

FACSIMILE COVER SHEET



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Regulatory Policy
Divisions of Regulatory Policy I, II, & III
10903 New Hampshire Ave., Building 51, 6th Floor
Silver Spring, MD 20993-0002
Phone: (301) 796-3601 and 3602
Fax: (301) 847-8440

DATE: October 15, 2010

TO: Charles J. Raubicheck of Frommer Lawrence & Haug LLP on behalf of
Flamel Technologies, S.A.,

FAX: 212-588-0500

FROM: David Joy

PAGES: 14 (Including Cover Sheet)

COMMENTS:

Attached is the response to your citizen petition, received on April 19, 2010, regarding Coreg (carvedilol phosphate) Extended-Release Capsules. (FDA-2010-P-0216).

The original will be placed in the mail to you.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other actions based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

• Charles J. Raubicheck
Frommer Lawrence & Haug LLP
745 Fifth Avenue
New York, NY 10151

OCT 15 2010

Re: Docket No. FDA-2010-P-0216

Dear Mr. Raubicheck:

This letter responds to your citizen Petition (Petition) received on April 19, 2010, submitted on behalf of Flamel Technologies, S.A., and the supplements submitted by Flamel on July 23, 2010¹ (Supplement 1), and August 16, 2010 (Supplement 2). You request that the Food and Drug Administration (FDA or the Agency) require any abbreviated new drug application (ANDA) or section 505(b)(2)² new drug application (505(b)(2) NDA) that references Coreg (carvedilol phosphate) Extended-Release Capsules (Coreg CR) 10 mg, 20 mg, 40 mg, and 80 mg, to include test results demonstrating bioequivalence for the pharmacokinetic parameter C_{min} in addition to traditional pharmacokinetic parameters. FDA has considered the information in your Petition, comments submitted on behalf of Mutual Pharmaceutical Company, Inc., dated May 24, 2010, and July 23, 2010, the supplements submitted by Flamel, and other information available to the Agency. Mutual submitted a third set of comments dated October 5, 2010, and Flamel submitted a third supplement dated October 8, 2010. The Agency was unable to consider these submissions prior to our deadline for responding to this petition under section 505(q) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 355(q). For the reasons set forth below, your Petition is granted in part and denied in part.

I. BACKGROUND**A. Coreg CR**

FDA approved Coreg CR on October 20, 2006. Coreg CR is an extended-release oral capsule intended for administration once daily in the morning with food. GlaxoSmithKline holds approved new drug application (NDA) 22-012 for Coreg CR. Carvedilol is a racemic mixture in which nonselective β -adrenoreceptor blocking activity is present in the S(-) enantiomer, and α_1 -adrenergic blocking activity is present in both

¹ Flamel's first supplement was submitted originally on June 14, 2010, and then resubmitted on July 23, 2010, with the correct verification statement required by section 505(q)(1)(I) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 355(q)(1)(I).

² Section 505(b)(2) of the Act, 21 U.S.C. 355(b)(2).

Docket No. FDA-2010-P-0216

R(+) and S(-) enantiomers at equal potency. Coreg CR is indicated for the treatment of the following:

- Mild to severe chronic heart failure
- Left ventricular dysfunction (LVD) following myocardial infarction (MI) in clinically stable patients
- Hypertension

Coreg CR hard gelatin capsules are filled with carvedilol phosphate immediate-release and controlled-release microparticles that are drug-layered and coated with methacrylic acid copolymers.

B. Statutory and Regulatory Basis for Approving ANDAs

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(j)), which established the current ANDA approval process. To obtain approval, an ANDA sponsor is not required to submit evidence to establish the clinical safety and effectiveness of the drug product, as is required for a new drug application (NDA). Instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective. To rely on this finding, the ANDA must contain (with certain exceptions) information to show that the proposed drug has the same active ingredient(s), indications, route of administration, dosage form, strength, and labeling as the RLD (sections 505(j)(2)(A) and (j)(4) of the Act), and is bioequivalent (section 505(j)(2)(A)(iv) of the Act). A drug's dosage form refers to the physical form of the drug product and the way in which it is administered, not to its release mechanism.³ Thus, a generic drug will not necessarily release its drug substance in the same manner as the RLD.

The basic assumption underlying the Hatch-Waxman Amendments is that bioequivalent drug products that meet the Act's criteria are therapeutically equivalent and may be substituted for each other. A generic drug product is bioequivalent to the RLD "if the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient" (section 505(j)(8)(B)(i) of the Act). FDA regulations at 21 CFR 320.1(e) specify that two drug products are bioequivalent if there is an

absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.⁴

³ *Pfizer Inc. v. Shalala*, 1 F. Supp 2d 38, 46-47, aff'd in part and rev'd in part, 182 F.3d 975 (D.C. Cir. 1999).

⁴ See also 21 CFR 320.23(b).

Docket No. FDA-2010-P-0216

C. Section 505(b)(2) Applications

A 505(b)(2) application shares characteristics of both an ANDA and a 505(b)(1) NDA (referred to as a stand-alone NDA). Like a stand-alone NDA, a 505(b)(2) application is submitted under section 505(b)(1) of the Act and approved under section 505(c). As such, it must satisfy the same statutory requirements for safety and effectiveness information as a stand-alone NDA. A 505(b)(2) application is similar to an ANDA because it may rely, in part, on FDA's finding that the listed drug it references is safe and effective as evidence in support of the proposed product's own safety and effectiveness.⁵ However, although a drug product approved under an ANDA is generally required to duplicate an innovator product (with a few limited exceptions), a 505(b)(2) application often describes a drug with substantial differences from the listed drug it references.⁶ These differences may include, for example, a different active ingredient or a new indication, dosage form, strength, formulation, or route of administration.⁷ A 505(b)(2) application must support those differences with appropriate safety and effectiveness information. Depending on the nature of a 505(b)(2) application, a demonstration of bioequivalence to the referenced drug may be needed.

D. Bioequivalence Standards

Section 314.94(a)(7) of FDA's regulations sets forth the bioequivalence requirements for an ANDA, and procedures for determining bioequivalence are set forth in 21 CFR 320. The regulations discuss the various methods of establishing bioequivalence in descending order of accuracy, sensitivity, and reproducibility. These include pharmacokinetic studies, pharmacodynamic studies, comparative clinical trials, and in vitro studies (21 CFR 320.24). In addition, as under section 505(j)(8)(C) of the Act, section 320.24(b)(6) of the regulations states that FDA has the flexibility to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence." It is well accepted that FDA has considerable discretion in determining how the bioequivalence requirement is met. FDA's discretion need only be based on a "reasonable and scientifically supported criterion, whether [the Agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs . . ." (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp 212, 218 (D.D.C. 1996) (quoting *Schering v. Sullivan Corp.*, 782 F. Supp 645, 651 (D.D.C. 1992), vacated as moot sub nom, *Schering Corp. v. Shalala*, 995 F.2d

⁵ A 505(b)(2) application must, like an ANDA, contain an appropriate patent certification or statement for each patent that claims the listed drug or a method of using the drug for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the Act (see section 505(b)(2)(A)-(B) of the Act). Also, the date of approval of the 505(b)(2) application, as with an ANDA, may be affected by such patents and by applicable periods of marketing exclusivity granted to the listed drug relied upon (see section 505(c)(3) of the Act).

⁶ Under 21 CFR 314.101(d)(9), we may refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Act.

⁷ See 21 CFR 314.54(a); see also the draft guidance for industry entitled *Applications Covered by Section 505(b)(2)* (October 1999), available on the Internet at <http://www.fda.gov/Drugs> under Guidances (Drugs).

Docket No. FDA-2010-P-0216

1103 (D.C. Cir. 1993))). Courts have expressly upheld FDA's regulatory implementation of the Act's bioequivalence requirements (see, e.g., *Schering Corp. v. FDA*, 51 F.3d 390 at 397-400 (3rd Cir. 1995); *Fisons' Corp. v. Shalala*, 860 F. Supp 859 (D.D.C. 1994)).

Standard bioequivalence pharmacokinetic studies are conducted using a two-treatment crossover study design, randomly separating a limited number of subjects into two groups. One group will first receive the test drug and then, after an appropriate wash-out period, will receive the reference drug. The second will first receive the reference and then the test drug. Single oral doses of the test and reference drugs are administered. Single-dose studies generally are more sensitive than multiple-dose studies in assessing release of the drug substance from the drug product into the systemic circulation, which makes it easier to detect differences in bioavailability attributable to formulation differences. FDA recommends administration of the test and reference drug products to healthy subjects with measurement of the plasma concentrations of the test and reference products over time. The rate and extent of drug absorption are statistically analyzed. The pharmacokinetic parameters calculated from these data include the area under the plasma concentration vs. time curve (AUC), calculated to the last measured concentration time (AUC_{0-t}), and AUC extrapolated to infinity ($AUC_{0-\infty}$). These parameters represent the extent of absorption. Another important pharmacokinetic parameter is the maximum or "peak" drug concentration (C_{max}). C_{max} provides information concerning the rate of absorption.

To establish bioequivalence, the calculated 90 percent confidence interval for the log transformed ratio of geometric means for AUC and C_{max} values between the generic product and the RLD should fall entirely within an 80 percent to 125 percent acceptance interval (0.8-1.25).⁶ The use of an 80 to 125 percent acceptance interval to compare two products with the same active ingredient, dosage form, route of administration, and strength is a scientific judgment about the best statistical practices for bioequivalence determinations, and reflects decades of scientific data on the variability of product characteristics within and between batches, as well as biological variability in patients. Because the point estimate of the test/reference ratio lies in the center of the 90 percent confidence interval, the mean of the data is usually close to 100 percent (a test/reference ratio of 1). The pharmacokinetic parameter T_{max} , the time to reach peak plasma drug concentration following dosing, is also a rough indicator of the rate of drug absorption and serves as supportive data in evaluating bioequivalence between products.

When it is appropriate to conduct multiple-dose studies (also referred to as steady-state studies), FDA advises ANDA sponsors to use additional pharmacokinetic data in evaluating bioequivalence, including individual and mean trough levels (minimum drug concentration) ($C_{min SS}$).

⁶ Orange Book, Chapter 1.3, *Statistical Criteria for Bioequivalence*; FDA guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (March 2003).

Docket No. FDA-2010-P-0216

1. *General Bioequivalence Guidance*

In 2003, FDA issued the guidance *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (general BA/BE guidance),⁹ which describes our general recommendations for demonstrating bioequivalence. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

2. *Draft Guidance on Bioequivalence Testing for Carvedilol*

In addition to our general recommendations, we provide product-specific recommendations for demonstrating bioequivalence. Our process for making product-specific bioequivalence guidance available to the public is explained in the guidance *Bioequivalence Recommendations for Specific Products*.¹⁰ In May 2008, we issued final guidance on bioequivalence testing of carvedilol oral tablets. In February 2010, we issued draft guidance on bioequivalence testing of carvedilol phosphate oral extended-release capsules. This draft guidance recommends three single-dose, two-way, crossover in vivo studies, one in fasted subjects, one in fed subjects, and one in which the drug is sprinkled on food. All the studies should be conducted at a strength of 40 mg. Analytes to be measured include carvedilol (racemate of parent drug)¹¹ and 4-hydroxyphenyl-carvedilol (active metabolite) in plasma. Waivers for in vivo testing of 10 mg, 20 mg, and 80 mg strengths will be provided based on (i) acceptable bioequivalence studies at the 40 mg strength, (ii) proportional similarity across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. The draft guidance further recommends dissolution testing using various concentrations of ethanol to address the possibility of dose dumping if an extended-release carvedilol phosphate product is taken with alcohol. The guidance and draft guidance applicable to carvedilol are available on the Internet at <http://www.fda.gov/Drugs> under Guidances (Drugs).

⁹ Available on the Internet at <http://www.fda.gov/Drugs> under Guidances (Drugs).

¹⁰ Available on the Internet at <http://www.fda.gov/Drugs> under Guidances (Drugs).

¹¹ As you know, the bioavailability studies supporting approval of Coreg CR included measurement of the individual plasma concentrations of the R(+) and S(-) enantiomers. For bioavailability studies supporting approval of an NDA, measurement of individual enantiomers is often important as this supplies basic information about the pharmacokinetic properties of the drug. For bioequivalence studies supporting approval of an ANDA, measurement of individual enantiomers is not recommended, in the absence of conditions not present with this drug; instead we generally recommend measurement of the racemate using an achiral assay, as is the case with carvedilol phosphate. This is explained in our guidance for industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, available on the internet at <http://www.fda.gov/Drugs> under Guidances (Drugs).

Docket No. FDA-2010-P-0216

II. DISCUSSION

A. Summary of Petitioner's Arguments Supporting Requested Action

In your Petition, you ask the Agency to require all ANDAs and 505(b)(2) applications that reference Coreg CR to "include the results of tests demonstrating bioequivalence for the pharmacokinetic ("PK") parameter C_{min} . . ." You also refer to C_{min} as the "trough plasma concentration," C_t or C_{tau} . We interpret your petition as asking the Agency to impose certain conditions on C_{min} (the minimum plasma concentration between doses at steady state),¹² as measured through multiple-dose PK testing.

In support of this request, you present a hypothetical PK curve (Profile A) superimposed on an actual PK curve for Coreg CR to illustrate your point that it would be possible, in theory, for a product to be bioequivalent to Coreg CR, according to the Agency's standard criteria for AUC and C_{max} , while having a C_{min} plasma concentration below that of Coreg CR (Petition at 4). In this illustration, the plasma concentration shown in "Profile A" remains below the C_{min} plasma concentration of Coreg CR for approximately 7 hours.

You state that maintaining a sufficient minimum concentration of carvedilol over Coreg CR's 24-hour dosing interval is vital to clinical efficacy, notably including survival in heart failure and post-myocardial infarction left ventricular dysfunction (post-MI LVD) patients. You cite five published articles as supporting this (Petition at 4). You state that FDA required Coreg CR to be bioequivalent to the twice-a-day, immediate-release carvedilol formulation (hereinafter "Coreg IR") in terms of C_{min} and other PK parameters (Petition at 4-5). You cite articles published in the scientific literature in which bioequivalence between Coreg CR and Coreg IR is established with reference to C_{min} and other PK and pharmacodynamic parameters (Petition at 5-10).

You cite literature documenting diurnal variation in cardiovascular events, suggesting a greater risk between 6:00 a.m. and noon (Petition at 10). You point out that the trough plasma concentration of carvedilol will occur during this period if patients take Coreg CR once daily in the morning, consistent with its labeling. You also present information in the Petition suggesting that beta-blockers may suppress an increased morning incidence of myocardial infarction (Petition at 10). You argue that it is therefore important that generic carvedilol extended-release formulations provide C_{min} levels no lower than those of Coreg CR during this period.

Finally, you acknowledge that an ANDA may obtain approval of a formulation of Coreg CR solely for the two indications not currently protected by patents, hypertension and left ventricular dysfunction, while carving out the heart failure indication from the generic product's labeling. You state that, despite such labeling, substitution of generic

¹² C_{min} is sometimes defined as the lowest concentration in the dosing interval and sometimes defined as the concentration at the end of the dosing interval. Because you also refer to C_{min} as the "trough plasma concentration" (Petition at 1), we interpret your petition as referring to the minimum plasma concentration at any point between doses.

Docket No. FDA-2010-P-0216

carvedilol for heart failure patients will take place, and that effective treatment for this life-threatening condition requires that the plasma concentration be maintained above a certain minimum (Petition at 11).

B. Discussion

1. PK Curves

The hypothetical PK curve presented on page 4 of the Petition shows it is possible in theory for two drugs to exhibit the same C_{max} and AUC, while differing significantly with respect to C_{min} . This hypothetical Profile A might apply to some drugs, but it is clear, based on the available data, that it could not apply to an extended-release carvedilol phosphate product.

Carvedilol is practically insoluble in water and exhibits pH-dependent solubility. Its solubility in water is $< 1 \mu\text{g/ml}$ above pH 9.0, $23 \mu\text{g/ml}$ at pH 7, and about $100 \mu\text{g/ml}$ at pH 5 at room temperature.¹³ Carvedilol is generally classified as a Biopharmaceutics Classification System (BCS) Class II drug (low solubility and high permeability).^{14,15}

Different drugs are absorbed into and eliminated from the body in different ways. In some cases, a drug is absorbed into the bloodstream, achieves rapid equilibrium with all tissue in the body, and is eliminated from the body at a predictable rate that is proportional to the amount of drug in the body (a first-order elimination). In this situation, the concentration of this drug is described by a one-compartment model (because the body is viewed as one "compartment") with first-order elimination. In other cases, a drug is absorbed into the bloodstream but does not distribute rapidly to all tissues. Distribution to some readily accessible peripheral spaces is much faster than to deeper tissues. In such cases the drug is being taken out of the vascular system not only through elimination but also through distribution to other tissues. A mathematical

¹³ Chakraborty S., Shukla D., Jain A., Mishra B., Singh S., Assessment of Solubilization Characteristics of Different Surfactants for Carvedilol Phosphate as a Function of pH. *Journal of Colloid and Interface Science* 335 (2009), 242–249.

¹⁴ The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability
- Class 4: Low Solubility – Low Permeability

¹⁵ Lofsson T., Vogensen S.B., Desbos C., and Jansook P., Carvedilol: Solubilization and Cyclodextrin Complexation: A Technical Note. *AAPS PharmSciTech* 9 (2) (2008), pp 425–430.

Docket No. FDA-2010-P-0216

description of this process requires accounting for the different rates of transfer between tissues, often through addition of more compartments to the model.

A simple analysis of the pharmacokinetic data (plotting log C versus time) for a drug can usually be used to determine what number of compartments provides the best description of a drug's concentration-time profile. For example, when plotting log C versus time, a single straight line is obtained in the downward part of the curve for a one-compartment model while a curve that is a combination of several straight lines will be obtained for a multi-compartmental model. However, when the absorption rate of a drug is much slower than its elimination rate (so-called "flip-flop" pharmacokinetics), a curve that is a combination of several straight lines may also be observed in the downward part of the log C versus time plot. Thus, a simple analysis may not be sufficient to determine the best description of drug pharmacokinetics for a drug that exhibits "flip-flop" pharmacokinetics.

Available data suggest that the pharmacokinetic profile of carvedilol (both immediate-release and extended-release) corresponds to a two- or three-compartment model (suggesting the possibility of tissue distribution), and/or "flip-flop" pharmacokinetics. The hypothetical Profile A presented on page 4 of the Petition, on the other hand, corresponds to a one-compartment model with zero-order absorption and first-order elimination.

If the pharmacokinetic properties of carvedilol are due to tissue distribution, any pharmacokinetic profile of this drug would have to follow a two- or three-compartment model, as the distribution and elimination kinetics are inherent to a drug molecule. In this case, the plasma concentration would not decay as quickly as it does in Profile A, and C_{\min} would fall close to that of Coreg IR or Coreg CR. Thus, Profile A cannot represent a realistic possibility for this drug.

Alternatively, if carvedilol exhibits flip-flop pharmacokinetics, this would suggest the absorption is limited by solubility and/or permeability. The facts that carvedilol has low solubility and (for purposes of the products that are the focus of this petition) is formulated in sustained-release formulations support the possibility of flip-flop pharmacokinetics. Rapid absorption and instant cut-off, which are characteristics of Profile A, do not correlate with this situation.

Therefore, according to either possible explanation for the observed pharmacokinetics of carvedilol, the proposed Profile A is not physiologically feasible. We consider Profile A to be very unlikely and would accept the possibility of a PK curve like that shown in Profile A only if we were presented with actual PK data showing that, contrary to existing evidence, carvedilol could produce a PK curve having this shape.¹⁶

¹⁶ If a bioequivalence study for a generic product did in fact present the profile illustrated by this hypothetical, the differences in T_{\max} and pharmacokinetic profile presented (compared to the RLD) would lead FDA reviewers to engage in further analysis as described in section II.B.5 of this response.

Docket No. FDA-2010-P-0216

2. *General Importance of C_{min}*

Your Petition cites five published articles as supporting the importance of maintaining a sufficient minimum concentration of carvedilol over the 24-hour dosing interval for an extended-release product for clinical efficacy in heart failure and post-MI LVD patients. Many drugs are not adequately effective unless a certain minimum plasma concentration is maintained throughout the dosing interval. This is not true of all drugs, however. In some cases, C_{min} does not play a critical role in a drug's effectiveness.

In the case of Coreg CR, a new once-a-day controlled-release formulation of carvedilol phosphate submitted as a 505(b)(2) application, the submission referenced and depended largely on our findings of safety and effectiveness for Coreg IR (NDA 22-012). Hence, it was critical to bridge the findings from Coreg IR by understanding the pharmacokinetic/pharmacodynamic (PK/PD) relationship between plasma carvedilol exposure and its effect on exercise-induced heart rate. This formed the basis for requiring repeat dose studies that would compare the PK and PD of Coreg IR and CR formulations. Because the PK-PD-clinical outcome relationship was unknown, we required the sponsor of Coreg CR to demonstrate (a) adequate minimum plasma concentrations (C_{min}), as well as (b) adequate effect at minimum plasma concentration (PD_{min} = exercise-induced heart rate at trough concentrations). This was intended to ensure that there will be a reasonably similar coverage of exposure and pharmacodynamic effect between the Coreg CR and IR formulations throughout the dosing intervals. This formed the basis of the Agency's expectation as outlined in the pre-NDA meeting minutes dated August 2, 2005. In short, a multiple-dose study was needed to explore the PK/PD clinical outcome relationship for Coreg CR, but, for the reasons explained in section II.B.5 of this response, is not needed to show bioequivalence between Coreg CR and a proposed generic equivalent.

3. *Diurnal Variation in Risk*

Regarding diurnal variation in cardiovascular events, the Petition cites four publications as supporting the assertion that the risk of myocardial infarctions is increased in the morning hours. We agree it seems reasonable to conclude there is an association between time of day and myocardial infarctions. The published studies cited in the Petition show an increase in the onset of these events in the time interval between 6:00 a.m. and noon. A more granular differentiation of events generally indicates that the peak event period occurs between 9:00 a.m. and noon. The cited articles demonstrate a correlation but do not establish a cause and effect relationship for the increased event rate during this time period or for the mitigation of this increased morning rate associated with beta-blockers. The number of subjects treated with beta-blockers in each of the studies is small. There is insufficient information as to which beta-blockers were used and the timing of the doses. It is also not clear that the cohort of individuals treated with beta-blockers was equivalent to the cohort not treated with beta-blockers. As stated above, however, based on currently available information, we agree that it is important for patients to maintain sufficient minimum concentrations of carvedilol over the entire dosing interval.

Docket No. FDA-2010-P-0216

4. *Substitution of Generic Products in Heart Failure Patients*

Your Petition explains that a generic extended-release carvedilol product may be approved with the heart failure indication carved out from its labeling because of patent protection. You state that a generic product may nevertheless be prescribed to treat heart failure patients and that there could be serious efficacy and safety repercussions for these patients if a generic product does not provide adequate minimum plasma concentrations throughout the dosing interval. Consistent with our discussion above regarding the general importance of C_{min} , we believe adequate minimum plasma concentrations are important for all patients treated with extended-release carvedilol products.

5. *Requested Action*

Based on the foregoing, you ask the Agency to require that ANDAs or 505(b)(2) applications referencing Coreg CR include “the results of tests demonstrating bioequivalence for the pharmacokinetic (“PK”) parameter C_{min} [to the listed drug]” (Petition at 1). In your Petition, you do not explain precisely what criteria you would have the Agency apply to the C_{min} parameter. With respect to C_{max} and AUC, the Agency considers products bioequivalent when the 90 percent confidence interval (CI) of the geometric mean ratio (GMR) of the log transformed PK parameter between the test and reference product falls within 80-125 percent.¹⁷ Flamel later clarified its view that “the [plasma concentration] levels should be 100% or more of the reference product’s C_{min} and not 80% to 125%” (Supplement 1 at 3). The Agency has not established strict criteria by which C_{min} is examined in those cases where C_{min} is considered important for safety or efficacy.

Your Petition asserts that, as part of the NDA approval process, the Agency required Coreg CR to be bioequivalent to Coreg IR by the C_{min} parameter (Petition at 4-5). In support of this, you quote the Clinical Pharmacology Review for NDA 22-012 and minutes of a July 21, 2005, pre-NDA meeting between FDA and the sponsor. The meeting minutes do indicate that Agency reviewers expressed an expectation that C_{min} of the CR formulation should be “at least as high as” C_{min} of the IR formulation. However, the cited Clinical Pharmacology Review suggests the Agency did not apply strict numerical acceptance criteria to the C_{min} parameter. Approval of some strengths of Coreg CR would not have been possible if the Agency had strictly applied the standard 80 to 125 percent acceptance interval to C_{min} or if the Agency had required the C_{min} of Coreg CR to be 100 percent or greater than that of Coreg IR (i.e., bounded exactly on the lower end). Specifically, as shown in the Agency’s statistical analysis of PK parameters for the R(+) enantiomer, the 90 percent confidence interval for the ratio of geometric means for C_{min} in the case of the 80 mg capsule fell outside the 80-125 percent equivalence range at 72-102 percent, with the point estimate being 86 percent.¹⁸ In

¹⁷ See FDA guidance for industry on *Statistical Approaches to Establishing Bioequivalence* (available on the Internet at <http://www.fda.gov/Drugs> under Guidances (Drugs)).

¹⁸ See Clinical Pharmacology Review, NDA 22-012, p. 124.

Docket No. FDA-2010-P-0216

addition, statistical analysis of PK parameters for the S(-) enantiomer shows the point estimate for the 80 mg capsule at 94 percent, with the confidence interval at 80-110 percent.¹⁹ For both R(+) enantiomer and S(-) enantiomer, their C_{min} are outside the standard advocated by Flamel in Supplement 1, 100% or more of the reference product's C_{min} . Likewise, the published articles reporting on pharmacokinetic testing of Coreg CR cited in the Petition do not advocate or reflect application of any particular pass/fail criteria, in statistical or mathematical terms, to the C_{min} parameter.

Thus, the record shows that the Agency recognized the importance of C_{min} during its evaluation of Coreg CR and sought to ensure there would be reasonably similar coverage of exposure between the Coreg CR and IR formulations throughout the inter-dosing interval. However, strict pass/fail criteria were not applied to C_{min} .

As noted above, the Agency's February 2010 draft guidance on bioequivalence testing of carvedilol phosphate oral extended-release capsules recommends single-dose studies. A single-dose pharmacokinetic study is generally more sensitive than a multiple-dose study in assessing bioequivalence (as indicated in FDA's general BA/BE guidance) and can often predict multiple-dose pharmacokinetic properties of a drug while avoiding unnecessary exposure of healthy test subjects to multiple doses of the drug.

C_{min} at steady state can be directly measured only through a multiple-dose bioequivalence study. C_{min} can, however, in many cases be reliably estimated based on data obtained in a single-dose study. A multiple-dose study has less ability to detect real differences, if such differences exist, between a test and reference product than does a single-dose study. Thus, FDA requires a single-dose study and has, as described below, used modeling to investigate whether adequate C_{min} can be ensured by a showing of bioequivalence with respect to parameters that can be measured in a single-dose study. With this drug, we have concluded that bioequivalence with respect to AUC and C_{max} as demonstrated in a single-dose study will reliably predict adequate C_{min} at steady state (provided T_{max} and the overall PK profile do not reveal any unexpected differences). Thus, FDA does not disagree with the petitioner that C_{min} is important for this drug. Instead, we disagree that demonstration of substantially equivalent C_{min} requires the use of less discriminating multiple-dose studies.

In the case of carvedilol phosphate, the Agency has used computer modeling and simulation, including both conventional pharmacokinetic modeling and physiologically based pharmacokinetic modeling, to confirm that equivalent AUC and C_{max} are sufficient to ensure adequate steady state C_{min} levels. A wide variety of possibilities was explored by changing parameters in the model to include as many hypothetical formulations with first-order absorption in the simulation as possible. Formulations with zero-order in vitro dissolution profiles with different release duration time were also evaluated. Thus, formulations with different release mechanisms were tested in the simulation. Steady-state pharmacokinetics were simulated based on single-dose pharmacokinetics of hypothetical formulations with different absorption modes. For hypothetical formulations showing bioequivalence to the RLD based on C_{max} and AUC at a single

¹⁹ See Clinical Pharmacology Review, NDA 22-012, p. 154.

Docket No. FDA-2010-P-0216

dose, their C_{min} at steady state based on simulation was further compared to the simulated C_{min} of the RLD at steady state. The modeling and simulation results indicate that products having equivalent AUC and C_{max} in a single-dose PK study provide equivalent C_{min} at steady state.

Therefore, for ANDAs seeking approval of modified-release products, the Agency will apply the standard AUC and C_{max} criteria, based on single-dose studies, to the bioequivalence evaluation, and not request submission of steady-state bioequivalence data. Additionally, as we routinely do for modified-release products, we will examine T_{max} and the pharmacokinetic profile during the review process to determine whether any difference between test and reference products may result in a lack of therapeutic equivalence. If necessary (perhaps because of observed differences in T_{max} or the pharmacokinetic profile), a steady-state simulation (e.g., superposition) using data from a properly designed single-dose pharmacokinetic study may be used to estimate C_{min} at steady state for both the test and reference products. These estimated values could be used in the same way the data submitted in NDA 22-012 were used to ensure there would be reasonably similar coverage of exposure without applying strict pass/fail criteria. To the extent that a 505(b)(2) application referencing our finding of effectiveness for Coreg CR seeks approval of a product for which bioequivalence to Coreg CR must be demonstrated, we would take this same approach.

6. *Alcohol-Induced Dose Dumping*

Finally, although this is not presented as a requested action in your petition filed on April 19, 2010, Flamel's Supplement 1 asks the Agency to require any ANDA seeking approval of a generic equivalent of Coreg CR to include the results of a clinical study to rule out alcohol-induced dose dumping and the associated potential for higher-than-expected peak and lower-than-expected trough plasma concentrations. As stated above, the Agency's February 2010 draft guidance on bioequivalence testing for carvedilol phosphate oral extended-release capsules recommends dissolution testing using various concentrations of ethanol to address the possibility of dose dumping if an extended-release product is taken with alcohol. This represents the Agency's current thinking. We believe the recommended in vitro dissolution testing is adequate to rule out the possibility of alcohol-induced dose dumping in the case of carvedilol phosphate extended-release oral capsules. Flamel's Supplement 1 does not include arguments or information to support a conclusion that this recommendation is inadequate. Accordingly, this request is denied.

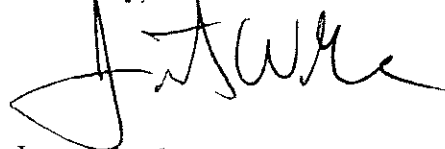
III. Conclusion

The Agency recognizes the importance of maintaining adequate blood levels of carvedilol phosphate in extended-release products. During its evaluation of Coreg CR, FDA sought to ensure there would be reasonably similar coverage of exposure between the Coreg CR and IR formulations. However, no formal statistical criteria were applied to C_{min} . For ANDAs referencing Coreg CR as the RLD and/or 505(b)(2) applications referencing our finding of effectiveness for Coreg CR, we believe that equivalent AUC

Docket No. FDA-2010-P-0216

and C_{max} in a single-dose study may be expected to provide equivalent C_{min} at steady state. Therefore, we intend to apply the standard AUC and C_{max} criteria to the bioequivalence evaluation of any ANDAs referencing Coreg CR. Additionally, we will examine T_{max} and the pharmacokinetic profile during the review process to determine whether any difference between test and reference products may result in a lack of therapeutic equivalence.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', written over a large, stylized, handwritten letter 'J' that serves as a signature flourish.

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research