CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20943

PHARMACOLOGY REVIEW(S)

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FEB 17 1998

NDA 20-943

PHARMACOLOGY REVIEW OF ORIGINAL APPLICATION

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SUBMISSION DATE: 23 December 1997
CENTER RECEIPT DATE: 29 December 1997
REVIEWER RECEIPT DATE: 05 January 1998

SPONSOR: élan pharmaceutical research corporation
Gainesville, Georgia

DRUG PRODUCT: Verapamil PM Extended Release Capsules

ACTIVE INGREDIENT: Verapamil Hydrochloride

FORMULATION: Hard gelatin capsules contain 100, 200 or 300 mg of verapamil HCl plus D&C Red#28, FD&C Blue #1, FD&C Red#40, fumaric acid, gelatin, povidone, shellac, silicon dioxide, sodium lauryl sulfate, starch, sugar spheres, talc and titanium dioxide. The formulation is designed to initiate the release of verapamil 4-5 hours after ingestion. (Intended for bedtime dosing and a maximum plasma concentration of verapamil in the morning hours.) This delay is accomplished by the use of a combination of water soluble and water insoluble polymers applied to drug loaded beads. "As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug."

PHARMACOLOGICAL CLASS: Calcium Ion Influx Inhibitor (L-type calcium channel blocker)

PROPOSED INDICATION: Essential Hypertension

PROPOSED DOSAGE REGIMEN: 200 mg once daily at bedtime. If adequate response is not achieved at this dose it may be titrated upward to 300 and, if needed, 400 mg once daily.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: None included. We are referred to Wyeth-Ayerst's NDA 19-614 for Verelan SR (verapamil HCl) Sustained-Release Pellet Filled Capsules (right to reference granted by Wyeth-Ayerst).

LABELING: Animal study based sections of the proposed package insert are identical to those included in the package inserts for marketed immediate and controlled-release verapamil HCl formulations.

EVALUATION: Sponsor has submitted an application for a new controlled release oral formulation of verapamil hydrochloride for an indication covered by previously approved applications for controlled and immediate-release oral formulations of this drug. We note that the maximum recommended dose of Verapamil PM (400 mg once daily) is lower than the maximum recommended dose of currently marketed sustained release formulations of verapamil hydrochloride (480 mg once daily). We further note that the Verapamil PM (capsule) product is similar to Searle's Covera HS (tablet) product (NDA 20-552) in that both are designed for bedtime administration with initiation of release of verapamil HCl 4-5 hours after ingestion. Non-clinical pharmacology and toxicology data have not been included in the submission. Sponsor refers us to Wyeth-Ayerst Laboratories NDA 19-614(letter of authorization from Wyeth-Ayerst Laboratories included in the submission) but NDA 19-614 does not contain such data. Non-clinical pharmacology and toxicology data are, however, not required, as the non-clinical biologic data needed to support the safety of the new élan controlled-release formulation is no different than that data which was required to support the first marketed immediate release oral formulation of verapamil (Knoll's Isoptin, NDA 18-593). Other than the clinical studies requirement, the subject application will be treated as if it were a generic drug. On June 20, 1997 the sponsor was apprised of this action (classification of the submission as a 505(b)(2) application) which is provided for under 21CFR314.54.

RECOMMENDATION: The application is approvable. As noted above, under LABELING, animal study based sections of the proposed package insert are identical to those included in the package inserts for marketed immediate and controlled-release verapamil HCl formulations. This should not be the case. Because the maximum recommended human daily dose (MRHD) of Verapamil PM is lower than the MRHD of the marketed products, animal:human dosage ratios for Verapamil PM should be larger than the corresponding ratios for the marketed products. The sponsor should be asked to recalculate those ratios and make the necessary corrections to their labeling.

/S/

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