

Review of Carvedilol in Extended-Release Formulation

by Greta Nemergut, PharmD

Column Editor: Lee Vermeulen, MS, RPh, Director, Center for Drug Policy, University of Wisconsin Hospital and Clinics

Carvedilol (Coreg®, GlaxoSmithKline) has been available in the U.S. since 1997.¹ It is safe and effective in the treatment of hypertension, left ventricular dysfunction and heart failure. In 2006, an extended release (ER) formulation of carvedilol (Coreg CR®, GlaxoSmithKline) was approved which allows for once daily dosing and may help improve compliance for patients who need to take a complicated medication regimen for the treatment of heart failure. Carvedilol ER capsules have not been directly evaluated in clinical trials for efficacy in heart failure and left ventricular dysfunction (LVD). The approval for use in these indications is based on equivalence of pharmacokinetic and pharmacodynamic parameters between carvedilol ER and carvedilol immediate-release (IR).

at each dose comparison tested, falling into the acceptable limits of the predefined FDA bioequivalence (80%-125%). The time to maximum concentration was delayed by approximately 3 hours for the carvedilol ER when compared to carvedilol IR in each study, which is consistent with the characteristics of the ER formulation. Based on the outcomes of the kinetic trials, carvedilol ER was approved as equivalent to carvedilol IR, in regard to $C\tau$, C_{max} , AUC, and duration of beta-blockade and has identical indications for use. Carvedilol ER has not been evaluated in clinical outcomes trials for the treatment of heart failure or LVD. Side effects were also recorded in the trials, with profiles being similar between groups. The carvedilol IR group did experience more adverse events than the ER group; however, these were not significantly different.

TABLE 1. FDA-APPROVED INDICATIONS

Indication	Carvedilol IR	Carvedilol ER
Mild-to-severe heart failure	✓	✓
Left ventricular dysfunction following myocardial infarction	✓	✓
Hypertension	✓	✓

Adapted from eFacts and Coreg CR package insert^{1,2}

PHARMACOLOGY/PHARMACOKINETICS

Carvedilol is a racemic mixture with nonselective beta-adreno-receptor blocking activity present in the S(-) enantiomer and alpha₁-adrenergic blocking activity is present in both R(+) and S(-) enantiomers. Carvedilol has no intrinsic sympathomimetic activity.²

The doses in the carvedilol ER formulation are larger, based on the use of carvedilol phosphate, which has a higher molecular weight than the free base in the IR formulation, and contain a higher amount of free base than the IR formulation to compensate for the lower bioavailability.³

When carvedilol ER capsules were opened and sprinkled on applesauce, there was no significant effect on area-under-the-curve (AUC) and only an 18% reduction in maximum plasma concentration (C_{max}).²

Three trials comparing the pharmacokinetic and pharmacodynamic profiles of carvedilol ER and IR were performed.⁴⁻⁶ The primary outcomes in each study were trough plasma concentration ($C\tau$), C_{max} , and AUC. In each study, the pharmacokinetic parameters were equivalent between the IR and ER formulations

CLINICAL TRIALS

There is currently only one published primary efficacy trial for carvedilol ER. Two additional trials are ongoing, one directly comparing the effects of carvedilol IR and ER on left ventricular ejection fraction in patients with heart failure and the other comparing the two agents in regard to adherence.^{7,8}

Weber et al evaluated the efficacy of once-daily carvedilol ER for the treatment of hypertension in a multi-center, double-blind, randomized, placebo-controlled, parallel-group study.⁹ A total of 338 patients, which consisted of three subsets (untreated essential hypertension, treated-controlled hypertension, and treated-untreated hypertension) were randomized to receive either 20 mg carvedilol ER for six weeks, 40 mg carvedilol ER (20 mg x two weeks, 40 mg x four weeks), 80 mg carvedilol ER (20 mg x two weeks, 40 mg x two weeks, 80 mg x two weeks), or placebo. The primary endpoint was change from baseline in mean 24-hour diastolic blood pressure (DBP) using ambulatory blood pressure monitoring (ABPM) compared to placebo. Baseline characteristics were similar between groups. About 75% of study participants were male, with about 80% not on prior anti-hypertensive therapy. The changes from baseline after subtracting the placebo group for the 20 mg, 40 mg and 80 mg groups, were -4.03 mmHg (95% CI -6.41 to -1.65; p=0.001), -7.56 mmHg (95% CI -9.95 to -5.16; p<0.0001), and -9.19 mmHg (95% CI -11.59 to -6.79; p<0.0001), respectively. The overall rate of adverse events, including dizziness, fatigue and headache, did not differ between groups; however, nausea was reported more frequently in the 80 mg dose group.



TABLE 2. PHARMACOKINETIC PARAMETERS

Parameter	Carvedilol IR	Carvedilol ER
Bioavailability	25%-35% due to 1st pass metabolism; no difference if taken with or without food	85% of the IR formulation; decreases 27% if taken on empty stomach; similar levels as IR if both taken with food
Half-life	7 to 10 hours R(+) enantiomer: 5 to 9 hours S(-) enantiomer: 7 to 11 hours	Pharmacodynamic effects last 24 hours
Maximum concentration (C _{max})	Delayed if taken with food	Decreases 43% if taken on empty stomach; similar levels as IR if both taken with food
Time to maximum concentration (T _{max})	~1.5 to 2 hours	5 hours
Protein binding	>98%, mostly to albumin	>98%, mostly to albumin
Volume of distribution	115 liters	115 liters
Metabolism	Aromatic ring oxidation and glucuronidation primarily	Aromatic ring oxidation and glucuronidation primarily
Metabolites	3 active, weak vasodilating activity, metabolized by conjugation via glucuronidation and sulfation	3 active, weak vasodilating activity, metabolized by conjugation via glucuronidation and sulfation
Metabolism by cytochrome P450 (CYP450)	Primary: CYP2D6 and 2C9 Secondary: CYP3A4, 2C19, 1A2, and 2E1	Primary: CYP2D6 and 2C9 Secondary: CYP3A4, 2C19, 1A2, and 2E1
Excretion	<2% of parent drug excreted unchanged in urine; metabolites excreted via bile into feces	<2% of parent drug excreted unchanged in urine; metabolites excreted via bile into feces
Elderly	Plasma levels ~50% higher than in younger patients	Plasma levels ~50% higher than in younger patients
Hepatic impairment	4- to 7-fold higher concentrations in hepatic cirrhosis	No studies completed
Renal impairment	Higher plasma concentrations, not cleared by hemodialysis, no dose adjustment necessary	No studies completed

Adapted from eFacts, Coreg CR package insert, Tenero et al¹⁻³

TABLE 3. DRUG INTERACTIONS

Drug	Interaction
Rifampin	Decrease AUC and C _{max} of carvedilol by 70%
Cimetidine	Increase AUC of carvedilol by 30%
Digoxin	AUC and C _{min} of digoxin increased by 14% and 16% respectively when given with carvedilol
CYP2D6 inhibitors (ex. quinidine, fluoxetine, paroxetine)	Have not been studied, but expected to increase levels of R(+) enantiomer of carvedilol based on kinetic profile
Catecholamine-depleting agents (ex. reserpine, MAO-I)	Potentiate hypotension and bradycardia in combination with beta-blocker
Clonidine	Combination with beta-blocker could potentiate blood-pressure- and heart-rate-lowering effects; if discontinued, remove beta-blocker therapy first
Cyclosporine	Increases in cyclosporine trough levels seen when given with carvedilol; monitor cyclosporine levels closely and adjust dose as needed
Calcium channel blockers	Isolated conduction disturbance with carvedilol and diltiazem concomitant therapy; if carvedilol given with diltiazem or verapamil, monitor ECG and blood pressure
Insulin or oral hypoglycemics	Beta-blockers may enhance blood sugar lowering ability; monitor blood sugar regularly

Adapted from Coreg CR package insert²; AUC=area-under-the-curve, C_{max}=maximum concentration; C_{min}=minimum concentration, CYP=cytochrome P450, MAO-I=monoamine oxidase inhibitors, ECG=electrocardiogram

**TABLE 4. CONTRAINDICATIONS/
WARNINGS/PRECAUTIONS**

CONTRAINDICATIONS

- Bronchial asthma or related bronchospastic conditions
- Second- or third-degree AV block
- Sick sinus syndrome or severe bradycardia, unless permanent pacemaker in place
- Cardiogenic shock
- Decompensated heart failure requiring use of intravenous inotropic therapy; wean intravenous therapy before starting carvedilol ER
- Not recommended in patients with clinically manifest hepatic impairment
- Hypersensitivity to any component

WARNINGS

- Do not discontinue abruptly; may exacerbate angina or acute MI or ventricular arrhythmia may occur
- May precipitate symptoms of arterial insufficiency in patients with peripheral vascular disease
- If continued perioperatively, care should be taken when anesthetic agents which depress myocardial function are used (ex. ether, cyclopropane, trichloroethylene)
- Beta-blockers may mask signs of hypoglycemia, particularly tachycardia. Non-selective beta-blockers may potentiate insulin-induced hypoglycemia. In heart failure patients, there is a risk of hyperglycemia.
- Beta-blockers may mask signs of hyperthyroidism, such as tachycardia. Abrupt withdrawal of beta-blockade may exacerbate symptoms of hyperthyroidism or cause thyroid storm.

PRECAUTIONS

- May cause bradycardia, if pulse <55 beats/minute, reduce dose
- May cause hypotension and postural hypotension and syncope; start at lowest possible dose and titrate
- Deterioration of renal function, rarely
- Worsening heart failure or fluid retention may occur in titration; increase diuretics and do not advance dose further until patient stabilized
- Patients with pheochromocytoma; initiate alpha-blocker first
- Patients with Prinzmetal variant angina; may provoke chest pain
- May affect blood glucose, monitor when initiated, adjusted, or discontinued
- May be more reactive to allergens if have history of severe anaphylactic reaction; may be unresponsive to usual dose of epinephrine
- Use with caution in patients with bronchospastic disease only if patients do not respond to or cannot tolerate other antihypertensive therapy

Adapted from Coreg CR package insert²

DRUG INTERACTIONS

Drug interaction data have been obtained from clinical trials of carvedilol IR. The only unique interaction for the ER formulation is with alcohol, as it may affect the release properties of the extended release medication, resulting in a faster rate of release, higher peak concentrations and lower trough concentrations. Administration of carvedilol ER should be separated from alcohol by at least two hours.² Table 3 lists additional drug interactions.

Carvedilol IR was also evaluated in combination with glyburide, hydrochlorothiazide, torsemide, and pantoprazole. The combination of these agents did not result in any change to the pharmacokinetic profile of any of the medications.²

CONTRAINDICATIONS/WARNINGS/PRECAUTIONS

In trials of carvedilol ER in patients with hypertension and LVD following myocardial infarction (MI), adverse events were similar to that of carvedilol IR. The data in Table 4 are from clinical trials with carvedilol ER as well as IR.

ADVERSE EVENTS

In trials evaluating the pharmacokinetics and pharmacodynamics of carvedilol ER compared to carvedilol IR, the adverse event profile was similar between groups, with headache being the most reported adverse event.² Since few differences were seen, the adverse events listed for carvedilol ER include those that have been reported in the carvedilol IR clinical trials. The most frequently reported adverse events for carvedilol (both ER and IR) are headache, orthostatic hypotension and dizziness.²

COST, DOSE, AND HOW SUPPLIED

Carvedilol ER is an extended-release capsule intended for once daily administration. It is available in 10, 20, 40, and 80 mg capsules. The average wholesale price (AWP) for all strengths of carvedilol ER is \$4.17 per capsule. The AWP for equivalent doses of carvedilol IR, based on the dosing conversion listed in table 5, is \$4.38. The patent for carvedilol IR is expected to expire in September 2007, at which time a generic formulation is expected to become available.¹⁰

Carvedilol ER should be taken once daily in the morning with food. Carvedilol ER should be swallowed whole, and should not be crushed, chewed, or taken in divided doses. However, the capsules may be opened and the beads sprinkled over a spoonful of applesauce. The mixture should be consumed immediately. Absorption of the beads sprinkled on other foods has not been evaluated. Carvedilol ER should be administered

TABLE 5. DOSING CONVERSION

Daily dose of carvedilol IR	Daily dose of carvedilol ER
3.125 mg twice daily	10 mg daily
6.25 mg twice daily	20 mg daily
12.5 mg twice daily	40 mg daily
25 mg twice daily	80 mg daily

Adapted from Coreg CR package insert²

TABLE 6. TITRATION SCHEDULES

Heart failure	Left ventricular dysfunction post MI	Hypertension
<ul style="list-style-type: none"> • 10 mg once daily x 2 weeks • May double dose every 2 weeks as tolerated • Doses beyond 80 mg daily not evaluated 	<ul style="list-style-type: none"> • 20 mg once daily • May double dose every 3 to 10 days as tolerated • Doses beyond 80 mg daily not evaluated 	<ul style="list-style-type: none"> • 20 mg once daily • May double dose every 7 to 14 days as tolerated • Maximum dose 80 mg

Adapted from Coreg CR package insert²

at least two hours apart from alcohol, including prescription and over-the-counter medications that contain ethanol. Patients on carvedilol IR should be switched to the ER formulation based on the dose conversion listed in Table 5.²

Doses of carvedilol ER should be individualized and closely monitored during titration. Table 6 lists the recommended titration schedules for each indication.

CONCLUSION

While carvedilol ER has been shown to be bioequivalent to carvedilol IR in pharmacokinetic studies, tolerability appears to be similar to the IR formulation and clinical outcome comparisons have yet to be determined. Carvedilol ER may improve adherence to a complicated heart failure drug regimen; however, the clinical trial that may demonstrate this effect is still ongoing, and historically, a change from twice daily to once daily dosing of medications has not statistically improved adherence.¹¹ Also, heart failure patients may also be taking other twice daily medications, so changing one medication from twice daily to once daily may have little impact on overall compliance.

Some patients who have difficulty tolerating carvedilol IR due to hypotensive side effects may benefit from once daily administration of carvedilol ER at bedtime, allowing the patient to sleep through the peak time of the side effect. However, most patients tolerate the twice daily dosing of carvedilol IR without incident.

As mentioned previously, the patent on carvedilol IR is expected to expire in September 2007. Due to this patent expiration, no long-term clinical outcome trials were completed for carvedilol ER. Heart failure outcome trials may take several years to complete. By the time the trial data would be available, a generic launch of carvedilol IR would have already occurred. Conversion from a generic medication, back to a brand medication is much more difficult, based on cost differences. Also, extended release formulations have shorter patent lives than the original chemical entity, allowing for generics to enter the market at an earlier time.

Since there are no completed clinical outcome or compliance trials for carvedilol ER, and tolerability is similar between dosage forms, current data do not support using the ER formulation over the IR formulation. At this time, carvedilol ER does not provide a clinical benefit over carvedilol IR and, heart failure patients, stable on their drug regimens, should not be converted. ●

Greta Nemergut is a clinical pharmacist and medication use policy analyst in the Center for Drug Policy, University of Wisconsin Hospital and Clinics.

REFERENCES

1. eFacts online database. *Wolters Kluwer Health, Inc.* 2007. St. Louis, MO. Accessed May 10, 2007.
2. Coreg CR (carvedilol phosphate extended-release). [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2007.
3. Tenero DM, Henderson LS, Baidoo CA, et al. Pharmacokinetic properties of a new controlled-release formulation of carvedilol. *Am J Cardiol* 2006; 98:5L-16L.
4. Tenero DM, Henderson LS, Campanile AM, et al. Development of a pharmacokinetic/pharmacodynamic model for carvedilol to predict beta1-blockade in patients with congestive heart failure. *Am J Cardiol* 2006; 98:27L-31L.
5. Packer M, Lukas MA, Tenero DM, et al. Pharmacokinetic profile of controlled-release carvedilol in patients with left ventricular dysfunction associated with chronic heart failure or after myocardial infarction. *Am J Cardiol* 2006; 98:39L-45L.
6. Henderson LS, Tenero DM, Baidoo CA, et al. Pharmacokinetic and pharmacodynamic comparison of controlled-release carvedilol and immediate-release carvedilol at steady state in patients with hypertension. *Am J Cardiol* 2006; 98:17L-26L.
7. Greenberg BH, Mehra M, Teerlink JR, et al. COMPARE: comparison of the effects of carvedilol CR and carvedilol IR on left ventricular ejection fraction in patients with heart failure. *Am J Cardiol* 2006; 98:53L-59L.
8. Hauptman PJ, Pressler SJ, Sackner-Bernstein J, et al. Rationale and design of CASPER: compliance and quality of life study comparing once-daily carvedilol CR and twice-daily carvedilol IR in patients with heart failure. *Am J Cardiol* 2006; 98:60L-66L.
9. Weber MA, Bakris GL, Tarka EA, et al. Efficacy of a once-daily formulation of carvedilol for the treatment of hypertension. *J Clin Hypertens (Greenwich)* 2006; 8:840-849.
10. FDA Center for Drug Evaluation and Research. Electronic Orange Book. Available at: http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?AppL_No=022012&TABLE022011=OB_Rx. Accessed May 25, 2007.
11. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001;23:1296-1310.

Staff Pharmacist

If you are looking for a change in your career, take the time to explore an opportunity with Phillips Health Mart Pharmacies. Phillips is an independent chain of four pharmacies located in scenic south central Wisconsin. Our areas of expertise include community/retail pharmacy, infusion therapy, nursing home services, durable medical equipment, and patient health screenings. More information is available on our website at www.phillipsrx.com.

We have full time and part time opportunities available for the new graduate as well as the experienced pharmacist. Phillips offers an attractive salary, a full range of benefits, and a 401K retirement plan.

If you're searching for a fulfilling career in health care that offers diversity and professional growth, while enjoying a great quality of life, please call 1-800-343-3784 and ask for Wayne MacArdy or Tamara Ryan. To forward a copy of your resume, mail it to Phillips Pharmacies, Human Resources, PO Box 136, Mauston, WI, 53948, or email it to tamara.ryan@phillipsrx.com.