CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 19834/S009

ADMINISTRATIVE DOCUMENTS

JAN 13 1998 DF

LABELING REVIEW

NDA 19-834/S-009 Plendil (felodipine) Extended-Release Tablets

Sponsor: Astra Merck
725 Chesterbrook Blvd.
Wayne, PA 19087-5677

Date of Original Submission: September 19, 1996

Date of Approvable Letter: May 13, 1997

Date of FPL Submission: October 2, 1997

BACKGROUND

The NDA for Plendil, an extended-release formulation, was originally approved as a once daily regimen for the treatment of hypertension on July 26, 1991. Based on a single food effect study in which Plendil was administered with a modest meal, no effect of food on the kinetics of felodipine was noted in the labeling. Recently a combination product containing sustained-release felodipine with enalapril (Lexxel) was submitted. When Lexxel was administered with food, however, there was a substantial increase in C-max with AUC being essentially unchanged. When this discrepancy was brought to the attention of the sponsor, they submitted study V-195. This study was completed in 1988, well before the NDA for the product was approved, and showed the effects of food on the kinetics of felodipine.

On September 16, 1996 a supplemental application was submitted to provide for a labeling revision to update the information on the effect of food on the pharmacokinetic profile of felodipine. The firm's original proposal was quite conservative, and it was revised extensively by Drs. Karkowsky, Parekh and Fadiran in their reviews. On May 13, 1997 an approvable letter issued. The sponsor was not pleased with the text proposed by the Agency and proposed alternate test in a submission dated June 20, 1997. This proposal was reviewed by Drs. Karkowsky (review dated 7/2/97) and Parekh (review dated 7/29/97); both reviewers recommended retaining the original text proposed in the approvable letter. On August 14, 1997, Mr. Roeder informed the sponsor that, after conferring with Drs. Lipicky, Karkowsky and Parekh, some minor revisions to the originally proposed text forwarded with the May 13, 1997 approvable letter could be made. The originally proposed revisions to the labeling were as follows:

> Under **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism**, the last paragraph was revised as follows:
>
> The bioavailability of Plendil is influenced by the presence of food. When administered either with a high fat or carbohydrate diet, C-max is increased by approximately 60%. AUC is unchanged. When Plendil was administered after a light meal (orange juice, toast and cereal), however, there is no effect on felodipine's pharmacokinetics. The bioavailability of felodipine was increased approximately two-fold when taken with grapefruit juice. Orange juice does not appear to modify the kinetics of Plendil. A similar finding has been seen with other dihydropyridine calcium antagonists, but to a

lesser extent than that seen with felodipine.

Under **DOSAGE AND ADMINISTRATION**, the following was added as the first sentence of the second paragraph:

Plendil should be taken regularly on an empty stomach or after a light breakfast (e.g., orange juice, toast and cereal).

The statement under **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism** remained as proposed, but the statement under **DOSAGE AND ADMINISTRATION** was revised as follows:

Plendil should regularly be taken either without food or with a light meal (see **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism**).

REVIEW

The FPL submitted by the firm was in accordance with the draft forwarded with the May 13, 1997 approvable letter and subsequent discussions with the Division. An approval letter will be drafted for Dr. Lipicky's signature.

/S/

Gary Buehler
Project Manager

Orig NDA
HFD-110
HFD-110 DRoeder
HFD-110 SBenton
HF-2 MEDWATCH

Minutes of a Meeting

Date: November 25, 1996

Application: NDA 20-668
Lexxel (enalapril maleate/felodipine) Tablets

Sponsor: Astra Merck

Subject: Labeling

Participants

FDA

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Director
David Roeder, HFD-111, Regulatory Health Project Manager

Sponsor

Mary Schleman, M.D., Clinical Development
Dan Cushing, Ph.D., Director, Regulatory Liason
Elliott T. Berger, Ph.D., Executive Director, Regulatory Affairs
Judy Molt, Regulatory Project Manager

Background

An approvable letter was issued to Astra Merck for NDA 20-668 on November 6, 1996. They submitted revised draft labeling dated November 19, 1996, and requested a meeting to discuss their proposals.

Discussion Point #1: Merging of the enalapril and felodipine components of the labeling.

Discussion: We had asked the sponsor to rewrite sections of the labeling by merging the information regarding the two monotherapies in a fashion similar to the Lotrel package insert. Dr. Fenichel noted that Astra Merck had not done this adequately in their revision. Information should be primarily sorted by topic (e.g., renal function, hepatic impairment, etc.) rather than by the drug components. The sponsor noted that this might be difficult since all changes to the enalapril text have to be cleared through Merck. They were concerned that this could take several months.

Decision: The sponsor will rewrite the labeling within the constraints of time and their business agreements with Merck. After approval, they will work on a more thorough merging of the information on the individual drug components.

Discussion Point #2: Food effect.

Discussion: The FDA proposed labeling that recommended Lexxel not be taken with food.

The sponsor counter-proposed wording that describes the pharmacokinetics of Lexxel when taken with food, but stopped short of recommending dosing on an empty stomach. Drs. Lipicky and Fenichel said that their primary concern was that the drug be taken consistently with regard to meals. This is especially important during titration. If the firm's proposed wording were modified and placed towards the beginning of the **DOSAGE AND ADMINISTRATION** section, it should adequately inform the prescribing physician.

Decision: The firm's proposal, as amended in attachment A, is acceptable.

Discussion Point #3: The **Dosage Guided by Clinical Effect** subsection.

Discussion: The sponsor had proposed that the **Dosage Guided by Clinical Effect** subsection be revised to recommend that Lexxel be used for patients who fail on "felodipine (or another dihydropyridine calcium channel blocker) or enalapril (or another ACE inhibitor)." Dr. Lipicky said that, even though similar wording was approved for Lotrel, the parenthetical statements would not be acceptable for Lexxel. In the case of Lotrel, the product came very close to being approved for initial therapy, so it is more reasonable that they would get these statements. The Lotrel combination allows much more flexibility for titration and the ability to give a higher dose of the ACE inhibitor than can be found with Lexxel.

The sponsor plans to submit a 5/2.5 mg enalapril/felodipine combination tablet that would allow titration through a greater range and to a higher dose of enalapril. Dr. Lipicky said that they would have a reasonable chance of adding the parenthetical statements to their labeling if this new dosage strength is available.

Decision: The sponsor agreed to delete the parenthetical statements. They will later submit a supplement for a new 5/2.5 mg enalapril/felodipine combination tablet. With this new dosage strength, they have a better chance of using these statements in their labeling.

Discussion Point #4: Listing of adverse reactions.

Discussion: We had requested that the sponsor list the overall incidence of adverse reactions rather than the sponsor's proposal to list only those that are considered to be related to the drug. The sponsor argued that the Lotrel package insert lists only those that are drug related, and it is important that the prescribing physicians be able to make meaningful comparisons between the two products.

Decision: Dr. Lipicky agreed to allow the sponsor to use their proposal, but we will later ask that both Lotrel and Lexxel labeling to be changed to list the overall incidence.

Discussion Point # 5: Analysis of efficacy by age.

Discussion: Under **CLINICAL PHARMACOLOGY: Pharmacodynamics and Clinical Effects**, the sponsor's proposal included a subgroup analysis of Lotrel's efficacy in the elderly. Dr. Lipicky pointed out that they did not appear to have adequate numbers to

make such a claim, and their statement did not make it clear whether the data they were using was placebo controlled.

Decision: The sponsor agreed to look more closely at the data and either revise their proposal or support it with more data.

Action Items

1) The sponsor will revise the labeling based on the discussions at this meeting and submit a draft in early December.

2) After approval, Mr. Roeder will initiate a request to the sponsors of both Lexxel and Lotrel to revise the listing of adverse reactions to include all ADRs, regardless of causality.

Minutes Preparer: _____
David Roeder

Concurrence Chair: _____
Raymond Lipicky, M.D.

dr/11-27-96/11-29-96

RD: RFenichel/11-29-96

cc: NDA 20-668
HFD-110
HFD-110/CSO