CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11961, S017

MEDICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 14, 1998

/S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approval action for Marplan (S-017)

TO: File, NDA 11-961/S-017 (Marplan)
[**Note:** This memo should be filed with the 2-18-98 submission.]

1.0 Background

I refer to my 9-11-97 memo for a detailed history of this complex and long-pending supplement. Our most recent action was an approvable letter (11-7-97), in which we requested the following: (1) draft labeling,

2.0 Safety of Marplan at Currently Recommended Doses

3.0 Dose/Response for Efficacy of Marplan

4.0 Repair of Labeling

In our 2-26-96 approvable letter, we had provided detailed advice about how to repair the labeling for Marplan.

5.0 Conclusions and Recommendations

I believe that the proposed safety study should adequately address our concerns about the safety of Marplan at the higher doses now being recommended for this product. While the proposed study will not address the question of dose/response for efficacy, I believe such information is not an absolute requirement for approval of this product, and this deficiency can be noted in labeling. I believe that Hoffman-LaRoche have submitted sufficient data to support the conclusion that Marplan is effective and acceptably safe in the treatment of depression. I recommend that we issue the attached approval letter with the version of labeling for which we were able to reach mutual agreement with the sponsor.

cc:
Orig NDA 11-961 (Marplan)
HFD-120/DivFile
HFD-120/TLaughren/PLeber/EHearst/PDavid
HFD-101/RTemple

DOC: NDA11961.04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 11961, S017

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 15, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 11-961/S-017 DESI Action

TO: Robert Temple, MD, Director, ODE 1
&
File NDA 11-961

This NDA was declared approvable on February 26, 1997.

In a letter dated April 28,1997, the sponsor, Hoffmann-La Roche

Beyond declaring this fact, Roche

outlined by the FDA in the February 26, 1996 Approvable letter."

Current Status

Setting aside for the moment the question of whether Roche should communicate with the agency in the manner they have regarding the conditions under which this pending DESI supplement/NDA for Marplan might be approved,

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the 1996 approvable action. The letter drafted by Dr. Laughren for Dr. Temple's signature can easily be modified for this purpose.

Given Marplan's age and likely market share, it is certainly possible that a second approvable action letter reiterating the requirements for approval announced in our 1996 action letter

I make mention of this largely to make clear that I offer my recommendation regarding this NDA fully mindful of that less than desirable potential outcome.

Recommendation

Issue an approvable action letter reiterating the conditions of approval cited in the February 1996 approvable action.

/S/

Paul Leber, M.D.
October 15, 1997

cc: NDA 11-961
HFD-101
Temple
HFD-120
Katz
Laughren
Fitzgerald
Hearst
David

RTemple

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: February 13, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 11-961/S-017 DESI Action

TO: Robert Temple, MD, Director, ODE 1
&
File NDA 11-961

Your memorandum of January 24, 1996 is not explicit, but allows the inference that you believe there is already sufficient evidence of safety in use to approve the Marplan NDA without asking the firm to collect further evidence of 'safe passage' at the doses recommended in the proposed labeling.

Tom Laughren, has, based on your suggestions, re-evaluated (see his memorandum of January 31, 1996) the information available and has adopted your view that the application may be approved provided that 1) labeling is extensively revised in regard to both format and content and 2) that the firm commits to conduct studies post-approval to provide a better (more precise) picture of the risks associated with the use of the drug at the higher doses found necessary to produce an antidepressant effect.

Although I believe one can defend an approval action under the conditions of use enumerated in the labeling that is incorporated in the draft approvable action letter being forwarded to the Office, I continue to prefer a not approvable action.

My preference, importantly, does not arise from a fear that we know too little about Marplan's common profile of untoward effects at the higher

doses that are recommended. In fact, it never did[1]. Indeed, my concern was and remains that the upper limit we can set on the incidence of adverse events so far NOT seen when Marplan is administered at doses in the 50 to 60 mg a day range is too high (i.e., about 1/35 by inverse rule of 3).

Given the importance you attach to Dr. Laughren's comments about the intent of a safety study in your 1/24/96 memorandum, I ought to make clear that I do not share Dr. Laughren's opinion that the long use of Marplan provides reassurance about idiosyncratic risks that occur at the highest doses or his view that such risks are not dose related[2].

Admittedly, the proposal we made years ago that 1000 patients be studied at the higher end of Marplan's dosing range is probably too demanding in view of current attitudes about risk taking. Nonetheless, I would be remiss if I allowed the approval action to go forward without emphasizing how relatively little we actually do know about Marplan at the doses to being recommended.

Tom Laughren and I have discussed this further. He takes comfort in the fact that pharmacokinetic variability ensures that some patients taking very low doses of Marplan are likely to have been exposed to levels of the drug that exceed what most patients will be exposed to at 60 mg a day. I am not comforted because pharmacokinetic variability also ensures that among patients exposed to 60 mg a day, there will be those exposed to levels that are far higher than those which obtained in the 90 or so subjects so far exposed in clinical testing.

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[1] Admittedly, I did not address Dr. Laughren's comments (page 5 of his 12/22/95 memorandum) in my earlier memorandum (January 17, 1996), but, at the time, I did not consider them especially critical to our recommendation. In fact, the issue only becomes important as a result of the prominence given to his comments in the opening paragraph of your 1/24/96 memorandum.

[2] I am aware that 'idiosyncratic events' are said not to be dose related, but an equally reasonable explanation is that they are dose related, but occur in only selected subgroups in the population. The distinction is critical and explains why experience with small samples taken from a mixture population can provide very misleading information about risks to the public health.

Dr. Laughren also suggests that overdose data might provide reassurance about high dose risks. I certainly think we could look at this, if the data were available, but I would like to know what it shows before we act, not after.

Summary:

The decision on this NDA clearly turns on a judgment about whether or not Marplan's proposed labeling provides sufficient information to allow the product to be used safely under the conditions of use recommended. Embedded within the safety question is not merely the question of whether the labeling accurately describes the known risks of the drug, but whether the level of assurance is adequate about the incidence of risks Marplan might cause that cannot be excluded. I would prefer that we get more information, but I can also accept approval under the restrictive labeling proposed that warns about the limitations of our knowledge concerning risks not seen.

/S/

_____

Paul Leber, M.D.
2/13/96

cc: NDA 11-961/S-017
HFD-100
Temple
HFD- 120
Laughren
Fitzgerald
David

Dr. Temple

Memorandum **Department of Health and Human Services**
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: January 17, 1996

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: NDA 11-961/S-017 DESI Action

TO: Robert Temple, MD, Director, ODE 1
&
File NDA 11-961

INTRODUCTION

Marplan, (isocarboxazid) a non-selective MAOI was approved for marketing as an antidepressant prior to the passage of the 1962 amendments. Under DESI it was allowed to remain on the market pending final resolution of its effectiveness status with labeling which indicated that it was "probably effective for the treatment of depressed patients ... refractory to tricyclic antidepressants or ECT and patients in whom tricyclic antidepressants are contraindicated."

Although a DESI supplement submitted in 1981 was found by the division to have provided 'substantial evidence' of Marplan's effectiveness as an antidepressant, the NDA was not deemed to be approvable because the conditions of use (i.e., doses) under which the product's effectiveness had been demonstrated had not been studied extensively enough to allow a conclusion that the product would be safe in use.

Marplan had originally been approved (i.e., found safe for use) at recommended doses of 30/mg/day. Evidence of effectiveness, however, had been obtained in clinical investigations in which the drug had been administered in doses as high as 80 mg/day. Because only 87 patients had been exposed in these trials, the agency concluded that Marplan could not responsibly be found safe for use in the absence of additional clinical experience documenting that

large numbers of patients could be treated uneventfully (i.e., have 'safe passage') at doses of 50 to 60 mg/day. This dose range was chosen because the bulk of the clinical experience obtained in the 3 randomized controlled trials cited had been gained in this range. (Dr. Laughren's memorandum of 12/22/95 explains these argument in detail).

Following the issuance of the NA letter, the agency and the firm discussed specific steps that the firm could take to repair this deficiency. Basically, we told the firm that an open trial involving perhaps a 1000 patients of whom several hundred would be exposed at the high end of the proposed dose range (i.e., 60 mg/d) would, if it demonstrated no unusual risk, be sufficient.

We did not learn of the firm's intended response until receipt of the current submission in October of 1995.

Current submission

Dr. Laughren reports that the firm did not follow our advice but elected, instead, to submit information presumably bearing on the safety of the their product consisting of 1) a retrospective survey of physicians who had treated patients with Marplan, 2) an updated summary of postmarketing reports on Marplan, and 3) a summary recapitulating the clinical experience gained in the 3 placebo controlled trials reports of which had been submitted to the agency in 1981.

Dr. Laughren concludes that these materials do not provide information of the sort we seek to gain assurance that Marplan is safe for use at doses at which we have confidence of its effectiveness. I agree with him although what is sufficient evidence of safety is always a matter of personal sentiment, even when offered by a professional.

Action letter

Dr. Laughren has drafted an action letter that explains why the firm's current submission does not repair the deficiencies identified in the NA action letter issued in 1988. He also provides the firm with sound advice concerning our likely reaction to their proposed effectiveness claim should they succeed in demonstrating Marplan's safety. Specifically, the letter

provides an explicit example of the kind of labeling that the division would consider appropriate for an antidepressant drug product marketed on the basis the evidence so far provided for Marplan.

Recommendation

Issue the not approvable action letter.

/S/

Paul Leber, M.D.
January 17, 1996

cc: NDA 11-961/S-017
HFD-100
Temple
HFD- 120
Laughren
Fitzgerald
David

MEMORANDUM

DATE: June 17, 1988

FROM: PAUL LEBER, M.D., DIRECTOR, DNDP [HFD-120]

TO: FILE of NDA 11-961
and
ROBERT TEMPLE, M.D., DIRECTOR, ODE I [HFD-100]

SUBJECT: EXPLICATION OF THE DIVISION DIRECTOR'S POSITION REGARDING THE REVISED MARPLAN ACTION LETTER.

The letter to Hoffman-LaRoche has been revised.

As suggested in the Office Director's memorandum (5/18/88), the Marplan action letter now recommends that a subgroup analysis of the Davidson study be conducted in an attempt to obtain corroborative evidence to support a dosing recommendation of up to 60mg/day. I am persuaded that this approach is acceptable from a regulatory standpoint although I personally favor requiring that a second confirmatory study be done.

My thinking on this issue is as follows. Roche has marketed Marplan at a seemingly ineffective dose for close to three decades. During that time, many patients must have appeared to respond to treatment with the product, many simply because episodes of depression often remit spontaneously. As a consequence of this collective 'experience' with Marplan at subtherapeutic doses, the medical community probably holds a series of beliefs, albeit mistaken ones, about Marplan's proper place in the psychiatric armamentarium.

Having Roche conduct a study of the sort I originally proposed (i.e., 3-way with both a standard antidepressant and placebo control),therefore, offered a definite advantage: it would, beyond providing information about dosing, have the potential to provide information about the comparative efficacy and safety of Marplan and a standard antidepressant when both are used in similar populations at presumably eqi-effective doses.

I acknowledge, however, that the demand for a completely new study may be unnecessarily burdensome on Roche, and perhaps, even be argued to represent a demand that we have no legal authority to make. Consequently, I have reconsidered my recommendation and have adopted the position suggested by the Office.

However, I hold entirely different views about the approach that must be taken to gain valid information about Marplan's safety in use under the dosage recommendations that will now have to be adopted if the product is to be considered effective in use.

Specifically, I am unwilling to endorse any approach short of a prospective safety tolerance study that evaluates, with very reliable follow-up, a cohort of at least a 1000 depressed patients treated with Marplan at the higher end of what will be the revised recommended dosing range.

In my view, it would be reckless to rely on spontaneous reports (or more properly, lack of reports) of adverse post-marketing experience collected in the past. Incidentally, it is important to understand that my judgment would not change even if it could be shown, and it cannot (see insert below), that a significant proportion of the patients treated over the past ten years were treated with doses of Marplan exceeding those recommended in its current labeling. To be clear, I understand fully the that the existence of a subgroup of depressed patients treated at doses above those recommended in current labeling is an essential prerequisite of the strategy proposed in the Office Director's memo. Unfortunately, the existence of the population is not sufficient to ensure that adverse events occurring in this or any other subset, if it actually had existed, would be reliably captured and reported.

> [INSERT: To check on the feasibility of the strategy proposed, I asked Dr. Laughren to check with DES on the use of Marplan at doses above that recommended. As I would have predicted, the average use is at a dose below (22mg) the maximum (30mg) recommended in current labeling. This, incidentally, is consistent with the way antidepressants of all types are ordinarily used in medical practice.]

In sum, I have no faith in the predictive value of post-marketing experience with long marketed drug products, even those actually used under the conditions recommended in their labeling. Indeed, time and time again, we have examples of post-marketing surveillance failing to predict drug associated risk, especially when older drug products are involved. Our colleagues in DES repeatedly tell us that reporting fractions, even for recently marketed products, are very low (? less than 1 %). Reporting trends document that the typical reporting fraction falls with the passage of time after marketing guaranteeing that it will be lower still for long marketed drugs than for recently marketed ones, especially for those first marketed during epochs when post-marketing reporting rates were low in general (e.g., the fifty's and sixty's). Indeed, we know from personal experience that postmarketing surveillance failed to identify fatal hemolytic anemia as a risk of nomifensine or seizure as a risk of clomipramine. Thus, I am convinced that the only way to discover and/or set upper limits on the risk of the even more common untoward events associated with the use of drug products is to conduct prospective cohort studies under 'representative' conditions, that is, conditions that will ensure full reporting of all significant adverse clinical events.

Since I have thought this matter through in generic terms very carefully, it would be misleading, even disingenuous, for me to endorse making a proposal to Roche to do anything other than a prospective cohort to gain the needed safety information.

Consequently, I have elected to retain in the revised action letter those sections requiring Roche to conduct the open safety tolerance cohort study of the size and type recommended in the letter originally proposed.

Finally, I note that the Office Director's memorandum raises the specter of Roche abandoning Marplan because of the weight of our regulatory requirements. I don't believe that this is a proper regulatory concern. Like the umpire at the ball game, we can only call them as we see them. Once we start worrying that a specific call will make somebody quit and go home, we will cease being effective in our role. Roche has marketed Marplan for decades with what can, in retrospect, be reasonably called misleading directions for use, directions that probably made Marplan little more than an active placebo for many, if not most, of the patients for whom it was prescribed. Roche, I suggest, therefore has some sort of 'moral' obligation to the public to do the 'right thing.' If they won't, and they certainly may not, I have to take that risk. Furthermore, there are other MAOIs on the market and I have yet to see convincing evidence that Marplan is an essential part of the psychiatric armamentarium.

Recommendation:

Issue the letter as revised. /S/

Paul Leber, M.D.
June 17, 1988

NDA/IND Original
HFD-83
HFD-85
HFD-100
RTEMPLE
HFD-120
LEBER
Laughren
Katz
DeCicco
doc:c:\wp\marplan2
revison of 6/17/88

MEMORANDUM:

DATE: May 3, 1988

FROM: DIRECTOR, DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

TO: FILE NDA 11-961/S-017 MARPLAN (isocarboxazide)

SUBJECT: MARPLAN DESI ACTION LETTER.

Introduction:

This memorandum summarizes my views on the Marplan Desi Action proposal presented in Dr. Thomas Laughren's review of January 5, 1988.

To begin, I concur with Dr. Laughren's two primary judgments:

1) that Hoffman LaRoche has presented results of two adequate and well controlled clinical investigations (Davidson and Giller) that provide independent and corroborative evidence of Marplan's antidepressant efficacy in samples of patients with a difficult to characterize subcategory of depressive illness.

2) that Roche has FAILED to provide evidence to show that Marplan is reasonably 'safe in use' under the currently recommended conditions of use, that is at daily doses exceeding 30mg. (The data submitted indicate that 60 to 80 mg a day of Marplan are necessary to achieve an antidepressant effect in the samples of depressed patients studied.

Consequently, I agree with Dr. Laughren's overall conclusion and his recommendation that a letter be issued informing Roche that they have failed to meet the requirements for being 'upgraded.'

However, there are some aspects of the proposed letter and his discussion with which I disagree.

1-Suggestions regarding the reanalysis of dose and dose response data:

Any post hoc analysis based on the selective exclusion of a subgroup of patients will lead to a comparison being made between non-randomized groups. Such comparisons may be systematically biased; for example, excluding high dose patients from the Marplan group may remove slowly improving patients or those with a poor prognosis. (Why? Because such patients are likely to be titrated to higher doses when they fail to respond.) However, similar individuals will not be excluded from the placebo group and this may introduce a systematic bias in the reanalysis when the original placebo group is being compared with the newly formed Marplan group.

[Dr. Laughren points out that in the current case the effect of the bias actually operates in the reverse direction. Specifically, patients at highest doses did very well; consequently, dropping them from the analysis would produce a bias against Marplan. Nonetheless, I remain against such post hoc maneuvers in principle; it sets a bad precedent and should not be adopted merely because it provides a 'useful' outcome in this particular instance.]

Consequently, I would not include a proposal for a reanalysis in our letter (see the second paragraph of Dr. Laughren's proposed letter). Instead, I would urge the sponsor to conduct a new RCT study of Marplan comparing doses not exceeding those recommended in labeling to placebo and a standard tricyclic antidepressant. The third treatment arm is not essential but may provide additional information about the patient sample and its responsiveness to traditional ADs.

2- Proposed Safety re-evaluations.

My concern is entirely with the minimum number of patients, 500, identified by Dr. Laughren as sufficient to assess the risks of Marplan under the recommended conditions of use. I believe the number is too small. Thus, I would advise the sponsor to conduct a larger open safety tolerance study at or around the highest doses of Marplan to be recommended. Remember, a representative sample of 1000 or more patients is sufficient (95% sure) to detect at least one example of an ADR that occurs at a rate of 1/300 or so. Such a sample, however, is not large enough to distinguish this incidence from a much lower or higher one, however.

Incidentally, the evidence from the current submission does not indicate that most ADRs are dose related; indeed, the highest incidence of ADRs and discontinuations were among Zisook's patients who received (compared to Davidson's and Giller's) the lowest mean daily doses of Marplan. Zisook also had smallest proportion of patients receiving more than 50mg a day (7/35) vs 15/30 for Giller and 11/22 for Davidson. In short, daily dose does not predict ADR incidence as much as physician and patient dyad does.

Proposed Claimed Indication:

While the claimed use need not be discussed until an approvable action is being contemplated, I will make clear a disagreement I have with Dr. Laughren's proposed labeling claim.

First, I believe the proposal to label Marplan for use in a population of depressed patients with 'clinically significant' anxiety is potentially misleading because it somewhat 'pseudospecific.' That is, the specificity of the claim arises because of the sponsor's decision to study the drug in the population, not because Marplan has been shown to work only in this population. (The claim implies, but the evidence presented does not allow the conclusion, that the presence of anxiety predicts responsiveness to Marplan, or conversely, that depressed patients with less anxiety are less suitable for treatment with Marplan.) The problem, of course, is that there is no way of knowing what role, if any, anxiety (manifest as a score on the Covi) plays in predicting the response to Marplan. Of course, I can imagine an experiment involving a standard antidepressant, Marplan, and placebo being randomly assigned to two strata of patients: those with and without manifest anxiety. Results of such a study might delineate the role of anxiety in predicting response to Marplan.

On the other hand, I agree with Dr. Laughren that a claim for efficacy in 'atypical' depression is inappropriate because it is improbable that there is any common understanding of the term 'atypical' among potential prescribers.

In any case, I would much prefer a claim that skirts the 'pseudospecific' problem. I would be satisfied if the claim merely states that Marplan has been shown to exert an antidepressant effect in a clinical studies which evaluated depressed patients who presented with an illness that met DSMIIIR criteria for major depressive disorder but who often exhibited signs and symptoms of anxiety (phobias, panics, etc.) This can be followed by a statement that Marplan's efficacy in endogenomorphically retarded and delusional depressed patients has not been established. Consequently, for these reasons, and because of the potentially serious consequences of its side effect profile, it is not to be considered as an antidepressant of first choice in the treatment of newly diagnosed depressed patients with, as Dr. Laughren puts it, prominent endogenous features.

Perhaps, if the sponsor is willing and does conduct new studies at lower daily doses, patients with more typical depressive illness can be included in a study that employs a standard antidepressant as an active control in addition to placebo. Such a study might allow us to draft more precise labeling.

Recommendation:

a) Regarding the Supplement S-017:
Issue a not approvable letter essentially similar to that proposed by Dr. Laughren, but revised to 1) exclude the recommendation to reanalyze existing data in the Davidson study 2) increase to 1000 the number of patients required for study at or near the recommended daily dose of 80mg/day.

b) Regarding the continued marketing of Marplan under its current labeling:

I will not offer a recommendation concerning what specific action(s), if any, the agency should take regarding the continued marketing of Marplan under its current labeling. To begin, although I believe that Marplan is likely to be ineffective in use under its current labeling, I also believe that Marplan is, until some legal action changes its status, 'safe in use' on the technical grounds that its NDA was allowed to become effective under the terms of the 1938 Act.

Clearly, however, the continued marketing of the product under its current labeling is not in society's interest. Which regulatory strategy will best serve to remedy the situation, however, is a complicated matter best resolved after full discussion and negotiation among several agency units. Consequently, I will defer my comments on this matter until I am fully informed about the possible practical remedies available.

/S/

Paul Leber, M.D.
May 3, 1988

cc: orig NDA
HFN-120
HFN/120/Pleber
/Tlaughren
/TDeCicco
doc c:\wp\marplan
5/2/88; 5/3/88 (revised)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 11, 1997 /S/

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approvable action for Marplan (S-017)

TO: File, NDA 11-961/S-017 (Marplan)
[**Note:** This memo should be filed with the 4-28-97 submission.]

1.0 Background

Since this supplement has a long and complex history, I will provide a somewhat detailed chronological history of the issues and actions leading up to this most recent submission (4-28-97):

8-28-81: S-017 initially submitted as part of a DESI submission
-Results of 3 independent trials (Davidson, Giller, and Zisook) were submitted as part of S-017, all 3 of the same design, i.e., Marplan (up to a maximum dose of 80 mg/day) vs placebo in depressed outpatients for 6 weeks. These data were reviewed by Dan Marticello (review dated 8-4-82); he found the Zisook study to be negative, and while he considered the other 2 trials potentially positive, he could reach no conclusion since the analyses provided by the sponsor were based on evaluable cases. We discussed these and other concerns with the sponsor in a teleconference dated 7-13-87, resulting in the 10-22-87 amendment.

10-11-82: Amendment to S-017
-This was a data tape for the 3 studies noted above

10-22-87: Amendment to S-017
-This amendment included: (1) re-analyses of the Davidson and Giller studies; (2) revised labeling recommending (a) 50 mg as the maximum dose rather than 80 mg and (b) targeting "atypical depression."

-Upon review of re-submitted efficacy data (see Jay Levine review dated 11-20-87 and Laughren review dated 1-5-88), we concluded that the data, as presented, supported only a recommended dose of 80 mg/day. We suggested, however, that the Giller study supported a recommended dose of 60 mg/day and that the Davidson study may be salvaged as a source of support for 60 mg/day upon re-analysis with exclusion of higher dose patients. Regarding safety, it was noted that the data did not support the safe use of Marplan at maximum dose of 60 or 80 mg/day.

10-27-87: Amendment to S-017
-Supplementary data to support the 10-22-87 submission

6-24-88: Not-Approvable letter issued in response to the original 8-28-81 submission and the 3 subsequent amendments
-This letter addressed both our efficacy concerns, i.e., the need to provide data in support of a 60 mg/day maximum dose, and our safety concerns, i.e., the need for additional safety data at the higher doses now being recommended. [See the following memos: (1) Leber-5/3/88; (2) Temple-5/18/88; (3) Laughren-5/20/88; and (4) Leber-6/17/88]

12-16-88: Amendment to S-017
-Re-analysis of Davidson study excluding the patients dosed at levels higher than 60 mg/day. I reviewed these data and found them sufficient to support a maximum dosing recommendation of 60 mg/day (see Laughren memo dated 12-22-95).

4-14-94: Agency letter acknowledging Hoffman-LaRoche's decision to voluntarily withdraw Marplan from marketing

10-27-95: Amendment to S-017
-This amendment was a response to the safety concern cited in our 6-24-88 NA letter, including: (1) results from a retrospective survey of physicians who had treated patients with Marplan, (2) an update on spontaneous reports for Marplan worldwide, and (3) another summary of the safety results for the 3 placebo controlled studies previously reported in the original supplement. Dr. Hearst reviewed these data (review dated 11-9-95) and I provided my own interpretation of the adequacy of these data in a memo dated 12-22-95. In summary, we agreed that these data did not meet the need for safety data noted in our 6-24-88 NA letter.

2-26-96: Approvable letter issued in response to the original 8-28-81 submission and the 5 subsequent amendments -Through internal negotiations [see the following memos: (1) Leber-1/17/96; (2) Temple-1/24/96; (3) Laughren-1/31/96; (4) Leber-2/13/96], we reached agreement to issue an approvable letter for S-017. This letter asked for a commitment to conduct post-approval studies of (1) dose/response for efficacy in the range of 30 to 60 mg/day; (2) a safety study to address the safety of Marplan in the dose range now recommended. In addition, we provided detailed advice on how to repair the labeling for Marplan.

4-28-97: This amendment represents a partial response to our 2-26-96 approvable letter

Thus, the response ncludes the following: (1) a re-analysis of pooled efficacy data from the Davidson and Giller studies to address the dose/response for efficacy concern, in lieu of an additional clinical trial; (2) a re-analysis of pooled safety data from the Davidson, Giller, and Zisook studies to partially address the safety concern;

once FDA has agreed with the above noted efficacy and safety proposals.

2.1 Re-Analysis of Efficacy Data from Davidson and Giller Studies

Oxford looked at a pool of data from the 2 positive studies out of the 3 sponsored by Hoffman-LaRoche, i.e., Davidson and Giller. These, of course, were titration studies, so in order to explore for dose response, they chose to focus on a subgroup of the total of 86 patients exposed to Marplan, i.e., those who were able to complete 6 weeks of treatment. This subgroup of 33 patients was further subdivided into 2 groups on the basis of the dose achieved by 6 weeks, i.e., n=17 patients taking < 50 mg/day (mean dose = 34

mg/day) and n=16 patients taking ≥ 50 mg/day (mean dose = 58 mg/day).

Oxford conducted a within Marplan group comparison of these 2 subgroups on several outcomes, all at week 6: Physician Global Evaluation (both mean score and a categorical approach to the distribution of scores); HAMD total score (mean change from baseline, mean % change from baseline, and a categorical approach to % change from baseline); HAMD Depressed Mood Item (mean change from baseline, mean % change from baseline, and a categorical approach to % change from baseline). For these 8 contrasts, there were 2 that reached statistical significance at the $p < 0.05$ level, i.e., $p=0.03$ (favoring the ≥ 50 mg/day subgroup) for the HAMD depressed mood item (both mean change from baseline and the categorical analysis of week 6 data).

Comment: On face, the outcome is only weakly suggestive of a superiority for the ≥ 50 mg/day group. There are, of course, the additional problems that the pooling was arbitrary, the selection of the subgroups to compare was arbitrary, and the selection of approaches to assessing change on the outcome measures was arbitrary. This post hoc, exploratory analysis is at best suggestive of dose response, and does not suffice for a demonstration of dose response.

2.2 Published Paper Regarding Dose Response for Efficacy

Oxford has also provided exceeding brief comments on a published paper (Davidson, et al, 1984) regarding a 4-week study comparing 2 fixed doses of Marplan (30 and 50 mg/day) in depressed patients. Apparently, patients were categorized as melancholic or non-melancholic prior to treatment and randomization was stratified on this categorization as well. There were apparently 4 outcomes, including HAMD total score, MADRS total score, CGI, and SCL-40. The outcome is unclear. The narrative suggests that significance favoring the higher dose group was found for all outcomes at week 4, but only for the non-melancholic group. On the other hand, the table provided suggests that significance favoring the higher dose group was found for both groups, but only for the HAMD total score.

Comment: The amount of information provided is insufficient to draw any conclusions. As noted there is an inconsistency between the narrative and the table, it isn't stated what analyses were provided, e.g., LOCF or OC, nor is other information critical to an interpretation provided.

3.0 Safety of Marplan at Currently Recommended Doses

In order to address our safety concerns some additional analyses of safety data from the 3 Hoffman-LaRoche sponsored studies

3.1 Re-Analyses of Existing Data

data from the Davidson, Giller, and Zisook studies, including 86 patients receiving Marplan and 85 patients on placebo. They compared risk of occurrence of adverse events and risk of dropout for adverse events for 3 groups: placebo (n=85), Marplan < 50 mg/day (n=86)), and Marplan ≥ 50 mg/day (n=52). Thus, they compared all the Marplan patients with a subgroup of that total sample who were titrated to doses of ≥ 50 mg/day. As we noted earlier, there were no prominent differences in the overall occurrence of adverse events across the 3 groups, while the adverse dropouts on Marplan tended to occur during early titration, not surprisingly.

Comment: These data are already familiar to us, and do not address our major concern, which is the overall very small sample of patients who have been systematically evaluated at the higher doses of Marplan now being recommended.

3.2 Proposal for Phase 4 Safety Study

The proposal is for an open study involving 200+ depressed patients treated with Marplan. Patients will be titrated with Marplan as follows: begin with 10 mg bid; increase the dose by 10 mg qd q2-4 days, to achieve a dose of 40 mg/day by the end of week 1; increase the dose, as tolerated, to a maximum dose of 60 mg/day by the end of week 2. Patients not tolerating the 50 or 60 mg/day dose may remain in the study at lower doses. Patients who do tolerate the 50 or 60 mg/day doses will remain in the study for six months. The plan appears to be to enter a sufficient number of patients to obtain a sample of at least 200 patients who are dosed at either 50 or 60 mg/day for a minimum period of 6 months.

Visits will be at baseline, 2 weeks, and the ends of months 1, 3, and 6. Patients will be contacted by phone to ascertain adverse events at the ends of months 2, 4, and 5. At scheduled and other visits patients will be assessed for adverse events and will have routine physical exams, vital signs, and laboratory assessments. Patients will keep diaries to record adverse events and will be instructed to call the study site as needed to report adverse events.

Comment: While not precisely what we had suggested in our 2-26-96 approvable letter, I believe that this study should be sufficient to address our safety concerns. However, we need to have clarified the implication about 200 patients being exposed to Marplan doses of 50 or 60 mg/day for at least 6 months.

4.0 Repair of Labeling

In our 2-26-96 approvable letter, we had provided detailed advice about how to repair the labeling for Marplan.
agreed to rewrite labeling according to our advice, but plans to do this only upon our acceptance of the other parts of their response to our approvable letter.

cc:
Orig NDA 11-961 (Marplan)
HFD-120/DivFile
HFD-120/TLaughren/PLeber/EHearst/PDavid
HFD-101/RTemple

DOC: NDA11961.3

David

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 31, 1996

FROM: Thomas P. Laughren, M.D. /S/
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for approvable action for Marplan (S-017)

TO: File, NDA 11-961/S-017 (Marplan)
[**Note:** This memo should be filed with the 10-27-95 submission.]

1.0 Background

In a 1-24-96 memo, Dr. Temple has proposed that we may already have sufficient information on the safety of Marplan to permit it to be approved at the higher maximum dose now recommended. He argues that, even though we may not have sufficient data to estimate adverse event incidence at the higher doses being proposed, some patients have already been shown to tolerate these higher doses and the drug could be approved with labeling that summarizes what data we do have and emphasizes the limitations of our knowledge and the need for caution.

I have reconsidered my earlier recommendation for a non-approvable action on this supplement (see 12-22-95 memo to file), and I now consider that an approvable action would be an acceptable alternative, providing that the sponsor is (1) willing to repair the labeling for Marplan and (2) willing to commit to post-approval studies designed to address the information gaps for this drug.

Dr. Temple has also raised the question of whether or not the data are sufficient to recommend 50 mg/day, rather than 60 mg/day, as the maximum dose. In my view, we have gone as far as we reasonably can with those data even to arrive at the 60 mg/day recommendation. I agree with Dr. Temple that, ideally, the sponsor would address the question of dose/response for efficacy in a post-approval study.

2.0 Repair of Labeling

If Marplan is to be approved at the higher recommended maximum dose, the labeling needs considerable work. I believe that we

should make a general requirement that the labeling be re-written to conform to the currently accepted format and content guidelines for labeling. In addition, however, there are specific requirements that I believe must be met as well:

CLINICAL PHARMACOLOGY: This section is currently identified as "Actions," and contains much information that either doesn't belong in labeling at all or belongs elsewhere in labeling. I believe that the LD50 and other animal toxicology data can be deleted from labeling. The reproduction data can be moved to the appropriate subsection of PRECAUTIONS. The revised CLINICAL PHARMACOLOGY section should have three subsections, i.e., Pharmacodynamics, Pharmacokinetics, and Clinical Trials. The pharmacology of isocarboxazid should be summarized under Pharmacodynamics. The sponsor needs to summarize what is known from the literature or other sources about the pharacokinetics of isocarboxazid under Pharmacokinetics. Finally, the results from the two positive Giller and Davidson studies need to be summarized under a Clinical Trials subsection.

INDICATIONS AND USAGE: As noted in my 12-22-95 memo, the language proposed for this section by the sponsor is unacceptable. Alternatively, the sponsor should be asked to incorporate the language proposed in my 12-22-95 memo.

ADVERSE REACTIONS: As Dr. Temple has noted, the current ADVERSE REACTIONS section is essentially useless. A revision of this section should include data pooled from the three placebo controlled studies (Giller, Davidson, and Zisook). Included should be a table providing adverse events occurring at an incidence of $\geq$ 1% for Marplan. In addition, although recognizing the difficulty in trying to examine dose/response from titration studies, some attempt should be made to explore for dose/response. The revised section should emphasize the sparseness of the systematically collected adverse event data for this drug, e.g., by including a statement noting that systematically collected data are available from only 87 patients exposed to Marplan, of whom only 66 received doses of $\geq$ 50 mg/day, including only 35 who were dosed at $\geq$ 60 mg/day. Given the limitations on the available data, labeling should include in this section a statement advising particular caution in patients for whom a dose of 40 mg/day is exceeded.

DOSAGE AND ADMINISTRATION: This section should also include a statement emphasizing the need for particular caution when exceeding doses of 40 mg/day, given the sparseness of systematically collected adverse event data at higher doses.

3.0 Post-Approval Studies

Given the weaknesses in the development program for this drug, I believe that its approval should be contingent upon the agreement of the sponsor to conduct, post-approval, additional studies to

generate the data needed to more adequately write labeling for this product.
conduct

4.0 Availability of Marplan for Current Users

Given that we are now recommending the approvability of this application, I think it is reasonable for us to suggest to the sponsor that they continue to make Marplan available to current users during the interval that the labeling and other issues are being resolved prior to the final approval of this product.

I have proposed comments for an approvable letter.

cc:
Orig NDA 11-961 (Marplan)
HFD-120/DivFile
HFD-120/TLaughren/PLeber/EHearst/PDavid

DOC: NDA11961.2

David

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 22, 1995

FROM: Thomas P. Laughren, M.D.
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation against approval of proposed labeling changes for Marplan (S-017)

TO: File, NDA 11-961/S-017 (Marplan)
[**Note:** This memo should be filed with the 10-27-95 submission.]

1.0 Background

Marplan was approved before the efficacy requirement and, thus, was subject to DESI review, resulting in interim labeling which classified it as "probably effective for the treatment of depressed patients who are refractory to tricyclic antidepressants or ECT and depressed patients in whom tricyclic antidepressants are contraindicated." The currently recommended maximum dose for Marplan is 30 mg/day. One of the requirements derived from the DESI review (stated in a 7-14-78 Federal Register notice) was the conduct of at least two adequate and well controlled studies to determine whether or not this product is effective. The original supplement (S-017; 8-28-81) in response to this DESI notice included the results of 3 placebo controlled studies regarding the safety and effectiveness of Marplan in depressed patients.

Efficacy

These three studies were reviewed (see my 1-5-88 review for a more complete discussion of these data), and we concluded that 2 of the 3 studies were positive (Giller and Davidson). However, in the proposed labeling included in a 10-22-87 amendment to S-017, the sponsor was recommending a maximum dose of 50 mg/day, despite the fact that patients were dosed in a range of up to 80 mg/day in those 2 studies. We concluded that, for the Giller study, 60 mg/day would be an acceptable upper dose, given the fact that only 1 patient was dosed above 60 mg/day in that study. This argument was not applicable to the Davidson study, in which 5 patients were dosed above 60 mg/day.

In a 1-24-88 non-approvable letter to the sponsor, we indicated that, based on the two positive studies, we would only be able to accept a maximum dose recommendation of 80 mg/day. However, we noted that the Giller study supported a maximum dose recommendation of 60 mg/day and we suggested that they might consider re-analyzing the Davidson study after excluding the 5 patients who were dosed above 60 mg/day. The sponsor accepted this option and submitted the results of a re-analysis of the Davidson study in a 12-16-88 amendment (see 2.0 Efficacy, to follow).

Safety

The 3 studies submitted in S-017 involved a total of 87 patients exposed to Marplan. Of these 87 patients, 66 received doses of $\geq$ 50 mg/day, including 35 who received doses of $\geq$ 60 mg/day. While nothing catastrophic occurred among these 87 patients and the adverse events seen were generally consistent with the recognized safety profile for this drug, this limited safety experience was not considered sufficient, given the higher doses used in the studies demonstrating efficacy (see my 1-5-88 review). This deficiency might have been mitigated by a finding that, in practice, Marplan was used at higher than currently recommended doses. However, as noted in my 5-20-88 memo, our limited data pertinent to this question suggested that Marplan was generally used at lower doses (average dose of 22 mg/day in a sample available to us at that time). We noted in our 6-24-88 letter that, even if we were to accept a maximum dose recommendation of 60 mg/day, we could not rely on this small a sample as a basis for establishing the safety of Marplan at doses up to 60 mg/day. We suggested the need for an open study involving at least 1000 patients exposed to Marplan, including several hundred at the higher end of the permitted dose range. The sponsor has now responded to this suggestion in the 10-27-95 amendment (see 3.0 Safety, to follow).

Proposed Indication

The sponsor has proposed that Marplan be indicated as follows: "patients suffering from atypical depression, a condition characterized by dysphoric mood, fatigue, anxiety and somatic complaints. Many of these patients have a history of phobic and/or panic symptoms; endogenous features are not usually prominent." In my 1-5-88 review, I discussed my concerns with such a claim, in particular, the fact that there is no concensus regarding a definition for atypical depression. As an alternative, I proposed a claim consistent with the population actually recruited in the studies supporting the effectiveness of Marplan. In addition, I suggested that the labeling recommend that (1) Marplan not be considered a first line drug, as is the case for the only other 2 MAOIs approved for depression; (2) Marplan has not been adequately studied in hospitalized depressed patients; and (3) the long-term effectiveness of Marplan has not been adequately studied.

In a 5-3-88 memo, Dr. Leber raised a concern that my proposed indication statement was pseudospecific, and he suggested alternative language that would not have this problem. I will revisit this issue of the language for the claim under 4.0 Proposed Indication, to follow.

Current Status of Marplan

On 3-31-94, the sponsor notified FDA that it would no longer market Marplan. Apparently, this decision resulted in a number of requests to the sponsor from patients and physicians to keep Marplan on the market. The sponsor has subsequently produced 3 lots and is currently providing Marplan at no cost to physicians for patients who need this drug. This is a temporary measure, and the sponsor would like to transfer the Marplan NDA to another pharmaceutical company for marketing. Before such a transfer can occur, the DESI issues need to be resolved. The sponsor has indicated that it will not produce more product once the current supplies are exhausted (estimated date about March, 1996).

2.0 Efficacy

I have looked at the results provided in the 12-16-88 re-analysis of the Davidson study based on a modified sample in which the 5 patients dosed with Marplan at doses > 60 mg/day were excluded. I've presented data in Table 1 on the level of significance for the Marplan-Placebo pairwise comparisons in the last observation carried forward analyses for 3 key variables (HAMD total, HAMD Item 1, and CGI improvement). Table 1 provides these data for both the original sample and for the modified sample. The findings are unchanged for HAMD Item 1 and CGI Improvement. For HAMD total, there is a decrease in significance at only 1 timepoint, i.e., week 4, when the 2-sided significance level drops from $p \leq 0.05$ to $p \leq 0.10$.

Comment: I consider these data adequate to support a claim of antidepressant effectiveness for Marplan up to a maximum dose of 60 mg/day.

3.0 Safety

The sponsor has not followed the advice given in our 6-24-88 letter to prospectively obtain additional safety data on at least 1000 patients treated with Marplan, including several hundred at the higher end of the currently recommended dose range of up to 60 mg/day. Rather, in their 10-27-95 amendment, they have provided (1) results from a retrospective survey of physicians who had treated patients with Marplan, (2) an update on spontaneous reports for Marplan worldwide, and (3) another summary of the safety results for the 3 placebo controlled studies previously reported in

the original supplement. Dr. Hearst has reviewed these data (review dated 11-9-95) and I will provide only my own interpretation of the adequacy of the data rather than another review.

Retrospective Study

This survey involved 237 patients exposed to Marplan. Of these 237 patients, 41 received doses of ≥ 50 mg/day, including 24 who received doses of ≥ 60 mg/day.

Spontaneous Reports for Marplan

The total number of patients for whom spontaneous reports have been received is 170, of whom only 11 were reported to be receiving doses ≥ 30 mg/day [**Note**: Dose was not reported for 65 patients].

1981 Studies

As noted earlier, these studies involved 87 patients exposed to Marplan. Of these 87 patients, 66 received doses of ≥ 50 mg/day, including 35 who received doses of ≥ 60 mg/day.

Comment: Thus, the spontaneously reported cases are of no direct value in addressing the question of the safety of Marplan in the currently recommended dose range. For the 3 placebo controlled studies and the retrospective survey, the total for Marplan patients exposed at doses ≥ 50 mg/day is 107, including only 59 exposeed at doses ≥ 60 mg/day. In addition, there is the question of whether or not ascertainment for adverse events was adequate in the retrospective survey.

Dr. Hearst notes in his review that "there have been no seriously alarming safety patterns revealed by this additional data which is consistent with what has been already known about the drug." He recommends accepting these data as "the best possible under the current circumstances" in order to permit the continued availability of this drug to those users who have been unable to successfully switch to other antidepressants.

I agree that no new and alarming adverse events have emerged from these data sources examined by the sponsor, however, I disagree that we can rely on these data in making a judgement about the safety of recommending Marplan at doses of up to 60 mg/day. There have been too few patients at the doses in question, and the methods of ascertainment in the sources used for this exploration are inadequate, in my view. I would not be concerned about continuing current users on doses they have already tolerated adequately

many of whom would be dosed at higher doses, according to dosing recommendations that would necessarily accompany the re-introinduction of this drug. We do not, in my view, have sufficient safety date to support such use.

I still believe that a prospective study is needed to obtain more safety experience at the higher end of the recommended dose range. However, I think we might reasonably settle for a smaller study than originally proposed in our 6-24-88 letter. We had originally proposed at least 1000 patients, including several hundred receiving doses at the higher end of the dose range. Rather, I would propose asking for an open study that has no defined number overall, but is required to include at least 300 patients treated with Marplan doses $\geq$ 50 mg/day, including 100 at doses of 60 mg/day. Although it's true that 300 patients having no events of a particular type only provides reassurance that the rate for any such event is no greater than 1/100, I am not greatly concerned about detecting unknown serious events, which I think is highly unlikely given the long marketing history of this drug and the fact that idiosyncratic events are generally not dose related. Rather, I think it is more important to try to adequately establish the incidence and severity of known adverse events at the higher end of the dose range. I believe that 300 patients dosed in this range and carefully monitored for adverse events could provide the needed experience.

4.0 Proposed Indication

While I consider S-017 still non-approvable because of insufficient safety data at the higher end of the recommended dose range, I believe that we should alert the sponsor to our intentions regarding the language for the claimed indication, since this knowledge is likely to influence their decision regarding whether or not to pursue this application. I propose the following language for the Indications and Usage Section:

"Marplan is indicated for the treatment of depression.

The efficacy of Marplan in the treatment of depression was established in 6-week controlled trials of depressed outpatients. These patients had symptoms that corresponded to the DSM-IV category of major depressive disorder, however, they often also had signs and symptoms of anxiety (anxious mood, panic, and/or phobic symptoms).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or

hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The antidepressant effectiveness of Marplan in hospitalized depressed patients, or in endogenomorphically retarded and delusionally depressed patients, has not been adequately studied. For these reasons, and because of the potentially serious consequences of its side effect profile, Marplan is not to be considered as an antidepressant of first choice in the treatment of newly diagnosed depressed patients with prominent endogenous features.

The effectiveness of Marplan in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Marplan for extended periods should periodically evaluate the long-term usefulness of the drug for the individual patient."

5.0 Conclusions/Recommendations

Although the sponsor has now provided sufficient data to support the antidepressant effectiveness of Marplan in the acute treatment of non-endogenous depression, they have not yet provided sufficient data to support the safety of Marplan in the dose range, i.e., up to 60 mg/day, that is now being recommended. Thus, I recommend that we again issue a non-approvable letter for this supplement. I recommend that we agree to a less demanding safety study, in terms of total numbers of patients exposed, but nevertheless one that will, in my view, adequately reveal the adverse effect profile of Marplan at the higher end of the dose range being proposed.

Since it is likely that the language we would permit for the antidepressant claim for Marplan may influence the sponsor's decision regarding whether or not to pursue this application, I recommend that we include our proposed antidepressant claim in the letter, even though we are not recommending an approvable action at this point in time.

I recognize that a possible outcome of taking the firm stand I have suggested may be that Marplan will cease to be available. However, two other MAOIs are marketed, and neither the sponsor nor anyone else has adequately made the case that Marplan is a critical member of the psychotropic armamentarium. Of course, it is possible that some individual patients may uniquely benefit from Marplan. It is obviously unknowable whether or not this is true. In any case, it seems likely to me that any re-introduction of Marplan into the market would be accompanied by heavy promotion to recruit new users. I think it is critical that any expanded use of this product at the higher doses that would necessarily be recommended be supported by adequate data establishing the safety of those

higher doses. In the meantime, the sponsor could, as a demonstration of its interest in the public good, continue to produce Marplan to supply the small group of current users.

I have proposed comments for a non-approvable letter.

cc:
Orig NDA 11-961 (Marplan)
HFD-120/DivFile
HFD-120/TLaughren/PLeber/EHearst/PDavid

DOC: NDA11961.1

TABLE 1 Summary of Significance Levels[1] (2-sided) for Pairwise Comparisons of Marplan vs Placebo in Davidson Study (Results from Last Observation Carried Forward Analyses)					
Key Outcome Variables	Marplan vs Placebo				
	Week[2]				
	1	2	3	4	6
HAMD Total					
Original Sample	-	-	-	*	*
Modified Sample[3]	-	-	-	t	*
HAMD Item 1					
Original Sample	-	-	-	*	*
Modified Sample	-	-	-	*	*
CGI Improvement					
Original Sample	-	-	t	*	t
Modified Sample	-	-	t	*	t

1 Based on analysis of covariance
* = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of weeks 1, 2, 3, 4, and 6

3 Modified Sample = Sample in which the 5 patients dosed at Marplan > 60 mg/day are excluded.

DAVIS

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JAN 24 1996

FROM: Director, Office of Drug Evaluation I, HFD-101

SUBJECT: Marplan

TO: Dr. Paul Leber
Dr. Tom Laughren

The proposed safety study is not intended to discover rare, idiosyncratic events (Laughren memo, p. 5) but to establish the incidence and severity of known adverse effects at the higher end of the dose range. One way of translating this situation, as we already know and acknowledge (proposed letter, p.2) that some patients can tolerate the drug, is that the requested safety study will not affect approvability but will permit us to write informative labeling allowing physicians to know, not so much what to expect, but how often to expect it. The question this raises is whether we already know enough to say that, for a last resort drug used with careful monitoring, we have enough information to tell how to use the drug safely (even if we don't know the ADR rates as well as we'd like). Please consider the following thoughts on safety and other matters:

1. The pooled results of the 3 controlled trials (even the not supportive one), give information about the more frequent adverse events, possibly enough to say something about their dose-response. As the studies are all titrational, the dose/time effects are confounded but, at least for the 6 week period, any notable increase in orthostatic, dizziness, blurred vision, etc. ought to be detectable. These studies should be displayed in labeling in a table (drug vs placebo) for overall rates and by dose and any D/R should be looked for over all doses, not just for the 60 mg. Current labeling for ADRs is wholly useless.

2. The results of the clinical studies (Laughren Table 2) showing what I presume is the pooled 3 efficacy studies (not giving actual ADRs but systems) give no real suggestion of dose relatedness for CNS, special senses, or other ADRs,