.

Enclosed are twelve copies of final printed labeling (CO:L5A and CO:L5B) for Coreg® containing the aforementioned wording. The first commercial use of this final printed labeling took place on May 4, 1999.
If you have questions regarding this supplement, please contact me by telephone at (610) 917-5368 or by facsimile at (610) 917-4708.

Sincerely,

Catherine K. Clark
Director
U.S. Regulatory Affairs