MEMORANDUM

DATE: October 13, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Director
Office of Drug Evaluation I

&

File, NDA 20-796

SUBJECT: Recommendation for Action on NDA 20-796, for the use of Entacapone in Patients with Parkinson's Disease

On 12/31/98, the Agency issued an Approvable letter to Orion Pharmaceutical for NDA 20-796, for Entacapone (a COMT inhibitor) as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's Disease who are experiencing end of dose "wearing-off" phenomena. The Approvable letter listed 3 main areas of concern which needed to be further addressed by the sponsor:

1) **Effectiveness**-although the sponsor had submitted the results of 2 randomized controlled trials in which the protocol specified primary outcome measures achieved statistical significance, only 1 (Study 33, performed in Scandinavia) of the 2 yielded robust results, with the results of the second study (Study 44, performed in the US and Canada) appearing to depend on one center and yielding marginal results on secondary outcomes, as well as demonstrating a relatively small treatment effect. An additional study, Study 52, was clearly negative.

We were aware at the time of the letter of 2 on-going studies, Studies 63 and 65, which appeared capable by design of providing useful effectiveness data, and the letter implied that data from one or both of these studies would be required for approval.

2) **Safety**-the letter listed a number of safety related concerns and requests (e.g., re-analyses of the mortality data and of certain specific adverse events, such as hypotension, falls, relationship of certain ADRs to weight, vital sign and EKG data, etc.).

3) **Biopharmaceutics**-the sponsor wished to market formulation 55, which was not studied in controlled trials (formulation 54 was studied). The difference in formulations was minor (slight color change) and was of the sort that would not have required a bioequivalence trial. However, the sponsor performed a BE trial, and while AUC was equivalent, Cmax was not, with formulation 55 yielding a Cmax that

fell outside the upper bound for equivalence (90% 98.9-140.0%). The letter asked the sponsor to further justify the approval of formulation 55.

In addition to these major issues, the sponsor was also requested to validate the mouse carcinogenicity study, or commit to performing a repeat study in Phase 4. In addition, the sponsor was asked to adopt specific dissolution specifications, and evaluate the interaction of entacapone with CYP450 enzymes. In addition, of course, there were multiple requests for information, clarification, etc., embedded in the draft labeling, though they were relatively minor.

The Agency met with the sponsor on 2/11/99, at which time these issues were discussed, in particular the necessity for additional effectiveness data. Although the sponsor argued that this data was unnecessary, the Agency determined at an internal meeting on 2/23/99 that we wanted the sponsor to submit the results of Study 63, a multi-center study performed in Austria and Germany. This was communicated to the sponsor. Because this study was designed as a safety study, even though measures of effectiveness were assessed, none were designated as primary. In addition, there was no requirement that patients have a fluctuating course to be enrolled (these were the type of patients enrolled in the previous studies, and constituted the type of patient for which the drug was proposed to be indicated). The sponsor submitted a response to the Approvable letter on 4/19/99.

At an internal meeting on 6/14/99 (attended by staff of the division, the reviewing statisticians, and Dr. Temple), the Agency determined that the following 3 measures would be analyzed as primary: 1) UPDRS Part II (ADL), 2) UPDRS Part III (motor function), and 3) Time Spent "ON".

The sponsor's response has been reviewed by Dr. Richard Tresley of the Division (review of Study 63 dated 7/20/99), Dr. Michael Sevka of the Division (review of the safety data dated 10/6/99 signed the same day by Dr. Burkhart, Safety Team Leader), Dr. Kun He of Biometrics (statistical review of Study 63 dated 9/15/99), Dr. Paul Roney, pharmacologist (review dated 8/6/99), and Dr. Sayed Al-Habet of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 9/3/99). In this memo, I will briefly review the issues and offer my recommendation for action on the NDA.

Effectiveness

As noted above, no primary efficacy measures were prospectively defined. The protocol did, however, (via amendment) establish a prospective definition of fluctuators, which differed from that employed in the earlier studies. For Study 63, a fluctuator was defined as a patient who experienced at least one-half hour of OFF time as recorded in their diary, as well as at least 4 ½ hours of OFF time for a 3 day period by diary (this definition was less stringent than those in earlier studies, in which, in one study for example, a patient needed at least 3 hours of OFF time/day).

A total of 301 patients (197 entacapone, 104 placebo) were randomized at 32 centers in Austria and Germany. As noted by Drs. Tresley and He, the comparisons between drug and placebo for UPDRS II and III reached statistical significance (p=0.015 and 0.041, respectively) but the comparison for total ON time did not (p=0.29). This latter comparison included only those patients who met the definition of fluctuator (over 85% of the total) and, despite the difference in definition of fluctuator in this study compared to that used in the 2 previous studies, the mean total ON and OFF times at baseline in this study were very comparable to those in the earlier study. For example, the mean total ON time and OFF time at baseline in this study were about 10 and 6 hours, respectively, compared to about 9 and 5 hours in Study 33. Drs. Tresley and He describe the results of the analyses of the many secondary outcomes assessed, and though they generally favor entacapone numerically, many fail to reach nominal significance.

Safety

Dr. Sevka has performed a detailed review of the sponsor's safety submission. As he notes, and as Dr. Burkhart agrees, there is little new in the data, and the issues about which we expressed concern in the Approvable letter have been adequately addressed. In particular, our concerns regarding the appropriate identification and classification of falls and orthostatic hypotension have been addressed and no specific adverse effect of entacapone has been identified. Similarly, questions about the incidence of specific adverse events by weight, as well as questions about any effect of entacapone on vital signs and EKG parameters have been addressed, and no specific adverse effect of the drug has been identified.

It should be noted that the sponsor identified no European post-marketing cases of rhabdomyolosis in response to our questions about this. However, we have received several reports (which are difficult to assess) to the IND since the sponsor's submission; these will be described in the labeling.

Biopharmaceutics

The sponsor continues to argue that entacapone absorption is highly variable, making Cmax an unreliable parameter on which to base bioequivalence between formulations.

Across studies, the CV for Cmax was about 45%, compared to about 25% for AUC, and additional evidence for entacapone's variability when given orally comes from a study in which the CV for AUC when given as an oral solution was about twice that when it was given intravenously (the CV for the Cmax of the oral solution was about that of the oral AUC).

The sponsor has also submitted some safety data in patients who received formulation 55. Apparently, the sponsor has documented that 84 patients received formulation 55 in Study 62, an open label extension study. They have compared ADR incidences for these 84 patients who received 1 year of double blind treatment with formulation 54 and then

up to 2 years of open label treatment with formulation 55 (see Dr. Sevka's 10/6/99 review, page 12). The table presented by Dr. Sevka includes only those ADRs which occurred at an incidence of at least 3% on formulation 55 **and** also at an incidence greater on 55 compared to 54. For these reasons, as well as the differences in conditions of use (open, longer duration), it is difficult to interpret these data.

Other Issues

Finally, most of the other issues in the Approvable letter (and draft labeling) have been addressed. Specifically, the sponsor has agreed to adopt the dissolution specifications proposed by OCPB, they have examined the interactions of entacapone and the CYP450 system.

However, as noted by Dr. Roney in his 8/6/99 pharmacology review, the sponsor has failed to validate the mouse carcinogenicity study. Specifically, the Agency informed the sponsor in the Approvable letter that they would have to demonstrate either that the absorption of entacapone was saturated at doses above 100 mg/kg (the mid-dose group) or that 100 mg/kg was appropriate as a back-up dose (i.e., about half the MTD-there were an unacceptable number of deaths in the high dose group-600 mg/kg). Both Drs. Roney and Fitzgerald agree that there is evidence that 100 mg/kg is considerably less than one half the MTD, and that saturation of entacapone absorption has not been demonstrated at this dose. For these reasons, the sponsor will be asked to commit to completing an appropriate mouse carcinogenicity in Phase 4.

Labeling

The labeling accompanying this package differs from that accompanying the Approvable letter in many particulars. The following represent the major differences:

1) CLINICAL PHARMACOLOGY

Pharmacokinetics

We asked the sponsor to describe certain aspects of the relationship between entacapone dose and COMT inhibition; they have done this.

Clinical Studies

This section now includes a description of the results of Study 63.

2) WARNINGS

Drugs Metabolized by COMT

We asked for a description of a patient who experienced ventricular tachycardia while receiving entacapone and propanolol; this was provided.

3) PRECAUTIONS

Hypotension/Syncope

We asked the sponsor to supply incidences of these events in various settings (e.g., controlled trials, etc.). There were minor numerical differences between drug and placebo, but the section has been left in.

Hallucinations

Again, the sponsor supplied requested incidences. A proposed second paragraph intended to describe more detailed information about the hallucinations (e.g., time course, responsiveness to lowering l-dopa dose, etc.) has been removed.

Other Events Reported with Dopaminergic Therapy: Rhabdomyolosis and Hyperpyrexia and Confusion

Minor changes have been made to reflect the few complicated post-marketing cases of rhabdomyolosis and the few cases of hyperpyrexia/confusion. The latter cases are poorly described, but they do not contain explicit descriptions of the events being related to withdrawal of drug (the language in the rest of this section describes these events as occurring with other dopaminergic agents on withdrawal or dose reduction). For this reason, a sentence has been added that states that no cases have been reported in association with dose reduction or withdrawal of entacapone.

Falls and Fractures

This section has been removed, because re-analyses suggest that there is no greater incidence of these events on drug compared to placebo

Anemia

This section has been restructured.

Renal Toxicity

This section has been newly drafted (in the Approvable letter, we asked the sponsor to draft this section).

Hematuria

This section has been removed; re-analyses suggested that this was not clearly related to treatment with entacapone.

Drug Interactions

The sponsor has drafted a section reflecting the results of their studies of in vitro human CYP enzymes.

4) ADVERSE REACTIONS

The sponsor has provided specific incidences in various places, as requested, and has constructed the Controlled Trials Adverse Event Table.

We have sent up the labeling without the Other Adverse Events Observed section. The sponsor's proposed list is extremely long and not particularly useful. We suggest that this list not be included in labeling, not only because it is fairly uninformative, but also because we are concerned that inclusion of an event in this list makes it "labeled", which may result in post-marketing cases not being reported (if they are serious) in real time.

COMMENTS

The sponsor has submitted the requested additional effectiveness data and safety re-analyses. I believe Study 63, despite the post hoc nature of the choice of primary outcome measures, provides additional evidence of the effectiveness of entacapone in Parkinson's patients with wearing off phenomena. The safety re-analyses have not revealed any issue that would preclude approval, and the labeling accompanying this package adequately describes the risks as we currently understand them. We have negotiated this labeling with the firm (most recently in a telephone conversation of 10/12/99), and they are in agreement with this version of labeling. Importantly, they have agreed to the exclusion of the Other Adverse Events Observed section.

I have reconsidered the acceptability of approving formulation 55. I believe that the data do support the view that the rate of entacapone absorption (and hence Cmax) is quite variable. I am particularly impressed by the multiple failures (in either direction) of Cmax in the several bioequivalence studies comparing various lots and formulations (in a personal conversation with Dr. Al-Habet, he tells me that these studies compared either different lots of the same formulations or trivially different formulations). This variability, coupled with the fairly trivial differences between formulations 54 and 55 (again, as noted by Dr. Al-Habet, these changes would not require the performance of a bioequivalence study), allow me to conclude that formulation 55 is acceptable without further supporting data.

Finally, I agree with Drs. Roney and Fitzgerald that the sponsor has not adequately validated the mouse carcinogenicity study and therefore must commit to conducting an adequate mouse study in Phase 4.

RECOMMENDATION

I recommend that the NDA be approved with the accompanying labeling, and that the attached Approval letter be issued.

/S/

APPEARS THIS WAY
ON ORIGINAL

Russell Katz, M.D.

Cc:
NDA 20-796
HFD-120
HFD-120/Katz/Kapcala/Sevka/Burkhart/Roney/Fitzgerald/Wheelous
HFD-710/He/Jin
HFD-860/Al-Habet

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: December 23, 1998

FROM: Deputy Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-796

SUBJECT: Supervisory Review of NDA 20-796, for the use of Entacapone in Patients with Parkinson's Disease

BACKGROUND

On October 27, 1997, Orion Corporation submitted NDA 20-796 for the use of entacapone, an inhibitor of catechol-o-methyl transferase (COMT), an enzyme that catalyzes the peripheral metabolism of levodopa to 3-O-methyldopa, in patients with Parkinson's Disease (PD). The decision was made to refuse to file the application, because it did not contain full reports of the serious adverse reactions. These reports were included in a submission dated 1/2/98, and the application was considered filed. The PDUFA date for action on this application is 1/2/99.

The application consists of reports of 2 controlled trials (Studies 33 and 44), each of about 6 months duration, that the sponsor believes support the conclusion that entacapone is effective in patients with PD with fluctuations; that is, in patients who experience periods of reasonably good functioning (ON periods) alternating with periods of poor functioning (OFF periods). They have also submitted the results of a third controlled trial (Study 52), designed to be a 1 year study, but which has had a 6 month interim analysis, as well as results of several much smaller, mostly cross-over studies.

The effectiveness data have been reviewed by Dr. Tresley, medical officer (review dated 11/2/98), and Dr. Japo Choudry, biostatistician (review dated 11/4/98). The clinical safety data have been reviewed by Dr. Michael Sevka, medical officer (review undated), and Dr. Greg Burkhart, safety team leader (review dated 12/16/98). The pre-clinical data have been reviewed by Drs. Thomas Steele (review undated, signed by Dr. Fitzgerald on 12/21/98) and Glenna Fitzgerald (reviews dated 12/21/98). Dr. Al-Habet, biopharmaceutics (review dated 10/28/98) and Dr. Martha Heimann, chemist (reviews dated 7/13/98 and 12/11/98) have also reviewed the submission.

Below, I will briefly review the relevant data, and offer my recommendations for action on the application.

STUDY 44

This was a randomized, double-blind, parallel group, multi-center trial performed in the US and Canada comparing the effects of entacapone and placebo in patients with PD who were experiencing clinical fluctuations (on/off periods).

Patients above the age of 30 with PD (Hoehn and Yahr stages 1.5-4.0 while OFF) receiving a stable regimen of l-dopa/carbidopa of between 4-10 doses/day were eligible for entrance into the study.

The study had the following periods:

1) a 4 week run-in, during which patients were stabilized on their l-dopa
2) a 6 month double blind treatment period, during which the l-dopa dose could be adjusted
3) a 4 week washout period, in which patients were randomly withdrawn from active treatment either after week 24 of treatment or after week 26 of treatment

Patients took a single dose of 200 mg of entacapone (or placebo) with each dose of levodopa/carbidopa.

Patients were to collect 24 hour diary data for the 3 days prior to an evaluation. This information was to include time ON, OFF, ASLEEP. At each evaluation, global ratings (assessments of the patient's condition during the week prior to a visit, and rated by the patient and investigator on a 7 point scale, centered at 0, and ranging from Very Well to Very Poor), UPDRS ratings, ratings of fluctuations in disability, and doses of, and frequency of dosing with, l-dopa, were assessed.

The primary outcome was to be the Change From Baseline in the Proportion of Awake Time Spent ON. This outcome was to be analyzed with a repeated measures analysis of covariance (ANCOVA) with the baseline proportion of ON time as the covariate, utilizing the data from weeks 8, 16, and 24 (at each of these time points, the mean of the 3 day diary data was used as the measure analyzed).

Secondary measures included those described above.

RESULTS

A total of 205 patients (entacapone-103, placebo-102) were enrolled at 18 centers. Although there were various baseline characteristics that differed between treatment groups (most notably a difference between the proportion of patients with a past history of Sinemet CR use-54% of the entacapone patients compared to 40% of the placebo

patients), none of these imbalances appeared to effect the outcome of the trial. The following table displays the disposition of patients throughout the study:

	Entacapone	Placebo
Randomized	103	102
Completed	90	91
D/C for:		
ADR	11	7
Lack of eff	0	0
Other	2	4

The following results were obtained for the primary outcome:

	Baseline	Mean Weeks 8, 16,24	P-value
Entacapone (N=103)	60.0	67.1	
Placebo (N=102)	60.8	63.1	0.0147

These results are obtained on the basis of the analysis of the observed cases. As Dr. Choudry explains in his review (page 5), this is the preferred cohort for a repeated measures analysis (results of the intent-to-treat population are similar).

Analyses of the same measure at all time points individually (Weeks 2, 4, 8, 16, and 24), though not protocol specified analyses, are all nominally significant, and remain so after a reasonable method of adjustment for multiple comparisons is applied (see Dr. Choudry's review, page 5).

Dr. Choudry has examined the results by center. Although a formal test of the treatment by center interaction was "negative" (p=0.24), placebo was numerically superior to entacapone in 9/18 centers. In particular, in 2 centers, the between treatment estimate of effect was greater than 8% in favor of placebo (compared to the overall estimate of about 4.8% in favor of entacapone), and in one center, the estimate was about 25%, in favor of entacapone. An analysis which excluded the 12 patients at this latter center was non-significant, lowering the estimate of the treatment effect to about 3.5 The sponsor suggested that the patients at the center with the greatest difference favoring placebo (Center 23) were milder on average than other patients, and that there might have been errors in the recording of diary data, although they submit no evidence for the latter.

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Secondary Measures

The following table, adopted from Dr. Tresley's review, page 64, displays the results of diary recorded data:

	Entacapone		Placebo		P-value
	Baseline	Wks 8,16,24	Baseline	Wks 8,16,24	
Daily ON time	10.2	11.2	10.3	10.7	NS
Daily OFF time	6.8	5.6	6.6	6.4	<0.01
L-dopa dose	803	710	758	777	<0.001
#of doses	6.2	6.2	6.0	6.2	NS
Mean ON time	10.2	11.2	10.3	10.7	0.04-0.06

The proportion of patients who improved from baseline by at least 1 category on the Patient's global was significantly greater in the entacapone treated patients compared to the placebo patients at the 3 time points, but this was not true for the Investigator's global.

There were no significant differences seen on outcomes related to the UPDRS, or on measures of the daily fluctuation of disability.

Withdrawal

Almost all measures of effect (Percent daily ON time, daily ON and OFF time, UPDRS) were statistically significantly worse than placebo at Days 1 and 2 of withdrawal, in both withdrawal groups (week 24 or 26).

STUDY 33

This was a randomized, double-blind, multi-center, parallel group trial performed in Scandinavia comparing the effects of entacapone to placebo in PD patients experiencing on/off phenomena.

The trial design was essentially the same as that of Study 44. Minor differences included the inclusion of patients receiving treatment with Sinemet CR, and levodopa/benserazide, as well as patients receiving levodopa/carbidopa combinations. A potentially important difference between this study and Study 44 is that in this study, patients were required to be in Hoehn and Yahr categories 1.5-4.0, measured in the ON state. For this reason, although other baseline parameters (duration of disease, daily l-dopa dose, etc.) do not suggest it, it is possible that patients in this study were more severely ill than those in Study 44.

Another slight difference between this study and Study 44 was that in this trial, the withdrawal period began for all patients at the last visit (week 24), and the effects were assessed at week 26.

This trial appeared to have 2 primary outcome measures: 1) the total ON time for an 18 hour day (recorded from 6AM to Midnight), and 2) duration of ON time after the first AM dose.

RESULTS

A total of 171 patients (entacapone-85, placebo-86) were enrolled at 16 centers. The following chart displays patient disposition:

	Entacapone	Placebo
Randomized	85	86
Completed	77	75
D/C for:		
ADR	6	5
Lack of eff	0	3
Other	2	3

The following results were obtained for the outcome **Change From Baseline in Mean ON Time during an 18 hour day** (as in Study 44, the analysis was performed on the observed cases cohort; results are the same for the ITT population):

	Baseline	Mean Weeks 8,16,24	P-value
Entacapone (N=85)	9.3	10.8	
Placebo (N=86)	9.2	9.5	<0.0004

As in Study 44, these differences were all significant at each evaluation (weeks 2, 4, 8, 16, and 24).

The following results were obtained for the outcome **Change From Baseline in Mean ON time after first AM dose**:

	Baseline	Mean Weeks 8,16,24	P-value
Entacapone (N=85)	2.1	2.3	
Placebo (N=86)	2.2	2.1	<0.001

Although not a protocol specified analysis, the sponsor computed the Mean Percent Change from baseline in the Proportion of Awake Time in the ON state, to compare the results of this trial with Study 44. The following results were obtained:

	Baseline	Mean Weeks 8,16,24	P-value
Entacapone (N=85)	62.7	72.0	
Placebo (N=86)	63.8	64.4	<0.001

Secondary Measures

The following table, adopted from Dr. Tresley's review, pages 57 and 59, displays the results of diary recorded data:

	Entacapone		Placebo		P-value
	Baseline	Wks 8,16,24	Baseline	Wks 8,16,24	
Daily OFF time	5.5	4.2	5.3	5.2	<0.001
L-dopa dose	701	614	705	720	<0.001
#of doses	6.1	5.8	6.3	6.3	<0.001
UPDRS (I-III)	38.5	34.1	37.4	36.3	<0.01

In addition, comparisons of Parts II and III, individually, demonstrated statistical significance in favor of entacapone.

Dr. Choudry examined the results by center in this study as well. Here, in only 2 centers was there a "marginally better" outcome favoring placebo over entacapone.

Withdrawal

The changes in essentially all measures (e.g., Daily ON time, OFF time, proportion of ON time, UPDRS, etc.) from Weeks 24 to 26 were significantly worse on entacapone compared to placebo.

STUDY 52

This trial was apparently designed as a trial to primarily assess the safety of entacapone, but it included several measures of effectiveness as well. The trial is a 1 year trial, but an interim analysis of both safety and effectiveness was performed. The results of this interim analysis are included in the NDA.

This was a randomized, double-blind, multi-center, parallel group study performed in Finland, in which patients with PD "needing an enhancement and/or smoothing of levodopa effects" were randomized to entacapone, 200 mg, or placebo, given with l-dopa (2-10 times/day). Patients could receive any l-dopa preparation.

The primary efficacy measure was the change in Subscale III of the UPDRS (Motor subscale), analyzed with an ANCOVA, with baseline score as the covariate. Secondary measures included: sum of UPDRS parts I-III, change in UPDRS parts I, II, IV, V, and VI, globals, change in l-dopa dose, change in the duration of benefit of the first AM dose, and change in the dosing interval.

Apparently, no formal sample size calculations were made.

RESULTS

A total of 326 patients (entacapone-218, placebo-108) were randomized at 20 centers. The following displays patient disposition:

	Entacapone	Placebo
Randomized	218	108
Completed	198	94
D/C for:		
ADR	17	11
Lack of eff	0	2
Other	3	1

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The following table displays the results of the trial. The first line displays the results for the primary outcome measure, Change in UPDRS Part III (motor score):

	Entacapone		Placebo		P-value
	Baseline	Month 6	Baseline	Month 6	
UPDRS-III	23.1	20.8	21.9	20.0	NS
UPDRS-I	1.2	1.3	1.3	1.2	NS
UPDRS-II	9.5	8.9	8.9	8.6	NS
Total-I-III	33.9	31.0	32.1	29.8	NS
L-dopa dose	605	567	662	651	<0.01
# of doses	4.2	4.1	4.3	4.3	NS
Benefit of AM dose	3.7	4.0	3.7	3.8	NS
Dosing interval	4.6	4.8	4.4	4.4	<0.01

There were no significant changes on the globals, nor were there significant differences in the proportion of OFF time.

SAFETY

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Exposure

As noted by Dr. Burkhart, a total of 1773 unique individuals have received at least one dose of entacapone, and more than 750 patients have received treatment for at least 1 year. However, as he points out, the sponsor has not submitted adequately described dose/duration data.

Deaths

Also as noted by Dr. Burkhart, the mortality in controlled trials was slightly greater in the placebo treated patients, although here again, there is a lack of relevant information (specifically, the time between last dose and death). In the overall database, the total of 35 deaths in entacapone treated patients yields rate of about 2/100 patient-years. While there did not, in general, appear to be any specific cause of death to warrant concern, the death of 2 patients secondary to complications related to falls is of considerable concern (see below).

Discontinuations

The risk of discontinuation in the controlled trials (Studies 33, 44, and 52) was about 18% in the entacapone treated patients compared to about 13% in the placebo patients. The risk of discontinuation attributed by the sponsor to adverse events was about 14% to about 9%, in entacapone and placebo patients, respectively.

The most common ADRs resulting in discontinuation were diarrhea, abdominal pain, nausea, dyskinesia, and hallucination.

Serious Adverse Events

According to Dr. Burkhart, the type of events classified as serious generally are similar to the type of event associated with discontinuation. However, as he points out, the sponsor has presented the risks for specific events in an unorthodox way (namely, they have utilized the total number of events as the numerator, rather than calculating the proportion of patients who had at least one such event).

Labs

There appeared to be a decrease in the mean hemoglobin in the controlled trials in patients assigned to entacapone, and a greater risk of decreases of 2 gms or more in entacapone treated patients (9/603, 1.5% entacapone vs. 2/400, 0.5% placebo), although other relevant parameters are not adversely affected (TIBC, ferritin). In addition, the risk of leukopenia (WBC<2800) was greater in the entacapone treated patients (10/603, 1.7%) than in the placebo treated patients (3/400, 0.8%). However, no patients were described has having had agranulocytosis or aplastic anemia. As Dr. Burkhart notes, there is a lack of adequate follow-up for the cases of hematologic abnormalities.

In particular, there seems to be no evidence that entacapone treated patients are at a greater risk of developing elevated liver enzymes than placebo treated patients, and there are no reported cases of liver failure.

Other Adverse Events

As Dr. Burkhart describes, a critical finding that has emerged out of the review team's analysis of the adverse event data is that most, if not all, of the risk for adverse events of interest occurs in the cohort of patients who have a weight at baseline of less than 65 kgs. Of particular interest is the relative risk of about 4 for falls in this group (about 8% in the entacapone treated patients compared to about 2% in the placebo treated patients), and the fact that 2 deaths were related to these events. Of further concern is the review team's finding that the incidence of falls is perhaps greater than that presented by the sponsor because of inappropriate coding (e.g., an adverse event coded as "purpura" is, in actuality, bleeding secondary to a fall). The causes of these falls are not well described. Whether they are as a result of hypotension, syncope, postural instability, or other mechanism is unknown, and will require additional work by the sponsor, as described in Dr. Burkhart's review.

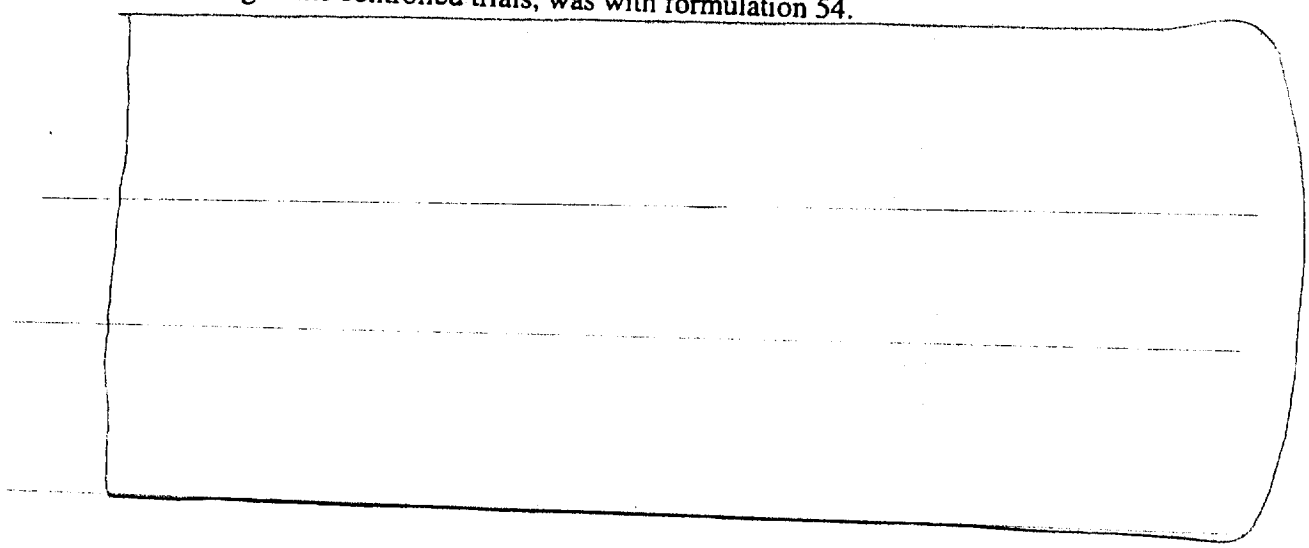
PHARMACOLOGY

Dr. Steele has recommended that the NDA not be approved because the mouse carcinogenicity study is inadequate, secondary to high mortality in the high dose group, leaving the middle dose (100 mg/kg) as the highest dose that could reliably be assessed. As discussed in a CAC memo of 11/24/98, this dose was not demonstrated to be a maximally tolerated dose (MTD). The committee recommended that the sponsor provide evidence that this dose resulted in saturation of absorption, and hence, could be considered an acceptably high dose, as well perform additional histopathology in all animals (which had not been done). Dr. Fitzgerald recommends that the application be considered approvable, with the firm's commitment to initiate these additional relevant studies immediately. If the mouse study cannot be validated, a short term alternative carcinogenicity study might be appropriate, to be completed in Phase 4.

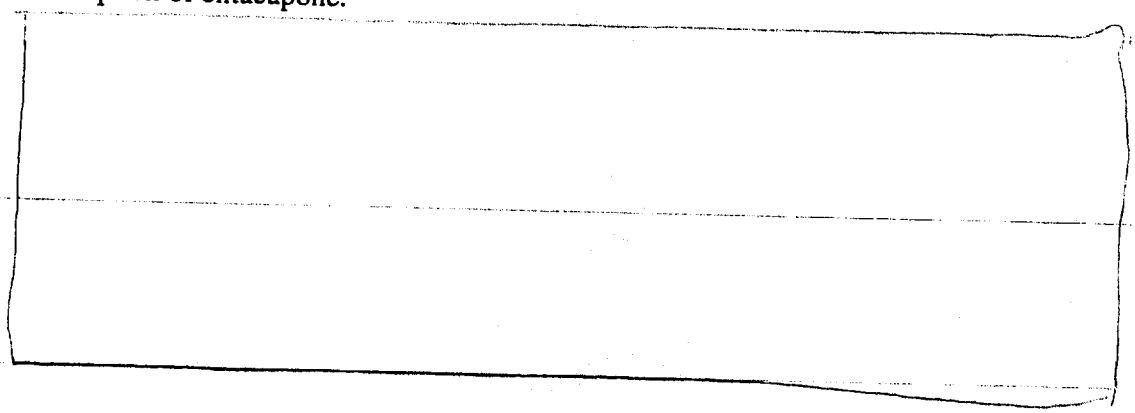
In addition, Drs. Steele and Fitzgerald note the finding of renal adenomas and carcinomas in the rat carcinogenicity study, and have asked the sponsor for additional information about this finding (the sponsor alleges that the mechanism underlying the formation of these tumors is not relevant for people, but that is not a universally held view). Finally, they have requested more detailed information about a finding of chronic nephropathy in rats.

BIOPHARMACEUTICS

The sponsor intends to market a formulation (called 55) that has, for all practical purposes, has not been studied clinically (it has apparently been used in the open extension of Study 33, but represents an unknown proportion of that exposure-2 of the 15 batches used in this extension were of the new formulation). Most of the experience, including in the controlled trials, was with formulation 54.



I do not agree. Although studies might not have been required, they have been done, and we must attend to the results. I have discussed this matter with Drs. Al-Habet and Baweja of OCPB. They are certain that the trivial change in components could not be responsible for the difference in bioavailability, and acknowledge the variability of absorption of entacapone.



COMMENTS

The sponsor has submitted the results of 2 completed randomized controlled trials in patients with PD who are experiencing motor fluctuations. Study 33, performed in Scandinavia, is a strongly positive trial, with statistically significant outcomes on most secondary measures. Study 44, performed in the US and Canada, is clearly positive on its primary outcome, with no consistent pattern of statistically significant outcomes in the secondary measures.

There is some discussion, in the reviews of both Drs. Tresley and Choudry, that the estimate of the treatment effect, especially in Study 44, although statistically significant, did not meet the sponsor's expectations as expressed in the protocol. Specifically, in Study 44, the sponsor expected the proportion of awake time spent "ON" in the entacapone treated patients to be 10% greater than that in the placebo patients; total awake time was considered to be 15 hours. Inexplicably, the sponsor calculated this 10% increase to be 1.5 hours. This is inappropriate; 1.5 hours is 10% of the total wake time, a measure that has nothing whatsoever to do with the effect of the drug. In reality, a 10% increase in the percent awake time compared to placebo would result in an increase in the percent of awake time spent "ON" to about [redacted] ((the proportion of awake time spent "ON" in placebo patients was about 60%), not very different from the actual realized amount of time spent "ON".

In any event, we would not ordinarily be concerned about the discrepancy between the expected size of the treatment effect and the actual estimate realized in the study, and I see no compelling reason to be so here. While it is true that the results of this trial are not as consistent as those of Study 33, and that the responses in the various centers were not as consistent as in Study 33, nonetheless, I conclude that the sponsor has submitted

results of 2 adequate and well controlled trials that constitute substantial evidence of effectiveness for entacapone for patients with PD characterized by clinical fluctuations.

Having said this, I am concerned that the safety of the drug has yet to be adequately characterized. As Dr. Burkhart notes, there is considerable evidence that the serious ADRs, particularly falls, appear to occur almost exclusively in patients with baseline weights under 65 kgs. Further, these ADRs have not been adequately described, or even enumerated, given the potentially misleading way that many of these events have been coded. Given these concerns, it is important to know if the effectiveness of the product is also largely restricted to the low weight cohort.

In addition to this critical lack of information, a number of other ADRs (anemia, etc.) are not yet adequately described or followed up, nor is there an adequate description of dose/duration data.

While I believe that the sponsor has submitted substantial evidence of effectiveness, I am nonetheless concerned that, at this time, we are sufficiently ignorant of the safety profile of entacapone be able to write adequate labeling. Indeed, without an accurate understanding of many of the adverse events (their character, incidence, etc.), it is impossible to say at this time that entacapone will ultimately be shown to be sufficiently safe to justify approval of the application. It is possible, for example, that the rate of serious falls in the low weight group may be sufficiently high to make use of entacapone in this cohort unacceptable, or at least unacceptable without extremely restricted labeling. Further, if it is determined that the evidence for effectiveness arises primarily from the low weight group, the ultimate action on the NDA might be quite different than if there is a dissociation between adverse events and effectiveness (in the former, a case might be made for non approvable; in the latter, labeling that restricts its use to the high weight patients may "solve" the problem).

The appropriate action to take on this application is not obvious. With regard to effectiveness, Study 44 is, in my view, rightly considered one source of data contributing to a finding of substantial evidence, but, as noted above, it is not as clearly positive a trial as Study 33, not only in regard to its lack of consistent results in the secondary measures (with a particular lack of consistent finding of functional improvement), but also in the wide range of responses across centers, where placebo was numerically superior to drug in fully one-half of the centers, and where the analysis of the primary outcome is no longer significant when patients from only 1 center are removed. In addition, as Dr. Choudry notes (page 6 of his review), other analyses of the time spent in the "ON" state do not yield significant results. In addition, with the clearly negative results at 6 months in Study 52, a study that appeared to be adequately designed to detect effectiveness, despite the fact that it was intended to be a "safety study', the case for effectiveness is relatively weak, although, as I stated above, I certainly believe it meets the minimum requirements as ordinarily interpreted. (The sponsor suggests that at least one reason for the failure of Study 52 to detect any meaningful between treatment differences was that non-fluctuators were included in the study; the implication is that non-fluctuators are not expected to respond to entacapone. We have no information about the number of non-

fluctuators in the trial, but beyond, this, tolcapone, an approved COMT inhibitor, has been shown to be effective in non-fluctuators).

On the safety side, the deficiencies noted above, coupled with the lack of an adequate mouse carcinogenicity study, could support the conclusion that this application should be judged Not Approvable.

However, I have no objection to the issuance of an Approvable letter, partly because I have seen no affirmative evidence to date that would preclude approval, although I fully acknowledge that this might change with the submission of additional required data. I also recommend that any Approvable letter should make it clear that considerable work needs to be done to further characterize the safety profile, and that the ultimate decision on the application is somewhat uncertain at this time (for example, the application might not be approved, or it might be approved with considerably different labeling than the draft labeling accompanying this package).

There are several other issues that need to be addressed in the letter.

First, Dr. Fitzgerald's recommendations regarding the mouse carcinogenicity deficiencies, as well as those related to the finding of kidney tumors and chronic nephropathy in the rat, should be transmitted to the sponsor.

Finally, as I discussed above, I recommend that the application be approved for formulation 54, with a request to the sponsor to further justify approval of formulation 55.

RECOMMENDATION

The attached Approvable letter, with attached draft labeling, should be sent to the sponsor.

/S/

Russell Katz, M.D.

Cc:
NDA 20-796
HFD-120
HFD-120/Katz/Tresley/Burkhart/Boehm/Knudsen/Fitzgerald/Wheelous
HFD-710/Choudry
HFD-860/Al-Habet/Baweja