Suitability Petition (Citizen Petition)

Nov 4, 2020

The undersigned submits this petition under § 512(n)(3) of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to approve a suitability petition.

A. Action Required

To allow us to submit an ANDA for our new Carvedilol bilayered extended release (ER) tablets using Coreg CR capsules as RLD.

B. Statement of Grounds

We are proposing Carvedilol bilayered extended release (ER) tablets as generic to Coreg CR capsules. Please see comparisons of proposed Carvedilol bilayered ER tablets to Coreg and Coreg CR in the table at the end of this document.

There are two applicable changes of the proposed Carvedilol bilayered extended release (ER) tablets compared to Coreg CR, which are permissible changes as per § 512(n)(3) of the FD&C Act.

1. From capsules of Coreg CR to tablets of proposed generic product
2. From Carvedilol phosphate as the active ingredient of Coreg CR to Carvedilol as of active ingredient of proposed generic product

Please notice the followings:

1. Both the RLD (Coreg CR) and proposed generic tablets are both controlled release form, though the proposed product is named extended release.
2. Carvedilol, as an active ingredient, has been proved safe and effective by the long-term use of Coreg.

Justifications for the proposed differences:

1. As extended release tablets, the proposed generic product improves medication adherence by patients compared to Coreg. So they have the same advantage of Coreg CR capsules.

2. As shown in the comparison table below, the proposed extended release tablets and Coreg CR capsules are similar in control release approach, they both contain IR component and CR component.

3. The proposed extended release tablets are simpler to manufacture and can lower the cost compared to Coreg CR capsules.

4. The proposed extended release tablets should have comparable therapeutic efficacy as Coreg CR capsules, once demonstrated by BE study.

5. The proposed extended release tablets have compared dissolution profiles and stability compared to Coreg CR capsules, data is available upon request.

C. Environmental Impact

We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

D. Economic Impact

The economic impact information will be submitted upon request of the commissioner.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Petitioner:

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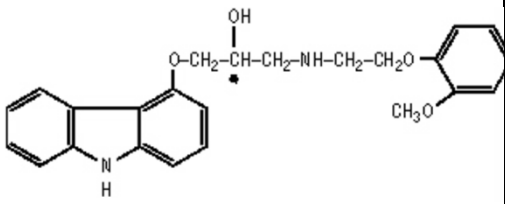
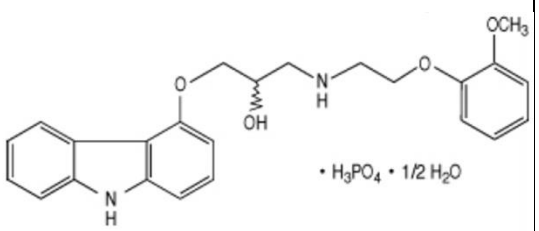
References:

1. Package insert for Coreg
2. Package insert for Coreg CR
3. Tenero, D. M., Henderson, L. S., Baidoo, C. A., Harter, A. H., Campanile, A. M., Danoff, T. M., & Boyle, D. (2006). *Pharmacokinetic Properties of a New Controlled-Release Formulation of Carvedilol*. *The American Journal of Cardiology*, 98(7), 5–16. doi:10.1016/j.amjcard.2006.07.014
4. US Patent 8101209B2
5. US Patent 8883207B2

Comparison of Coreg, Coreg CR and Proposed Carvedilol Bilayered Extended Release (ER) Tablets

Product Name	**Coreg (Carvedilol IR Tablets)**	**Coreg CR (Carvedilol phosphate CR Capsules)**	**Carvedilol Bilayered ER Tablets**
Regulatory Status	NDA # 020279, approved in 1991, RLD	NDA 022012, approved in 2006, RLD	NA
Indication	Heart Failure Left Ventricular Dysfunction following Myocardial Infarction Hypertension	Heart Failure Left Ventricular Dysfunction following Myocardial Infarction Hypertension	Heart Failure Left Ventricular Dysfunction following Myocardial Infarction Hypertension
Dosage Form	Immediate-release, film-coated, tablets	Extended-release, hard gelatin capsules containing carvedilol phosphate immediate-release and controlled-release microparticles	Extended-release, bi-layered tablets consisted of an immediate-release layer and an extended-release layer
Administration	Twice daily, oral	Once daily, oral	Once daily, oral
Active Ingredient	Carvedilol free base, $C_{24}H_{26}N_2O_4$, MW=406.5 	Carvedilol phosphate, $C_{24}H_{26}N_2O_4 \bullet H_3PO_4 \bullet 1/2\ H_2O$, MW=513.5 	Carvedilol free base, same as Coreg
Strength	3.125 mg, 6.25 mg, 12.5 mg & 25 mg	10 mg, 20 mg, 40 mg & 80 mg (Free base equivalent to 8.1 mg, 16.2 mg, 32.4 mg, and 64.8 mg, respectively[3])	8 mg, 16 mg, 32 mg & 64 mg
Inactive	Sucrose	Microcrystalline cellulose	Immediate-release (IR) layer:

Product Name	**Coreg (Carvedilol IR Tablets)**	**Coreg CR (Carvedilol phosphate CR Capsules)**	**Carvedilol Bilayered ER Tablets**
Ingredient[1,2]	Lactose Povidone Crospovisone Colloidal silicon dioxide Polysorbate 80 Magnesium stearate Hypromellose Polyethylene glycol Titanium dioxide	Povidone (binder) Methacrylic acid copolymers Hydrogenated castor oil Hydrogenated vegetable oil Crospovidone Magnesium stearate	Lactose monohydrate (filler), HPMC K100 LV (binder), Magnesium stearate (lubricant) <u>Extended-release (ER) layer:</u> Corn starch (filler), HPMC K15M (matrix former), Povidone K29/32 (solubilizer), Magnesium stearate (lubricant)
Drug Product Feature	NA	Hard gelatin capsule was filled with immediate-release (IR) and controlled release (CR) microparticles that are drug-layered and then coated with methacrylic acid copolymers.[2] IR microparticle-12.5% dose[454] CR microparticle IIa-37.5% dose[4,5] CR microparticle IIc-50% dose[4,5]	Bi-layered extended release tablet consists of an immediate-release layer and an extended-release layer IR layer-12.5% dose- release content in the stomach ER layer-87.5% does- release drug while passing into small intestine.
Advantages	NA	1. Improved medication adherence compared to Coreg	1. Improved medication adherence compared to Coreg 2. Simpler manufacturing process and lower cost compared to Coreg CR 3. Comparable therapeutic efficacy as Coreg CR, once demonstrated by BE study