and, if one were to pool the 50-70 mg groups, include some 65 exposed patients, probably enough to see something if it was there. (I gather from the 1988 Laughren review, p. 3, that the sponsor did just that, showing no excess for the higher group.) In addition, the 40-49 mg group is not irrelevant; that group too took considerably more than the previously recommended dose, apparently with no striking effect. Although one might make the case that there ought to be 300 exposed patients to have a chance of detecting a 1% rate of something serious and unexpected, you do not need numbers like that to see if the more common events at 30 mg are increased in frequency at 50-60 mg. It might be enough to say, in labeling, that experience beyond 40 (or so) mg is limited and that patients need to be particularly closely watched if that dose is exceeded.

3. I note that although a fair number of patients had a dose above 50 mg at some point, few had mean doses greater than 50. I wonder if that suggests that a top dose of 50 mg could be recommended at this point. There is not a shred of evidence as to what dose is actually needed. Dosing in the effectiveness trials was to tolerance, not effect. For all we know, 40 mg (or 30) is plenty.

4. If a further study is needed it could be simple, with close attention at 2 or so weeks to adverse events, with focus after that on events leading to change in dose or discontinuation of treatment. Alternatively, and what I would most like to see, they could agree to a modern D/R study (say 30 vs 60) (or highest tolerated) vs placebo with about 40 patients per group. That might be asked for as a post-approval study, either in unselected or in poorly responsive patients.

5. Current labeling gives not only word of clinical pharmacology; actually, in the tradition of pre-1962 labeling it gives only <u>in vitro</u> and animal data. That section needs a complete re-do, with some PK mechanism, and clinical trial results.

/S/

Robert Temple, M.D.

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 11-961

SPONSOR: Hoffman-La Roche

DRUG: Marplan

MATERIAL RECEIVED: Response to Approvable letters

DATE SUBMITTED: Feb 18TH, 1998

DATE RECEIVED: Feb 19TH, 1998

I. REVIEW

Roche has responded to our Approvable letters dated 2/26/96 and 11/7/97. They have revised labeling to conform more closely with the currently accepted format and content guidelines. I have reviewed the labeling and they have incorporated the changes we requested in our previous communications. Oxford agrees to our request to increase the safety study from 200 to 300 patients upon obtaining ownership of the Marplan NDA. Their response to our request for an adequate well controlled dose response study raised in our 11/7/97 letter is reproduced in italics below.

Dose Response Study

In response to the Agency's request to commit to conducting an "adequate and well-controlled study to explore dose response for the effectiveness of Marplan in depression agrees to conduct the study as outlined below.

the cost of conducting such an "adequate and welt-controlled study" would likely exceed the value of this product.

the data on the dose/response for the 60 mg dose is limited. However, this drug is not a new chemical entity. Marplan has a good safety profile, having been on the market for many years. The dosage form of Marplan to be used is a 10 mg tablet, which will be titrated, according to the labeling, to a dose level sufficient to control the patient's symptoms (up to a dose of 60 mg). In effect, each patient will be his/her own "dose/response" study. We believe that the approval requirements

for this drug need to take into consideration the small population of patients receiving this product. Imposition of requirements

proposes to provide sufficient data to reaffirm the safety and efficacy for 30 mg, 50 mg, 60 mg doses in the following matter:

1 The proposed product labeling recommends that each patient receiving Marplan should be titrated according to his or her dose response for efficacy.

2. Physicians prescribing Marplan will be asked to complete a patient report recording dosage; side effects (if any); and effectiveness evaluations. This data will be collected on 300 patients meeting the FDA request.

3. This follow-up data on 300 patients receiving Marplan will be collected from physicians geographically disbursed throughout the United States. These investigative centers will be selected based on the amount of patients prescribed Marplan and physician's commitment to participate in the clinical study.

4 A dose response/safety statistical analysis will be performed on an annual basis. Within this analysis, final doses of 30 mg, 50 mg, and 60 mg will be analyzed for efficacy and safety.

The data emanating from the actual use of Marplan will provide (1) adequate information to the Agency concerning the safety and dose response information requested for the 30 mg, 50 mg, and 60 mg dosages and, (2) simultaneously allow patients who are receiving Marplan to continue their therapy.

II. CONCLUSIONS

I find that I have agreed with a numbers of the sponsor's points

through out this period of discussion. I believe the drug is well known to the medical community and has been used with a reasonable safety profile for years. A relatively small number of patients take this drug and their supply of Marplan may be jeopardized with further delay. Most patients are on this drug due to lack of response to other antidepressants. In each individual case the physician hopefully will titrate the patient to the lowest effective dose. The sponsor continues to decline doing an adequate well controlled dose response study and production of Marplan may be threatened shortly.

I believe even though we do not have an ideal proposal the submission is adequate and their proposal should be accepted as a compromise to keep Marplan on the market for those patients who benefit by taking it.

I do feel the labeling for Marplan should display the second line indication for new patients more prominently rather than including it in the 4th paragraph of the indications section.

/S/ 3/4/98

Earl D. Hearst, M.D.,
Psychiatric Clinical Reviewer
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation and Research
Center for Drug Evaluation and Research

7-14-98

I agree that this supplement can now be approved. The labeling needed considerable work, however, this has now been accomplished and we have reached agreement with the sponsor. See my memo to file for more detailed comments.

(3) — /S/
TL, HFD-

cc: Original NDA 11-961
HFD-120/
/EHearst/
/TLaughren/
/CSO/PDavid/

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 11-961

SPONSOR: Hoffman-La Roche

DRUG: Marplan

MATERIAL RECEIVED: DESI submission, summary of current information and protocol proposal

DATE SUBMITTED: April 28th, 1997

DATE RECEIVED: May 5th, 1997

I. REVIEW

This submission refers back to the supplemental New Drug Application for Marplan(isocarboxazid) tablets which was originally submitted as part of a DESI submission on August 28, 1981 and amended on October 22, 1987, October 27, 1987, December 16, 1988 and October 27, 1995. Subsequent to the last amended submission, Hoffmann-La Roche Inc.(Roche) received an FDA

Approvable letter outlining the recommendations proposed by the FDA to resolve the DESI status for this product.

response and proposed resolution to the outstanding issues outlined by the FDA in the February 26, 1996 Approvable letter. I will quote details of our letter below in italics.

Although the supplement is now approvable, there are several issues that need to be addressed before this application can be finally approved. (1) Although we believe there are sufficient data to permit the marketing of Marplan® at the higher doses now recommended, we continue to believe there are important gaps in the knowledge base for this drug. Although we acknowledge that you have now provided sufficient data to support the effectiveness of Marplan® in the acute treatment of non-

endogenous depression in a dose range of up to 60 mg/day, you have not addressed the question of dose/response for the efficacy of Marplan® in the dose range of 30 to 60 mg/day. In addition, it continues to be our view that you have not yet provided sufficient data regarding the safety of Marplan® in order to fully inform clinicians about the incidence of adverse events in the dose range that is now being recommended. Consequently, we ask that, as a condition of approval, you commit to conducting additional studies post-approval to address these deficiencies. (2) The labeling for Marplan® is also deficient, and we have provided comments below regarding what is needed to repair the labeling for this product. (3) Finally, we have commented below on what we consider to be an appropriate response on your part to the continuing need for Marplan® by current users during this time interval before the supplement can be finally approved.

The sponsor's reply to our letter is listed in the sections to follow.

Approach to Analysis of Dose/Response Information Using the Davidson and Giller Clinical Studies:

The data from Jonathan Davidson, M.D. and Earl Giller, M.D., Ph.D., two investigators participating in the study conducted according to Protocol Number 2032A/B were pooled.

Data from Sidney Zisook, M.D., the third investigator, were not included in the reanalysis as FDA had previously determined that this study did not demonstrate the antidepressant efficacy of Marplan.

In the data analyses only patients who received Marplan and had efficacy evaluations at the Week 6 visit were included. The dose levels presented in the analyses pertain to the dose the patients were taking at the Week 6 visit. This visit was chosen because all patients in this dose escalation study would have been taking the Week 6 dose level for at least the previous two weeks. Patients who were taking Marplan in doses $\geq$ 50 mg/day were compared to patients taking doses < 50 mg/day and to patients in the placebo group, both at baseline and at the Week 6 visit.

The Physician's Global Evaluation Score, the Hamilton Depression Scale (HDS), Total Score and the HDS Score for Depression were the parameters evaluated.

A total of 171 patients were enrolled in the two studies of whom 86 patients received Marplan and 85 placebo. Seventeen patients were taking less than Marplan 50mg per day (the average dose in these patients was 33.8mg/day), and 16 patients were taking Marplan in doses of 50mg per day or higher (mean dose

57.5mg/day). Nine of 17 patients who were taking less than 50mg/day received 40mg/day and ten of 16 patients taking ≥ 50mg/day were taking the 60mg/day dose.

The physician's mean Global Evaluation was "Much better" both in patients taking < 50 mg per day at the Week 6 visit and in patients taking ≥ 50 mg/day. The mean score was 2.06 for patients taking < 50mg/day and 1.94 for patients taking ≥ 50mg/day.

Twenty-nine percent (5 of 17) patients taking < 50mg/day were very much better compared to 44% (7 of 16) patients taking ≥ 50mg/day, p=0.392, (Chi-square test without continuity adjustment).

Overall, the difference between < 50 mg and ≥ 50 mg was not statistically significant, p=0.518, (Mann-Whitney test).

The total score of the HDRS was analyzed. The maximum (worst) possible total score was 62 and the best possible score 0. Patients treated with < 50mg/day had a mean improvement in the Total Score of 16.12 compared to an improvement in Total Score of 23.56 for patients taking ≥ 50mg/day, p=0.052 (t-test).

The number of patients taking < 50Mg/day and > 50mg/day by percentage improvement in Total Score is analyzed next. Sixty-five percent (11 of 17) patients taking < 50mg/day improved in the Hamilton Depression Scale Total Score by ≥ 50% compared with 88% (14 of 16) patients taking ≥ 50 mg/day, p=0.127 (Chi-square test, without continuity adjustment). Overall, the difference between doses was not statistically significant, p=0.109 (Mann-Whitney test).

Depressed mood per se was part of the total score and was evaluated on a five point scale. The Mean Depression Score improved by 65% (from 2.53 to 0.88) in patients treated with < 50mg/day and by 88% in patients treated with ≥ 50mg/day. At the Week 6 Visit 47% (8 of 17) of patients taking < 50mg/day were free from depression compared to 88% (14 of 16) of patients taking ≥ 50mg/day. p=0.014 (Chi-square test, without continuity adjustment). Overall, the difference between < 50 mg and ≥ 50 mg in the number of patients with depression scores of 0-4 at week 6 visit was statistically significant, p=0.031 (Mann-Whitney test).

Published Literature Articles:

Two published articles were reviewed by the sponsor for information pertaining to the effect of doses of 30 mg/day compared to doses of 50 mg/day. Both clinical information e.g., HDS scores and information on the inhibition of platelet monoamine oxidase activity are presented below.

Methods

The sponsor reports that two fixed doses of isocarboxazid 30 mg/day and

50 mg/day were studied over a four week period in 39 patients who fulfilled DSM-III criteria for major depression. Patients with an antecedent diagnosis of schizophrenia, mania or organic brain disease were excluded from the study. Prior to treatment patients were categorized as having either melancholia or non-melancholia according to DSM-III criteria.

The study was conducted in a double-blind manner. Randomization was balanced for diagnostic type (endogenous and non-endogenous depression).

Results

The two treatment groups were comparable with respect to the demographic variables according to the sponsor. There was no difference between the 30 mg and 50 mg doses in patients with endogenous depression. However, the 50 mg/day dose was significantly better than the 30 mg/day dose with respect to the Hamilton Scale ($p < 0.05$), the Montgomery-Asberg (MADRS), the Clinical Global Improvement (CGI) and self rated SCL-90 in patients with non-endogenous depression at Week 4.

Patients in the 30 mg/day group had an average of 0.4 adverse experiences compared to 1.0 in the 50 mg/day group.

There is another analysis of data from the previous study. The sponsor reports that platelet monoamine oxidase activity was measured in a subset of patients. The data showed that 50 mg isocarboxazid resulted in significantly greater enzyme inhibition than did 30 mg at two of the four timepoints, using phenethylaniine as substrate. The author commented that 85% inhibition was rarely attained with 30 mg.

Safety Information:

The sponsor reports that for safety purposes data from all three investigators, Drs. Davidson, Giller and Zisook, who participated in Protocol Number 2032A/B/C were pooled. The incidence of adverse experiences and treatment discontinuations due to adverse experiences which occurred at doses < 50 mg/day were compared to the incidence on doses ≥ 50 mg/day and to the incidence in the placebo group. All adverse experiences were included regardless of treatment attribution. Therefore, a patient could appear in both the < 50 mg and ≥ 50 mg group because adverse events throughout the entire study period were included.

Eighty-five patients received placebo and 86 Marplan. Since the dose of Marplan was uptitrated to attain maximum therapeutic effect all 86 patients in the Marplan group received doses < 50 mg per day, 52 of whom had their dose uptitrated to ≥ 50 mg per day.

The incidence of adverse events in the placebo group and at doses of Marplan < 50 mg per day and ≥ 50 mg per day is displayed in Appendix Table 10.

The incidence of adverse experiences on doses of Marplan ≥ 50 mg per day is similar to the incidence on placebo and ≥ 50 mg per day. The incidence of dizziness was 14% (12 of 85) in the placebo group, 29% with

doses of ≤ 50 mg per day (25 of 86) and 15% (8 of 52) with Marplan ≥ 50 mg per day. The adverse events that occur more often in the high dose group as compared to the lower dose group on Marplan are as follows: Orthostatic Hypotension 4% vs 3.5%, Urinary Hesitancy 4% vs 1%, Insomnia 6% vs 3.5%, Tremor 4% vs 3.5%, Blurred Vision 6% vs 3.5%.

Patients Discontinued with Adverse Events:

Four of 85 (5%) patients in the placebo group were prematurely discontinued from the study because of adverse events as were 12% (10 of 86) patients taking Marplan in doses of < 50 mg per day and 2% (1 of 52) patients taking doses ≥ 50 mg per day. The specific adverse events necessitating treatment withdrawal are displayed in Table 11. The sponsor reports that patients who were able to tolerate Marplan at doses of < 50 mg per day were able to tolerate doses ≥ 50 mg per day. The sponsor reports that no patient was discontinued from the study due to syncope or orthostatic hypotension at doses ≥ 50 mg per day. Most of the patients in the Marplan group who were prematurely discontinued from the study were treated by one investigator, Dr. Zisook, whose data were not poolable with data from the other two centers with respect to efficacy.

Labeling Information:

The sponsor agrees that the labeling for Marplan will be modified to conform to the currently recommended format and content guidelines once FDA reaches a decision regarding the adequacy of the enclosed information to support the remarketing of Marplan. Additionally, all specific labeling modifications as outlined in the February 26, 1996 FDA letter will also be incorporated. The sponsor indicates that there is no information available from the literature or other sources about the pharmacokinetics of isocarboxazid.

II. CONCLUSIONS

The sponsor had agreed to our suggested labeling. They have provided an analysis of existing data and a literature review which is supportive of the safe use of Nardil in the 50-60 mg range. They are committing to a study which is not exactly what we requested but should still provide further useful information on the use of Marplan in this higher dosing range.

I believe, taken as a whole, the submission is adequate, and their proposal should be accepted in order to keep Marplan on the market for those patients who benefit from it's use.

/S/ 5/19/97

Earl D. Hearst, M.D.,
Psychiatric Clinical Reviewer
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation and Research
Center for Drug Evaluation and Research

cc: Original NDA 11-961
HFD-120/
/EHearst/
/TLaughren/
/CSO/PDavid/

9-11-97

This review document is not very useful, in my view, since it consists largely of verbatim sections of the sponsor's document. There is very little in the way of critical, thoughtful commentary on what the sponsor has done. I have provided an independent review of this material in a 9-11-97 memo to the file.

Thomas P. Laughren, MD
TL, PDP

3 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

DAUD

REVIEW & EVALUATION

NDA: 11-961

SPONSOR: Roche Pharmaceuticals

DRUG: Marplan

MATERIAL SUBMITTED: Retrospective study results and labeling changes

DATE SUBMITTED: October 27, 1995

DATE RECEIVED: October 30, 1995

I. Review

The sponsor is considering transferring Marplan to another pharmaceutical company and would like to clear up outstanding DESI issues. In June 1988, the FDA wrote a letter requesting an in depth safety study in at least 1,000 patients once the maximum dosage for efficacy was agreed upon (60 mg/day was proposed by Roche Pharmaceuticals). The sponsor never did the study and now feels that the total population on Marplan may be less than 1,000 patients. They have instead provided us with the retrospective analysis of the post marketing safety database. They have provided us with a report on this analysis along with the reported adverse events received by Roche drug safety worldwide and the safety results of studies submitted in 1981.

The sponsor has also revised the INDICATION and DOSAGE AND ADMINISTRATION sections reflecting both the reanalyzes of their efficacy studies and the results of the retrospective analysis.

ROCHE DRUG SAFETY CUMULATIVE DATA

Data on adverse events associated with Marplan regardless of causality from all sources worldwide has been collected from the first case in 1967 through March 15, 1995, in total 170 patients reported 321 adverse events. The outcome was known for 191 (82%) of the 232 events: 122 (64%) had abated and 62 (32%) remained under treatment; none had residual sequelae at the time of reporting. The remaining 7 (4%) adverse events (in 4 patients) resulted in death. The four deaths were due to: suspected drug

overdose, possible neuroleptic malegment syndrome, cardiovascular collapse of unknown cause, and seizure of unknown cause.

11 patients who received Marplan and daily doses greater than 30mg reported 17 adverse events. The outcome was known for 9 (53%) of the 17 events: 3 (33%) had abated and 3 (33%) remained under treatment, none had residual sequelae at the time of reporting. The remaining 3 adverse events (in 2 patients) resulted in death. The 2 deaths were due to mixed drug overdose and drug interaction. The distribution of adverse events is summarized in Table 1.

RESULTS OF THE 1981 CLINICAL STUDIES

3 single center clinical trials were conducted in patients diagnosed as having atypical depression. Patients were started on Marplan and a dosage of 20 mg/per day, gradually increasing to 80 mg/per day by the third week of treatment. The length of the studies were 6 weeks and mean daily dosage by week were calculated for each patient. The most frequent reported adverse events included dizziness, headache, and blurred vision. Other adverse events reported included orthostatic hypertension, dry mouth, constipation, and insomnia. No deaths were reported. The distribution of adverse events is summarized in Table 2.

RESULTS OF THE RETROSPECTIVE STUDY

A total of 153 physicians provided data collected from 237 patients. These physicians were the ones who objected to the discontinuation of Marplan and asked for compassionate use. 72 of the 237 patients reported 111 adverse events regardless of causality. The distribution is shown in Table 3 and demographic data of these patients is shown in Table 4. The most frequently reported adverse events included changes in blood pressure, sexual disfunction, constipation, and insomnia. Other adverse events reported included dizziness, light headiness, confusion, headaches, weight gain, and musculoskeletal affects, there were no deaths.

LABELING CHANGES

The sponsor also wishes to change the INDICATIONS section from its prior version recommending Marplan's use in refactory patients to an indication for patients suffering from atypical depression. The sponsor has also rewritten the DOSAGE AND

ADMINISTRATION section decreasing the initial dose to 20 mg/per day rather than 30 mg daily. The maximum dosage has been raised to 60 mg/per day divided into 2 or 4 doses.

II. Conclusions

Although it is hard to make any firm conclusions from the data provided, it is possible to say 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. As there are a core group of Marplan users who have not been able to switch successfully to other antidepressants it would seem worthwhile that this drug remain available. I would recommend that this data be accepted as the best possible under the current circumstances to fulfill the DESI requirement.

Regarding the proposed labeling change, I do not feel the data warrants a change in the INDICATIONS sections as a primary treatment for patients suffering from atypical depression. I would continue to recommend the previous indication in the treatment of depressed patients who are refractory to other primary treatments.

The changes in the DOSAGE and ADMINISTRATION section appear to be consistent with the data and I recommend they be accepted.

/S/ 11/9/95

Earl D. Hearst, M.D.

Psychiatric Clinical Reviewer
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation and Research
Center for Drug Evaluation and Research

12-22-95
I disagree with the above recommendation for approval of S-017. See my detailed comments in memo to file.
/S/
OC, TDT

cc: Original NDA 11-961
Div File /HFD-120
/Ehearst
/Tlaughren
/PDavid

Table 1. Roche Drug Safety Data of Reported Adverse Events Frequency Distribution of Adverse Events according to System Organ Class (Number of Patients=170)

System Organ Class (SOC)	N	(%)
Central & Peripheral Nervous System (CNS)	64	(20.1)
Body as a Whole – General	43	(12.5)
Psychiatric	40	(12.5)
Gastrointestinal System	28	(8.7)
Musculoskeletal	24	(7.5)
Cardiovascular – General	22	(6.9)
Skin and Appendages	16	(5.1)
Heart Rate & Rhythm	16	(5.1)
Respiratory System	11	(3.1)
Urinary System	9	(2.9)
Fetal	7	(2.2)
Vision	7	(2.2)
Hearing & Vestibular	6	(1.9)
Reproductive – Female	5	(1.6)
Liver & Biliary System	4	(1.3)
Endocrine	4	(1.3)
Vascular (Extracardiac)	3	(0.9)
Reproductive – Male	2	(0.7)
Autonomic Nervous System	2	(0.7)
Red Blood Cells	2	(0.7)
Platelet – Bleeding and Clotting	2	(0.7)
All other SOC Categories (1 report/SOC)	4	(1.3)
TOTAL	321	(100)

N=number of adverse events.

(5)

Table 2. 1981 Isocarboxazid (Marplan®) Clinical Studies
Distribution of Adverse Events According to System Organ Class by Dosage Group

System Organ Class	Isocarboxazid <30 mg		30-39 mg		40-49 mg		50-59 mg		60-69 mg		70+ mg	
	N[1]=85		N[1]=63		N[1]=52		N[1]=31		N[1]=28		N[1]=7	
	No. of AE's	%	No. of AE's	%	No. of AE's	%	No. of AE's	%	No. of AE's	%	No. of AE's	
Miscellaneous	9	10.6	9	14.3	5	9.6	1	3.2	3	10.7	1	14.3
Integumentary	0	0	4	6.3	0	0	0	0	0	0	0	0
Musculoskeletal	1	1.2	3	4.8	0	0	0	0	1	3.6	2	28.6
Cardiovascular	1	1.2	3	4.8	1	1.9	1	3.2	2	7.1	0	0
Gastrointestinal	5	5.9	10	15.9	6	11.5	2	6.5	4	14.3	1	14.3
Urogenital	1	1.2	2	3.2	5	9.6	1	3.2	2	7.1	1	14.3
Central Nervous System	9	10.6	13	20.6	6	11.5	3	9.7	4	14.3	0	0
Special Senses	3	3.5	15	23.8	11	21.2	2	6.5	5	17.9	2	28.6
Total Adverse Events	29	34.2	59	93.7	34	65.3	10	32.3	21	75	7	100
Total Patients Experiencing AEs	13	15.3	29	46	18	34.6	7	22.6	11	39.3	3	42.9

[1] N = number of patients in each dosage regimen. A patient may have been counted in more than one dosage regimen.

Table 3. Retrospective Study
Distribution of Adverse Events According to System Organ Class (SOC) by Dosage Group

System Organ Class	Marplan® Dose Per Day Number of Adverse Events*						
	<30 mg (N=141)	30-39 mg (N=79)	40-49 mg (N=55)	50-59 mg (N=17)	60-69 mg (N=15)	70+ mg (N=9)	Total (N=237)
Autonomic Nervous System	15	9	4	3	1	0	30
Central and Peripheral Nervous Systems	13	2	1	0	1	2	18
General Body Systems	0	3	4	0	3	1	11
Musculoskeletal	5	7	1	0	0	1	14
Psychiatric	17	9	5	2	1	2	33
Skin and Appendages	0	2	0	0	0	0	2
Urinary System	2	2	0	0	0	0	2
Visual System	1	1	0	0	0	0	1
TOTAL[1]	53	35	15	5	6	5	111

N = number of patients with study data.
**Adverse events may have occurred over more than one dosage group (e.g., some patients experienced adverse events while receiving isocarboxazid in daily doses of 20-30 mg). They are counted in each dosage group but only once in the total number of adverse events.*
[1] Patients may have experienced adverse events over more than one dosage group

Table 4. Demographic Data Summary

Parameter	Marplan® Dose Per Day						
	<30 mg	30-39 mg	40-49 mg	50-59 mg	60-69 mg	70+ mg	Total Patients
Total Patients with Study Data*	141	79	55	17	15	9	237
Age							
N	139	74	54	15	14	9	228
Mean ± SD	60 ± 14	55 ± 16	56 ± 17	53 ± 15	49 ± 15	47 ± 12	58 ± 15
Range							
Sex							
N	139	75	55	16	15	9	231
Female	96	43	32	9	9	5	141
Male	43	32	23	7	6	4	90
Race							
N	139	78	54	16	15	9	234
Caucasian	137	78	51	16	15	9	229
African-American	0	0	0	0	0	0	0
Asian	2	0	0	0	0	0	2
Iranian	0	0	3	0	0	0	3
Length of Treatment (yrs)							
N	122	75	53	16	13	8	203
Mean ± SD	6.6 ± 7.7	4.8 ± 5.3	5.6 ± 6.5	4.1 ± 4.6	5.0 ± 6.8	6.0 ± 6.5	7.9 ± 7.4
Range							

N = number of patients for whom physicians provided data in each category
** Patients' data may fulfill criteria for more than one dosage group.*

BEST POSSIBLE COPY

NDA SUPPL AMEND...

ROCHE **Hoffmann-La Roche**

Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199

Direct Dial 201-235-4692

December 16, 1988

11-30-91
Sponsor has not yet submitted safety data. will issue approval date only when all required data is submitted /S/

Division of Neuropharmacological Drug Products
Center for Drug Evaluation and Research, HFD-120
Attn: DOCUMENT CONTROL ROOM 10B-30
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: **Marplan (isocarboxazid) Tablets - NDA 11-961**

Reference is made to the Agency's non-approvable letter dated June 24, 1988 for supplemental submission S-017 for the above-mentioned product and Hoffmann-La Roche's letter of July 1, 1988 indicating our intent to amend this application.

We are herewith amending this application and submitting a statistical reanalysis of the efficacy data for the Davidson Study as per your June 24, 1988 letter. This reanalysis excludes patients in the Davidson Study who received Marplan doses of 80 mg/day and substantiates the efficacy of Marplan for atypical depression at doses up to 60 mg/day in that study.

In response to your concerns about insufficient safety data for Marplan at doses in the recommended dose range, we are currently reviewing all clinical data available for this product including clinical studies, postmarketing experience, published literature and data on file in order to assess the currently available safety information. Once this review is complete, we intend to request a meeting with the Agency to discuss if and what additional safety information is necessary for this application.

If you have any additional questions concerning this submission, please contact the undersigned at 201-235-4692.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J. Jack

Margaret J. Jack
Manager,
DRA and Data Services
Drug Regulatory Affairs

MJJ/cs
Attachment
HLR No. 88908

Review and Evaluation of Clinical Data
NDA 11-961/S-017

Sponsor: Hoffman-LaRoche

JAN 4 55 PM 1988
JAN - 5 1988

Drug: Marplan (isocarboxazide) Tablets

Drug Category: Antidepressant

Material Submitted: Original supplement (S-017) dated August 28, 1981 (30 volumes); October 22, 1987 amendment (4 volumes); October 27, 1987 amendment (1 volume).

Background

The original supplement (August 28, 1981) was submitted in response to a Federal Register notice (July 14, 1978) that stated the conditions under which isocarboxazide tablets could remain on the market. One of the requirements was the conduct of at least two adequate and well controlled studies to determine whether or not this product is effective. [Note: As a result of the DESI review, Marplan has an interim labeling which classifies 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.] As a result of meetings and discussions with the Agency, the sponsor developed a protocol designed to compare Marplan and placebo in the treatment of patients with "atypical depression." Three different investigators (Davidson, Giller and Zisook) independently conducted studies utilizing this protocol, and the results were submitted in the August 28, 1981 supplement. These data were reviewed by Dan Marticello of the Division of Biometrics (August 4, 1982), who concluded that, while two of the studies looked fairly positive (Davidson and Giller), no conclusions could be drawn about the efficacy of Marplan from these studies since many patients were excluded from the efficacy analysis. The sponsor had used a rule excluding patients from the analysis if they had not participated in the study for a minimum of three weeks.

In a July 13, 1987 teleconference with representatives of Hoffman-La Roche, Jay Levine (of Biometrics) and I asked the sponsor to focus on the Davidson and the Giller studies and to conduct a reanalysis for five variables (HAM-D total score, HAM-D depressed mood item, HAM-D retardation factor, physician global change score and Covi anxiety score) on intent-to-treat samples for these two studies (i.e., all patients randomized who received at least one dose of drug and for whom assessments were available at baseline and at least one follow up time). We asked for last-observation-carried-forward and observed-cases analyses to be done at each week of these six week studies, in order to permit us to assess the effect of dropouts on the outcomes. We agreed that analysis of covariance was the appropriate statistical test. The issue of a difference in duration of depressive symptoms between the Marplan

and placebo groups in the Giller study was raised. We suggested that adding this variable as a covariate in the analysis of covariance might be preferable to the approach used in the 1981 supplement (i.e., adding a term to the model). We asked for copies of the SAS printouts, and indicated that it would not be necessary to rewrite the reports or create new tables in this submission. Finally, we expressed our concern about the lack of data to support the safety of the higher dose range for Marplan suggested in the labeling proposed in the August 28, 1981 supplement (i.e., up to 80 mg/day).

The October 22, 1987 submission is a response to our requests in the July 13, 1987 meeting. Jay Levine has reviewed the reanalyzed efficacy data and has concluded that these reanalyses confirm our earlier impression that the Davidson and Giller studies demonstrate the antidepressant efficacy of Marplan.

The sponsor has also addressed the safety issue. The protocol provided for dosing up to 80 mg/day with Marplan, a level considerably above the maximum recommended dose of 30 mg/day in current labeling for Marplan. While in the original supplement (August 28, 1981) the sponsor proposed labeling that recommended dosing up to a maximum of 80 mg/day, in the October 22, 1987 amendment, the maximum recommended dose is 50 mg/day.

This review will focus on the following issues:

1. Safety of Marplan at the higher doses utilized in the Davidson, Giller and Zisook studies, and the adequacy of these data as a basis for the proposed higher maximum dose.

2. The adequacy of the efficacy data from the Davidson and Giller studies, and the adequacy of the maximum 50 mg Marplan dose proposed in the sponsor's current labeling recommendations.

3. "Atypical Depression" as the sponsor's proposed indication for Marplan.

1. Safety

Extent of Exposure:

The following table enumerates the patients exposed to Marplan or placebo in the 3 studies included in this supplement:

	Marplan	Placebo
Davidson	22	22
Giller	30	30
Zisook	35	35
Total	87	87

Patients assigned to Marplan were to be started on 10 mg bid, with increases of 1 tablet every 2 to 4 days, to attain a total dose of 40 mg/day by the end of the first week. Doses were then to be increased by 1 tablet every 2 to 4 days, as tolerated, until a therapeutic effect was achieved, but with a maximum limit of 8 tablets/day. Doses were to be administered on divided schedules ranging from 2 a day to 4 a day. The planned treatment was for 6 weeks. Patients were to be seen and assessed at weeks 1, 2, 3, 4 and 6.

The mean Marplan dose actually received overall was 38.7 mg/day. Of the 87 patients who received Marplan, 51 received daily doses of 50 mg/day or more for at least part of the 6 week period. The following table provides greater detail on the actual extent of exposure at doses greater than 50 mg/day, as follows: mean dose for patients in each study; an enumeration of patients in each study whose mean dose was greater than 50 mg/day; the mean dose for the patient with the highest mean dose of all patients in each study; an enumeration of patients in each study receiving a maximum dose of 60, 70 or 80 mg.

	Mean Dose by Study	Mean Dose Greater than 50 mg	Highest Mean Dose	Maximum Dose 60 mg	70 mg	80 mg
Davidson	40 mg	4	58 mg	6	2	3
Giller	43 mg	8	56 mg	14	0	1
Zisook	34 mg	2	53 mg	5	2	0

In summary, 38 percent (33/87) of the patients received a dose of greater than 50 mg/day at some time during their participation. However, only 14 of the 87 patients had a mean dose level greater than 50 mg/day. Even among these patients, the highest mean dose was 58 mg/day.

Adverse Events:

The sponsor prepared a table (Sponsor's Table 6, included as Appendix 1) comparing adverse events experienced by patients during dosing of greater than or equal to 50 mg/day compared to dosing at less than 50 mg/day. They determined that the percentages of patients experiencing adverse events (both overall and adverse events rated as severe) were comparable for both groups.

Adverse event experiences in the individual studies were as follows:

a. Davidson

There were slightly (but clinically insignificant) greater decreases in blood pressure and pulse rate in Marplan patients compared to placebo patients, over the course of the study. There were no

laboratory changes of clinical significance. One of the 22 Marplan patients dropped out for adverse experiences (EDP0016-sweating, weakness, urinary retention and hyperreflexia). One placebo patient also dropped out for adverse experiences. Overall, 68% of Marplan patients reported ADRs compared with 50% of placebo patients. There were no serious ADRs, Marplan was generally well tolerated, and the reported ADRs were consistent with the current Marplan labeling. The following adverse events were more common in Marplan patients than in placebo patients: drowsiness, lethargy, muscle contraction, weakness, dry mouth, sleep disturbance, blurred vision and dizziness.

b. Giller

There were slightly (but clinically insignificant) greater decreases in blood pressure and pulse rate in Marplan patients compared to placebo patients over the course of the study. One Marplan patient (EDP0017) had increases in SGOT (a maximum of 499) and SGPT (a maximum of 118) after 6 weeks of treatment, but these levels returned to normal after discontinuation. This patient experienced no clinical symptoms. Another Marplan patient (EDP0052) had a slight increase in SGPT (maximum of 71), which was thought to be alcohol related. Another Marplan patient (EDP0009) had an increase in blood pressure after eating cheese, but this was judged to be a mild reaction, and the patient was continued in the study. One of the 30 Marplan patients dropped out for adverse experiences (EDP0020-facial swelling, folicular papules on the toes, heavy feeling). One placebo patient also dropped out for adverse experiences. Overall, 45% of Marplan patients reported ADRs compared with 14% of placebo patients. There were no serious ADRs, Marplan was generally well tolerated, and reported ADRs were consistent with the current Marplan labeling. The following adverse experiences were more common in Marplan than in placebo patients: increased blood pressure, orthostatic hypotension, ejaculatory difficulties and dizziness.

c. Zisook

There were slightly (but clinically insignificant) greater decreases in blood pressure and pulse rate in Marplan patients compared to placebo patients, over the course of the study. There were no laboratory changes of clinical significance. Nine of the 35 Marplan patients dropped out for adverse experiences: EDP0003-lethargy, peripheral edema, urinary frequency, leg numbness, dizziness; EDP0009-orthostatic hypotension, paresthesia; EDP0024-syncope, constipation, dizziness; EDP0032-panic, tremor; EDP0033-dry mouth, urinary retention, impotence, blurred vision; EDP0040-hyperactivity, orthostatic hypotension, thoughts racing, sleep disturbance, increased SGOT; EDP0048-headache, insomnia, dizziness; EDP0058-nervousness, sweating, palpitations, headaches; EDP0061-syncope, constipation, dry mouth, urinary hesitancy,

dizziness. Two placebo patients also dropped out for adverse experiences. Overall, 74% of Marplan patients reported ADRs compared to 51% of placebo patients. There were no serious ADRs, and the reported adverse experiences were generally consistent with the current Marplan labeling. The following adverse experiences were more common in Marplan than in placebo patients: syncope, orthostatic hypotension, dry mouth, nausea, urinary hesitancy, headache, sleep disturbance, tremor and dizziness.

The sponsor also included a paper by Davidson summarizing results of a separate study comparing Marplan at 2 doses: 20 patients at 30 mg and 19 at 50 mg. Only 1 of the 50 mg patients discontinued for an adverse experience (dizziness). Slightly more adverse experiences occurred at the 50 mg dose (0.4/patient at 30 mg vs. 1.0/patient at 50 mg). Marplan was generally well tolerated at both dose levels.

Comment:

While nothing catastrophic happened among the 87 patients who received Marplan in these 3 studies, and the adverse effects observed are generally consistent with the currently approved labeling for Marplan, this limited experience is simply not sufficient to provide reassurance about the safety of Marplan use in the dose range permitted in these studies (i.e., up to 80 mg/day). Even if we were to accept the sponsors current recommendations for a maximum Marplan dose of 50 mg/day (which I argue against in section 2, "Efficacy"), these data would still not be sufficient.

Once a decision can be made regarding an appropriate maximum recommended dose (see section 2, "Efficacy"), the sponsor will need to obtain additional safety data for a sufficient number of patients treated in this recommended dose range. This could be an open trial, and would need to complete at least 500 subjects, including several hundred at the higher doses in the recommended range.

2. Efficacy

As noted in the Background section, I will focus here only on the Davidson and Giller studies, since the Zisook study was essentially a negative study which did not discriminate Marplan from placebo (see review by Dan Marticello). The protocol utilized by Davidson and Giller in their independently conducted studies provided for a comparison of Marplan and placebo in outpatients with "atypical depression" [Note: A discussion of the entry criteria and a characterization of the patients actually entered into these studies will be presented in section 3, "Atypical Depression."] The plan was for randomized, double blind, parallel group comparisons of Marplan and placebo over a six week treatment period. [Note: The dosing schedule and actual doses received were fully described in section 1, "Safety."] Patients were seen and assessed at weeks 1, 2, 3, 4 and 6. We asked the sponsor to focus on the following behavioral measures obtained at these visits: HAM-D (Total Score, Depression Item, Retardation Factor), Physicians Global Change Score, Covi Anxiety Scale.

We asked the sponsor to focus on intent-to-treat samples for these two studies, and to conduct last-observation-carried-forward and observed cases analyses at each assessment time (see discussion in Background). My comments on the efficacy data will be brief, and will focus on the salient findings from these two studies. [Note: The reader is referred to the statistical reviews by Dan Marticello (August 4, 1982) and Jay Levine (November 2, 1987) for more complete assessments of these data.]

Of the 60 patients actually entered into the Giller study (Marplan-30; placebo-30), only 57 were actually considered for analysis in the October 22, 1987 amendment (Marplan-29; placebo-28), since the additional 3 patients were not part of the database at the time of the original analysis for the August 28, 1981 submission, and the sponsor wanted the analyses to be comparable. Of these 57 patients, only 54 met the criteria for the intent-to-treat sample (Marplan-28; placebo-26). The numbers (and percentages) of patients from this intent-to-treat sample actually participating at various times during the Giller study were as follows:

GILLER

Groups	Numbers and Percentages of Patients Participating (by week)				
	1	2	3	4	6
Marplan	28 (100%)	27 (96%)	25 (89%)	25 (89%)	22 (79%)
Placebo	26 (100%)	23 (88%)	21 (81%)	13 (50%)	13 (50%)

Of the 44 patients actually entered into the Davidson study (Marplan-22; placebo-22), only 37 met the criteria for the intent-to-treat sample (Marplan-20; placebo-17). The numbers (and percentages) of patients from this intent-to-treat sample actually participating at various times during the Davidson study were as follows:

DAVIDSON

Groups	Numbers and Percentages of patients participating (by week)				
	1	2	3	4	6
Marplan	20 (100%)	17 (85%)	16 (80%)	14 (70%)	11 (55%)
Placebo	16 (94%)	17 (100%)	14 (82%)	12 (71%)	9 (53%)

Results:

The following table provides the p-values for Marplan-placebo comparisons (two-tailed) in the analysis of covariance for the Giller study. In all comparisons, Marplan was favored over placebo numerically. The reader is referred to Jay Levine's review for the adjusted means and mean differences for the 5 variables of interest.

GILLER

Variable	P-values for Marplan-Placebo Comparisons (by week)				
	1	2	3	4	6
Global Improvement	.810	.712	.031	.014	.002
HAM-D Dep. Mood	.572	.987	.009	.002	.001
HAM-D Ret. Factor	.367	.996	.157	.155	.001
HAM-D Total	.585	.919	.015	.013	.001
Covi Anx.	.841	.445	.008	.001	.001

The following table provides the p-values for the Marplan-placebo comparisons (two-tailed) in the analsis of covariance for the Davidson study. In all comparisons, Marplan was favored over placebo numerically. The reader is referred to Jay Levine's review for the adjusted means and mean differences for the 5 variables.

DAVIDSON

Variable	P-values for Marplan-Placebo Comparisons (by week)				
	1	2	3	4	6
Global Improvement	.849	.389	.085	.028	.073
HAM-D Dep. Mood	.563	.206	.174	.007	.019
HAM-D Ret. Factor	.384	.968	.250	.000	.005
HAM-D Total	.597	.548	.283	.043	.033
Covi Anx.	.224	.470	.174	.114	.033

Comments:

The Giller study provides strong evidence for the effectiveness of Marplan on 4 of the 5 variables (i.e., all except the HAMD retardation factor) by week 3, with a persistence of these effects through week 6. By week 6, the retardation factor was also statistically significantly superior to placebo.

While the Davidson study does not demonstrate statistically significant results as early as the Giller study, Marplan is favored over placebo on 4 of the 5 variables (i.e., all but the Covi anxiety scale) by week 4. These results are generally persistent through week 6, at which time Marplan also beats placebo on the Covi anxiety scale.

For both studies, most of the significant findings occurred initially at a point when at least 70% of both treatment groups were still participating.

As noted in the Background section, the sponsor is now recommending a maximum Marplan dose of 50 mg/day in the labeling proposal provided with the October 22, 1987 amendment, despite the actual maximum dose of 80 mg permitted in the two studies supporting the effectiveness of Marplan. Jay Levine has argued in his review that, since 54% (15/28) of the patients in the Giller study and 55% (11/20) of the patients in the Davidson study received doses greater than 50 mg/day at some time during their course of participation, 50 mg is not reasonable as a maximum dose (from the standpoint of efficacy). He suggests a maximum dose of 60 mg would be more reasonable, since only 4% (1/28) of the patients in the Giller study and 25% (5/20) of the patients in the Davidson study received a dose greater than 60 mg. I agree with this argument for the Giller study, since one patient is unlikely to have determined the outcome of that study. However, for the Davidson study, it is not so clear that those 5 patients (out of 20) who received Marplan doses of 70 or 80 mg for at least part of their participation may not have had an important influence on the outcome. Therefore, I am not inclined to agree that accepting a maximum dose recommendation of 60 mg is reasonable, at least based on the Davidson study, unless the sponsor can demonstrate (perhaps with a reanalysis of the Davidson study which excludes those 5 patients) that the Davidson study provides support for a 60 mg maximum dose. Otherwise, it will be necessary to either 1) recommend 80 mg as the maximum dose, and also provide safety data to support this higher dose, or 2) conduct one additional study utilizing 60 mg as the maximum dose, in which Marplan can be demonstrated to be effective.

3. Atypical Depression

The sponsor has proposed that Marplan be indicated for "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."

However, there is no consensus as yet regarding a definition for the term "atypical depression," and it is not included as a recognized category in DSM IIIR (third edition, revised, 1987). Davidson, et al [Davidson RT, et al. Atypical depression. Archives General Psychiatry 39: 527-534, 1982] suggest that the term "atypical depression" generally refers to either depression accompanied by severe anxiety (type A) or by atypical vegetative symptoms, i.e., increased appetite, weight, sleep or libido (type B). They suggest that the term is too vague, and recommend instead the use of standard nomenclature. Ronald Pies, another expert on atypical depression, agrees that the term is not consistently defined and overlaps with several diagnostic categories, including borderline personality disorder. [Pies R. Atypical Depression. Psychiatric Times, Volume IV, Number 5, May 1987].

The study protocol instructed investigators to enter nonpsychotic outpatients in whom the "most prominent disturbance was a relatively sustained mood of depression with significant levels of anxious, somatic, phobic and/or panic symptoms." The selection criteria included the following:

a) All patients had Dysphoric Mood (described as depressed, sad, blue, hopeless, low, or down in the dumps).

b) Two or more of the following symptoms were present:

   1) Complaints or evidence of diminished ability to think or concentrate, such as slowed thinking, or indecisiveness (not an obvious formal thought disorder).

   2) Loss of energy, fatigability, or tiredness.

   3) Loss of interest or pleasure in usual activities, including social contact or sex.

c) In addition, two or more of the following symptoms were present:

   1) Poor appetite or weight loss or increased appetite or weight gain (change of one pound a week over several weeks or ten pounds a year when not dieting).

   2) Sleep difficulty or sleeping too much.

   3) Psychomotor agitation or retardation (but not mere subjective feeling of restlessness or being slowed down).

   4) Feelings of self-reproach or excessive or inappropriate guilt.

   5) Recurrent thoughts of death or suicide, or any suicidal behavior.

6) Nonverbal manifestations of depression such as tearfulness or sad face.

7) Pessimistic attitude.

8) Brooding about past or current unpleasant events.

9) Preoccupation with feelings of inadequacy.

10) Demandingness or clinging dependency.

11) Self-pity.

12) Excessive somatic concern.

d) Depressive symptoms were present for at least one month.

e) Moderate or greater depressive symptomatology--as reflected by a minimum baseline total score of 20 on the Hamilton Depression Scale (ECDEU-NIMH 24-item version).

f) Moderate or greater anxiety symptomatology--as reflected by a minimum baseline total score of 8 on the Covi Anxiety Scale with a minimum baseline Somatic Item score of 3.

Patients diagnosed as suffering from panic attacks were considered suitable for inclusion provided they met the depression criteria. Patients with previous alcohol or drug abuse considered secondary to an anxiety or depressive disorder could be included provided they had been free from these problems for at least one year, had normal liver function tests at baseline, and met the other criteria.

It should be noted that these selection criteria overlap extensively with the dianostic criteria for "major depressive episode" as defined in DSM IIIR. The major difference is the additional requirement for significant levels of anxiety, somatic, phobic and/or panic symptoms in these study populations.

The baseline scores on the HAM-D and the Covi anxiety scale for Marplan patients confirm that the patients selected had significant depression along with significant anxiety: Davidson (mean HAM-D total=22, mean Covi=8); Giller (mean HAM-D total=27, mean Covi=9).

Consequently, I think it would be more appropriate to characterize the patients in the Davidson and Giller studies using DSM IIIR terminology. Furthermore, given 1) the significant risk of adverse drug interactions between this monoamine oxidase inhibitor (MAOI) and sympathomimetic drugs, and 2) the lack of any demonstrated advantage of Marplan over standard antidepressants, I feel that Marplan should not be an antidepressant of first choice. This position is consistent with current labeling for the only other two MAOIs approved for use in depression (i.e., Nardil and Parnate). Therefore, I recommend the following wording for the Indications section of the Marplan labeling:

Marplan is indicated for the treatment of depression that is associated with clinically significant anxiety. The efficacy of Marplan was established in two six week trials with nonpsychotic, depressed outpatients whose diagnoses corresponded most closely to the DSM III category of major depressive disorder, but who in addition had prominent associated anxiety symptoms (Covi anxiety score of at least 8).

A major depressive episode implies a prominent and relatively persistent depressed or dysphoric mood that usually interferes with daily functioning (nearly every day for at least 2 weeks); it should include at least 4 of the following 8 symptoms: change in appetite, change in sleep, psychomotor agitation or retardation, loss of interest in usual activities or decrease in sexual drive, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration and a suicide attempt or suicidal ideation.

It is unknown how Marplan compares with more commonly used drugs for treating depression, and it is not the drug of first choice, especially for patients with prominent endogenous features. The antidepressant action of Marplan in hospitalized patients has not been adequately studied.

The effectiveness of Marplan in long term use, that is for more than 6 weeks, has not been systematically evaluated in controlled trials.

Conclusions

The Giller and Zisook studies provide evidence of the antidepressant efficacy of Marplan in patients best characterized as having major depressive disorder (DSM-IIIR) with associated prominent anxiety symptoms. However, unless the sponsor can demonstrate, either by reanalysis of the Davidson study or by conduct of another study, that Marplan is superior to placebo in a dose range up to 60 mg/day, the maximum recommended dose would have to be 80 mg/day. However, whatever is ultimately decided upon as the maximum recommended dose for Marplan, the existing safety data are insufficient to demonstrate the safety of Marplan at doses above the currently recommended maximum dose of 30 mg/day. Consequently, additional safety data are needed to support the safety of Marplan at the higher doses required in these studies to demonstrate efficacy.

In essence, these data and our review of them do not support the effectiveness of Marplan under the conditions of use recommended in current labeling, i.e., at doses up to a maximum of 30 mg/day. Furthermore, they do not provide sufficient evidence to show that Marplan is safe in use at the doses required to render it effective, i.e., up to 80 mg/day (or 60 mg/day, if this can be established). Consequently, Marplan does not meet the current test of law that permits marketing of drugs only if they are the subject of an approved NDA which contains evidence of safety and effectiveness in use under the conditions of use recommended.

Recommendations

1. I recommend that the following comments be conveyed to the sponsor in a nonapprovable letter:

You have partially met the requirements stated in the July 14, 1978 Federal Register notice for keeping Marplan on the market, in that you have conducted two adequate and well controlled studies that demonstrate the antidepressant efficacy of Marplan. We believe that the Davidson and Giller studies are positive, while the Zisook study is not. However, Marplan was administered at doses up to 80 mg/day in both the Davidson and Giller studies, a dose far exceeding the maximum dose of 30 mg/day recommended in currently approved labeling for Marplan.

We note that in your October 22, 1987 amendment, you have recommended a maximum dose of 50 mg/day in your labeling proposal. Since 11 of the 22 patients assigned to Marplan in the Davidson study and 15 of the 30 patients assigned to Marplan in the Giller study received Marplan doses greater than 50 mg during at least part of the trial, we do not agree with this maximum dose recommendation. Since only one patient assigned to Marplan in the Giller study received a dose greater than 60 mg/day, this study would support a maximum dose recommendation of 60 mg/day. However, this is not true of the Davidson study, in which five Marplan patients received doses greater than 60 mg/day during their participation in that trial. You might consider reanalyzing the Davidson study after excluding the five subjects who received doses greater than 60 mg/day, in order to provide additional support for a 60 mg maximum dose recommendation. Alternatively, you would need to conduct a separate study demonstrating the effectiveness of Marplan in patients who are treated with Marplan up to a maximum dose of 60 mg/day. However you choose to resolve this issue, you need to provide adequate support for the effectiveness of the dose range to be recommended in the labeling. Based on currently available data, we would only be willing to accept a maximum dose recommendation of 80 mg/day.

Once the issue of maximum recommended dose is resolved from the standpoint of efficacy, the issue of safety needs to be addressed. Whether the maximum recommended dose ultimately agreed upon is 60 or 80 mg/day, the safety data you have provided are insufficient. While nothing catastrophic happened to the patients who received Marplan in your studies, only 87 patients actually received Marplan, and an even smaller number received Marplan at the higher doses in the permitted dose range. Consequently, we cannot rely on these data as a basis for establishing the safety of a maximum recommended dose of 60 or 80 mg/day. You would need to obtain additional safety experience in the recommended dose range, once this range is established.

For a maximum recommended dose of 80 mg/day, we would want at least 500 additional patients treated with Marplan at doses ranging up to a maximum dose of 80 mg/day, including several hundred receiving doses at the higher end of the permitted dose range. These data could be obtained in an open study.

Should you wish to conduct additional clinical trials, Division of Neuropharmacological Drug Products staff would be happy to meet with you to discuss the design of such studies.

2. I also recommend that we consider notifying the applicant and affording an opportunity for a hearing on a proposal to withdraw approval of this application, in accordance with 21CFR314.150(a)(2)(iii).

/S/ 1-5-88

Thomas P. Laughren, M.D.

Group Leader,

Psychiatric Drug Products Group

cc: Orig.NDA
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Appendix 1

Table 6 - Clinical Adverse Experiences (AEs) in Patients:
Marplan Dosage Above and Below 50 mg/day vs. Placebo
Davidson, Giller and Zisook Studies

	Marplan			Placebo
	Any Dose	Dosage > 50 mg/day	Dosage < 50 mg/day	
Patients Treated	87	51*	86*	87
Number of days on Treatment		1085	1636	
Average Number Days on Treatment		21.3	19.0	
AEs				
Number of AEs	194	79	117	83
Number of Patients with AEs	59	26*	46*	36
Percent of Patients with AEs	67.8	51.0	53.5	41.4
Severe AEs				
Number of Severe AEs	16	6	10	16
Number of Patients with Severe AEs	12	4*	9*	9
Percent of Patients with Severe AEs	13.8	7.8	10.5	10.3

*Some patients experienced AEs at both higher and lower dosages and thus were counted twice.