CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19834/S002

ADMINISTRATIVE DOCUMENTS

SEP 22 1994

CSO Review of Final Printed Labeling

Application: NDA 19-834/S-002
Plendil (felodipine) Tablets

Sponsor: Astra/Merck Group

Letter Date: September 2, 1994

Receipt Date: September 6, 1994

Review

NDA 19-834/S-002 provides for a new dosage strength, 2.5 mg tablets and for final printed labeling revised to reflect this change as well as a change in the maximum recommended dose from 20 mg to 10 mg.

An approvable letter was issued on July 27, 1994. A marked-up draft was included in the letter. Subsequent to receiving this letter, Dr. Elliott Berger discussed several issues with me in a telephone conversation (see memo of telecon of August 3, 1994) in which minor changes in the marked-up draft were agreed upon (with Dr. Lipicky's concurrence).

The following changes were made in the labeling in accordance with the approvable letter and with the telephone discussion of August 3, 1994:

Under **DESCRIPTION**, the last two sentences of the third paragraph were revised to read a follows:

> They are available as tablets containing 2.5 mg, 5 mg, or 10 mg of felodipine for oral administration. In addition to the active ingredient felodipine, the tablets contain the following inactive ingredients: Tablets Plendil 2.5 mg -- hydroxypropyl cellulose, lactose, FD&C Blue 2, sodium stearyl fumarate, titanium dioxide, yellow iron oxide and other ingredients. Tablets Plendil 5 mg and 10 mg -- cellulose, red and yellow oxide, lactose, polyethylene glycol, sodium stearyl fumarate, titanium dioxide and other ingredients.

Under **ADVERSE REACTIONS**, an asterisk was added following the 20 mg heading in the second table, and the following sentence was added just below the table:

> *Exceeds the maximum recommended daily dose.

Under **DOSAGE AND ADMINISTRATION**, the first paragraph was revised as follows:

> The recommended starting dose is 5 mg once a day. Depending on the patient's response the dosage can be decreased to 2.5 mg or increased to 10 mg once a day. These adjustments should occur generally at intervals of not less than two weeks. The recommended dosage range is 2.5 -10 mg once daily. In clinical trials, doses above 10 mg showed an increased blood pressure response but a large increase in

the rate of peripheral edema and other vasodiliatory adverse events (see ADVERSE REACTIONS). Modification of the recommended dosage is usually not required in patients with renal impairment.

The following text was added to the beginning of the **HOW SUPPLIED** section:

No. 3584 -- Tablets PLENDIL, 2.5 mg, are sage green, round convex tablets, with MSD 450 on one side and PLENDIL on the other. They are supplied as follows:

NDC 0006-0450-28 unit dose package of 100
NDC 0006-0450-58 unit of use bottles of 100
NDC 0006-0450-31 unit of use bottles of 30.

The firm deleted "/MSD" from the generic name throughout the package insert. They also added a bar-coding system to the package insert so that the circular can be attached to the outside of the bottle in their new "carton-less" packaging system.

I recommend that the supplement be approved. An approvable letter will be drafted for Dr. Lipicky's signature.

/S/

David Roeder
Consumer Safety Officer

dr/9-12-94

cc: Original NDA
HFD-110
HFD-111/DRoeder
HFD-111/SBenton

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — Public Health Service

Memorandum

DATE : JUL 27 1994

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval of NDA 19-834/S-002, Felodipine 2.5 mg strength, Merck Sharp and Dome.

TO : NDA File

Felodipine is an antihypertensive calcium channel blocker that is approved as an antihypertensive agent in this controlled release dosage form. This supplement simply adds a lower (2.5 mg) unit dosage strength to the already approved line. Clearly the 2.5 mg controlled release dosage form of felodipine is approvable. The previously submitted clinical trials show that 2.5 mg produces an antihypertensive effect greater than that of placebo. The current submission documents the satisfactory nature of the manufacturing and controls and the bioequivalence of the 2.5 mg dosage form.

In addition to adding this lower unit dose, the sponsor wishes to delete reference to using 20 mg as an allowed upper limit of dosing from the Dosage and Administration and from Adverse Reactions sections of the labeling. I can see little reason to conform with this request. The 20 mg upper limit of dosing is already approved, there are no data that show it is a public health problem, although it is clear that the incidence of peripheral edema increases dramatically with only a slightly increased antihypertensive effect. That phenomenon is already in labeling.

In fact, omitting the 20 mg dose results from the Adverse Reactions section would leave health care personnel with less information than they now have. I certainly do not think that would be appropriate under any circumstances. The 20 mg results must remain in the Adverse Reactions section, in a table, just as they now do.

It is not unreasonable to limit the dose to 10 mg a day. However, the Dosage and Administration Section now points out the marginal value of going to 20 mg a day. Nonetheless, in some patients it may be worth the effort, particularly before adding the dose-independent side effect problems of a second drug. So, on balance, I do not think it is a good idea.

My comments are marked on the draft package insert. It is approvable. They can send in final printed labeling.

/S/

Raymond J. Lipicky, M.D.

cc: Orig. NDA
HFD-110
HFD-110/CSO
HFD-110-RLipicky
RL:ef:7/20/94