

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20939

PHARMACOLOGY REVIEW(S)

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NDA 20-939

PHARMACOLOGY REVIEW OF ORIGINAL APPLICATION

C.A. Resnick, Ph.D.

SUBMISSION DATE: 5 November 1997
CENTER RECEIPT DATE: 7 November 1997
REFUSE TO FILE DATE: 13 January 1998
FILE OVER PROTEST DATE: 15 April 1999

SPONSOR: Biovail Corporation International

DRUG PRODUCT: Diltiazem HCl Extended-Release Capsules, USP

ACTIVE INGREDIENT: diltiazem HCl

FORMULATION: 120, 180, 240 or 300 mg diltiazem HCl in an extended release capsule intended for once daily administration. Excipients include black iron oxide, D&C Yellow #10, FD&C Green #3, Polyacrylate Dispersion 30% (Eudragit® NE 30D), Gelatin NF, Hydroxypropylmethylcellulose USP, Magnesium Stearate NF, Microcrystalline Cellulose NF, Polysorbate NF, Povidone USP, Simethicone USP, Sucrose Stearate, Synthetic Red Iron Oxide, Talc USP, Titanium Dioxide USP. The formulation was designed to be bioequivalent to Hoechst Marion Roussel's Cardizem CD capsule.

PHARMACOLOGICAL CLASS: Calcium Antagonist

PROPOSED INDICATION: Hypertension

PROPOSED DOSAGE REGIMEN: Proposed labeling states that, "when used as monotherapy, reasonable starting doses are 180 to 240 mg once daily, although some patients may respond to lower doses". It further notes that "individual patients may respond to higher doses of up to 480 mg once daily."

NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: None included. Sponsor claims right of reference to Watson Laboratories' (approved) NDA 20-092 for Dilacor XR capsules (Letters of authorization from Watson included in amendment to NDA 20-939 dated 6 August 1999.)

LABELING: Proposed labeling is similar (but not identical) to the approved labeling for Hoechst Marion Roussel's Cardizem CD capsules (NDA 20-062). It is recommended that the animal study sections used for labeling of the product that is the subject on the current NDA (20-939) be the same as approved for Biovail's NDA 20-401 for Tiazac capsules. Tiazac labeling, like Dilacor XR labeling but unlike Cardizem CD labeling, mentions, under PREGNANCY, the association of diltiazem with abnormalities of the heart, retina and tongue and with reduced pup weights and pup survival.

EVALUATION: This NDA is for a *new* controlled-release formulation of a marketed calcium antagonist. Both marketed and proposed formulations are indicated in the management of hypertension and the recommended doses are similar. Biovail is the holder of one of the approved NDAs (Tiazac, NDA 20-401). Biovail has no pre-clinical data of their own. Their approved NDA is supported by right of reference to Hoechst Marion Roussel data and their pending application is supported by right of reference to Watson data. The referenced data from Watson Laboratories, which had been used to support the safety of the active ingredient in Dilacor XR (a Rhone Poulenc Rorer product at the time of NDA approval), is considered to adequately support the safety of that same active ingredient (diltiazem HCl) in Biovail's new product.

** Refuse to File action based on absence of pharmacology or toxicology data or the right to reference pharmacology or toxicology data contained in another sponsor's application.*

RECOMMENDATION: Approvable with recommended changes in labeling (see above).

/S/ 

**Charles A. Resnick
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cc:
Orig.NDA 20-939
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