CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-014

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

MEMORANDUM

DATE: January 10, 2000

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

TO: Director
Office of Drug Evaluation I/HFD-100

&

File, NDA 21-014

SUBJECT: Review of Sponsor's Response to Approvable Letter and Division Recommendation for Action on the NDA

On 9/24/99, the Agency issued an Approvable letter to Novartis Pharmaceuticals Corporation for NDA 21-014, for the use of Trileptal (oxcarbazepine) in patients with partial seizures. The letter outlined several areas of labeling that we felt deserved special mention, and in the letter we requested that the sponsor perform additional analyses of some of these issues. The following issues were highlighted in the letter:

1) Indications

2) **Warnings**-The letter contained requests for additional analyses for several issues:

Hyponatremia-we noted the increased occurrence of hyponatremia in the NDA database (Na<125) compared to placebo and asked the sponsor to perform additional analyses to further characterize this problem.

Cognitive/Neuropsychiatric Adverse Events-Trileptal appeared to produce a number of the CNS adverse events that seem to be typical of anti-convulsants (e.g.,

cognitive and behavioral events, as well as somnolence). We asked for additional analyses to clarify the events, as well as their incidence.

In addition, we asked the sponsor to further clarify signals of potential risk, including hepatic and hematological risk, as well as to more clearly define the number of patients exposed to the higher doses (2400 mg/day). The letter also asked for clarification of a number of additional potential safety concerns. Finally, a number of minor CMC and Biopharmaceutics requests (including adoption of a specific dissolution specification) were made.

The sponsor initially responded to the Approvable letter in a submission dated 11/15/99, and has made a number of additional submissions in response to questions posed by Agency reviewers. These submissions have been reviewed by Dr. Boehm of the Division Safety Team (review dated 1/3/00), Dr. Hershkowitz of the Division Neurology Team (review dated 1/4/00), Dr. Tammara of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 1/10/00), and Dr. Christodoulou, Chemist (review dated 12/14/99). I will briefly summarize the issues as they stand now, and offer the Division's recommendation for action on the NDA.

1) Monotherapy-The sponsor proposes that we grant a claim for use of Trileptal as monotherapy in children. In support of this claim, the sponsor offers 4 arguments:

   a) A meta-analysis performed utilizing data from the 29 pediatric patients included in the controlled monotherapy trials yields nominally statistically significant results
   b) An analysis of pharmacokinetic data obtained from pediatric patients in adjunctive trials, but who were apparently not receiving concomitant AEDs that materially interfered with Trileptal metabolism, demonstrates similar Trileptal PK to adults given the drug as monotherapy
   c) Safety data in 185 patients receiving Trileptal monotherapy, and
   d) A statement by the International League Against Epilepsy asserting the similarities between adult and childhood epilepsies

As reviewed by Dr. Hershkowitz, the results of the meta-analysis are superficially impressive (Median Time to Reach Endpoint about 60 days in Trileptal patients, about 12 days in placebo patients, p=0.017). As Dr. Hershkowitz notes, however, there are difficulties surrounding the interpretation of these analyses, and I am reluctant to accept them as providing definitive evidence of effectiveness.

More critically, the assertion by the sponsor that the clearance of MHD (a metabolite of oxcarbazepine believed to be the active moiety) is essentially the same in pediatric patients and adults does not stand up to a detailed analysis of the PK data. As reviewed by Dr. Tammara, the evidence suggests that the PK in older children (8 and above) is similar to that of adults, but it is [redacted] than adults in younger children. Further, as noted by Dr. Hershkowitz, these comparisons are based on data from the pediatric **adjunctive study**; we have no data on the kinetics of Trileptal or MHD when given as

monotherapy in the pediatric patients. As noted by Dr. Hershkowitz, while the sponsor asserts that the pediatric patients that they included in their analyses were not taking AEDs expected to produce important PK interactions with Trileptal, it is possible that they were receiving other AEDs (e.g., benzodiazepines) that might have had an effect.

The evidence of safety of Trileptal when given as monotherapy to pediatric patients is not relevant to the question of its effectiveness, and the ILAE statement is of interest, but it does not speak to the critical question of what dose of Trileptal can be considered effective as monotherapy in the pediatric population.

If we are to conclude that Trileptal is effective as monotherapy in pediatric patients in the absence of a controlled trial that examines that question (an approach that, as I noted in my initial memo, could be considered reasonable, given the results of the adult studies and the pediatric adjunctive study, and that to some extent would be consistent with the ILAE statement, but one that it is important to note we have never previously taken), I would recommend that we have considerable assurance that an effective dosing regimen be able to be defined. One possible approach would be for the sponsor to identify a plasma range of MHD that is associated with effective seizure control (difficult to do with data from trials that did not randomize patients to fixed concentration ranges) in adults when Trileptal was given as adjunctive therapy, and compare these ranges with the analogous ranges from the pediatric adjunctive studies. If the levels associated with seizure control in adults as adjunctive therapy are essentially the same as those associated with control in the pediatric adjunctive trial, then it might be reasonable to conclude that the plasma levels shown to be effective as monotherapy in adults might be effective as monotherapy in pediatric patients. Of course, such an approach would require that we have useful plasma level data in pediatric patients given Trileptal as true monotherapy, so that we could have confidence about the dosing regimens necessary to produce these levels. At the moment, we do not seem to have this data. An approach based on comparing dosing regimens, not plasma levels, provides less assurance in my view, but could be considered. In regard, it should be noted that the doses (on a mg/kg basis), seen to be effective in adults as adjunctive therapy (10-20 mg/kg, with the highest, but untolerated dose being 40 mg/kg, for a 60 kg person) were not those studied in the pediatric adjunctive study (30-40 mg/kg/day).

For these reasons, I believe that we need to have considerably more detailed dosing information from pediatric patients given Trileptal as monotherapy, as well as additional detailed analyses of the PK/PD relationships when Trileptal is given as adjunctive therapy in both adults and pediatric patients, before a claim is granted for Trileptal as monotherapy in pediatric patients without a controlled trial in this setting. It is particularly important, if this approach is taken, to have detailed information about these matters in the various pediatric sub-groups, given what we believe to be important age related changes in clearance.

Regarding the sponsor's claim that Trileptal is effective down to the age of 3 years, Dr. Hershkowitz has examined the sponsor's arguments. Analysis of the data reveal that there are treatment related differences favoring Trileptal over placebo down to the age of

4 (actually 3, but there was only 1 such patient in each treatment group), except for 7 year olds, in which the treatment difference was in favor of placebo. Dr. Yan's finding that there was no efficacy below the age of 8 was based on exploratory analyses that grouped patients arbitrarily, and reflected what appears to have been an anomalous finding in 7 year olds. I would conclude on the basis of these analyses that the finding in 7 year old is, indeed, anomalous (there being no obvious reason for this finding, which could be considered analogous to a finding of a reverse treatment effect in a single center of an otherwise consistently positive multi-center study) and that, therefore, the indication should include patients down to the age of 4 years.

2. Labeling

   a. **Hyponatremia**- Dr. Boehm had performed a detailed review of this issue. Overall, 2.7% of patients developed at least 1 episode of Na<125 mmol/L, compared to 0 such placebo patients. The additional analyses suggest that there is a slightly increased risk of developing hyponatremia in patients taking concomitant medications known to be associated with hyponatremia compared to patients not taking these medications, but in this latter group, there dose appear to be a dose related increase in the risk for developing hyponatremia, whereas in the former group, there is no evidence for such a dose effect. In addition, while most of the occurrences of hyponatremia occur within the first 3 months of initiation of treatment, cases do occur well beyond this. While in a number of patients the hyponatremia was transient and resolved with continued treatment, it persisted in a number of patients, and in a number of patients, clinical intervention was taken (discontinuation of treatment, fluid restriction, etc.). These latter patients did not experience important clinical sequelae of the hyponatremia. Some patients appeared to have experienced adverse events in association with hyponatremia, but in general there were too few such events to adequately assess this relationship. We have extensively changed the language in this section of labeling compared to that proposed in the draft labeling accompanying the Approvable letter.
   b. **Cognitive/Neuropsychiatric Adverse Events**-The rates of these events were in general not greater in Trileptal treated patients than in placebo treated patients in monotherapy trials, but they were greater in the adjunctive setting. The relative risks for experiencing such an event in the adjunctive setting were about 5 for cognitive ADRs, 3 for somnolence, and less than 2 for psychiatric events. For this reason, we have chosen to not highlight the psychiatric events in this section of labeling. While none of these events were considered serious, the relative risks for discontinuing treatment for cognitive and somnolence related ADRs was about 8 and 10, respectively. In addition, because ataxia and coordination difficulties were common, we are adding these events to this section of labeling. Because of the lack of serious events of in this category, we are moving the description of these events to Precautions, and have amended the language originally proposed in this section.

Exposure

The sponsor has documented that a total of 277 patients received a daily dose of greater than or equal to 2400 mg/day, with 120 of these receiving this dose for at least 1 year.

Hepatic Risk

As noted by Dr. Boehm, there appeared to be an increased risk for AST elevations (outliers) but not for ALT. Additional analyses revealed 14 patients with AST >2xULN, with 10 of these patients also having elevated ALT. Of these 14, 1 was an error, 1 had the elevation at baseline, and 9 had a single, transient elevation that resolved on continued treatment. Of the remaining 3, one discontinued due to the elevation, 1 discontinued for seizures, and 1 discontinued for drowsiness and depression. None of these patients had a concomitant elevation of bilirubin.

Again, as noted by Dr. Boehm, the sponsor provided additional details of a case of liver injury described in the NDA. This was a 49 year old man who was being treated with lamotrigine, carbamazepine and phenobarbital who experienced elevated LFTs (bilirubin 3.3, AST 1186, ALT 1623 CPK 1000, DH 2157) 31 days after initiation of treatment with oxcarbazepine, coincident with admission to the hospital for increased seizure activity and confusion. The oxcarbazepine was discontinued, and an ultrasound exam was read as being consistent with liver enlargement and "steatotic hepatopathy signs". The patient was apparently discharged 24 hours after admission with normal labs. No definite cause was identified (tests for Hepatitis A, B, and C were negative).

Hematological Risk

There were 2 patients identified in the original NDA review with pancytopenia for whom we had incomplete information, as well as several post-marketing reports of various cytopenias. For one of the 2 non-post marketing cases, the bone marrow biopsy was not consistent with aplastic anemia. The second patient was diagnosed with pancytopenia 3 days after starting treatment with oxcarbazepine; the drug was discontinued 2 days later. The nadir of lab values (Hgb 7.6 g/dL, WBC $2.2x10^9$/L (ANC 374), platelets $22x10^9$/L was reached about 6 weeks after discontinuation of oxcarbazepine. A bone marrow aspirate (taken at an unknown time) was not entirely consistent with aplastic anemia. There was no additional information submitted for the post-marketing cases. Because none of these cases can clearly be called a case of aplastic anemia, we are not including a special section describing these events in labeling.

Additional descriptions of specific adverse events can be found in Dr. Boehm's review. No other adverse event requires additional language in labeling not already included in the draft label accompanying the Approvable letter.

Many other changes, most minor and/or in response to our requests, have been made in the earlier draft labeling in many sections, including Clinical Pharmacology, (including in the Clinical Studies sub-section), Precautions, (in many sub-sections), Adverse

Reactions, and Dosage and Administration. Regarding the changes in the Clinical Studies sub-section of the Clinical Pharmacology section, a few points need to be made.

We had asked, in the draft labeling, that the sponsor put results of seizure frequency analyses, for the monotherapy studies, presumably because the results as presented (Kaplan-Meier curves of Time to Event) are not as easily understood by the prescribing community. Unfortunately, we are not sure about the validity of these analyses. For example, in one study, patients were permitted to be switched to active treatment after reaching an exit criterion. It appears that the seizure frequency analyses may have included data from patients switched to open label Trileptal. In another study, it appears that seizure frequency data were not obtained. For these reasons, we have chosen to not include these statements. Further, the sponsor wished to remove "statistically" from the statements describing the results, so that the description would state that the results were highly significant. We believe that this is inappropriate, implying that the effect was highly clinically significant, a conclusion we are unwilling to draw. In addition, upon further reflection, we believe the use of the word "highly", even applied to the statistical significance achieved, is also inappropriate; for this reason, we have described the results of these trials simply as "statistically significant", and then give the p-values obtained.

In the Drug Interactions sub-section of the Precautions section, a table describing the interactions of Trileptal with other AEDs is not yet complete, because we have not come to agreement with the sponsor on some of the entries. This is being negotiated with the sponsor.

In the section on CNS Adverse Events (Coordination Difficulties) section of the Precautions section, we have asked the sponsor to provide some specific incidence rates; this information is pending.

In Dosage and Administration, the sponsor proposed several changes which we have not adopted.

First, of course, they have provided recommendations for pediatric monotherapy. Because we are recommending that Trileptal not be approved for this indication, we have, of course, removed these dosing recommendations.

They have also proposed that there not be a recommended maximum daily dose in adults for adjunctive use. Recall that the maximum dose used in this study was 2400 mg/day, but that 65% of patients discontinued this dose. We had proposed that 1800 mg/day be the maximum recommended dose, but that too was an error, given that the maximum dose that was reasonably tolerated in this study was 1200 mg/day. We have proposed that this be recommended as the maximum recommended daily dose in this setting.

In general, the sponsor has proposed that the drug be titrated to the desired clinical response for adults and children. While I have no doubt that clinicians dose patients according to their personal view of the patient's response, I believe that labeling should incorporate the data from the trials as conducted in this section of labeling, which is what

we have generally proposed; none of the statements we have proposed would preclude a practitioner from dosing according to his or her best judgment.

In addition, in the dosing recommendations for pediatric adjunctive therapy, we have included a statement that calls attention to the increased clearance of MHD in patients under the age of 8 years.

We have discussed the revised labeling with the sponsor in a telephone call on 1/10/00. We and the sponsor agree on the labeling accompanying this package, with the exception of the table of AED interactions in the Precautions section, which still needs to be discussed between the firm and the OCPB review team (OCPB members were not present at the phone call).

Biopharmaceutics

The sponsor has proposed, and OCPB has agreed to, dissolution specifications, and all other issues have been addressed.

CMC

Dr. Christodoulou cites one deficiency in her review, relating to the box label. This has been dealt with, and the letter will contain language pertaining to a commitment from the firm to make certain changes in the future.

RECOMMENDATION

The Division recommends that the sponsor be sent the attached Approval letter, once the AED interaction table has been agreed to.

APPEARS THIS WAY
ON ORIGINAL

/S/

Russell Katz, M.D.

APPEARS THIS WAY

Cc:
NDA 21-014
HFD-120
HFD-120/Katz/Hershkowitz/Burkhart/Boehm/Fisher/Fitzgerald/Christodoulou/Guzewska
HFD-710/Yan/Jin/Chi
HFD-860/Tammara

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DATE: September 17, 1999

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

TO: File, NDA 21-014

SUBJECT: Supervisory Review of NDA 21-014, for the use of Trileptal (oxcarbazepine) in the treatment of partial seizures in patients with epilepsy

On 9/25/98, Novartis submitted NDA 21-014 for the use of Trileptal (oxcarbazepine), an anti-convulsant structurally related to carbamazepine, in the treatment of partial seizures in patients with epilepsy. In support of this application, the sponsor submitted the results of 6 controlled trials, in addition to safety experience in almost 2400 subjects, over 2200 of whom had epilepsy. The clinical efficacy data were reviewed by Dr. Norman Hershkowitz of the division (review dated 8/13/99) and Dr. Sharon Yan of the Division of Biometrics (review dated 8/31/99). The safety data were reviewed by Dr. Jerry Boehm of the Division (review dated 7/23/99) and Dr. Greg Burkhart, Safety Team Leader (memo dated 8/25/99). Additional reviews were performed by Dr. Ed Fisher (pre-clinical review dated 8/20/99), Dr. Christodoulou, chemist, (reviews dated 7/16/99 and 7/30/99), and Dr. Sekar, Division of Clinical Pharmacology and Biopharmaceutics (review dated 8/20/99).

In this memo, I will briefly review the controlled trials and safety experience, and offer my recommendations for action on the NDA.

EFFICACY

As noted, the sponsor submitted the results of 6 randomized controlled trials, 4 examining the effects of oxcarbazepine as monotherapy, 2 as adjunctive. One of the adjunctive studies was performed in children; all of the other trials were performed in adults.

Monotherapy Studies

Study 04

This was a randomized, double blind, placebo controlled parallel group trial in patients being evaluated for epilepsy surgery. Patients were off other AEDs, and those with between 2-11 seizures in 48 hours were randomized to placebo or 1500 mg/day on Day 1, followed by 2400 mg/day for the next 9 days, or until one of the following exit criteria occurred:

1) a fourth partial seizure

2) 2 new onset generalized tonic-clonic seizures, if none had occurred during the previous year
3) serial seizures or status epilepticus

The primary outcome measure was to be Time to Exit Criteria, as analyzed by logrank test.

RESULTS

A total of 102 patients (51 each on drug and placebo) were randomized at 10 centers in the United States. The following table displays the disposition of patients in the trial (taken from Dr. Hershkowitz' Table 2, page 17):

	Drug	Placebo
Randomized	51	51
Met Exit Criteria	21	43
Completed 10 days	27	6

The results of the logrank test were highly significant in favor of drug on the primary outcome, Time to Exit Criteria (p=0.0001) (see Kaplan-Meier curve, page 20 of Dr. Hershkowitz' review).

As Dr. Hershkowitz notes, many patients had received AEDs up to 48 hours prior to study drug treatment (for example, almost 60% of each group had received carbamazepine up until 48 hours prior to randomization). Some had received AEDs with relatively long half-lives (e.g., lamotrigine, phenytoin). Only 1 patient was noted to have received a concomitant AED after randomization.

In addition to the primary analysis, analyses of the proportion of patients meeting exit criteria (under worst case assumptions) as well as partial seizure frequency/9 days were highly significant in favor of drug.

Study 025

This was a randomized, double blind, placebo controlled, parallel group multi-center trial in patients not currently receiving treatment with AEDs. Patients were not to have received any AEDs for 90 days prior to a 56 day baseline period (which could have been retrospectively documented). In order to be eligible for randomization, they had to experience at least 2 seizures/month during this baseline period.

Upon randomization, patients received 300 mg BID and were titrated over 7 days to 600 mg BID (1200 mg/day), and then followed for an 84 day Maintenance Phase, after which they were eligible to enter an open, uncontrolled extension phase.

The primary outcome measure was Time to First Partial Seizure. Seizure Frequency and Proportion of Seizure Free patients were also examined.

RESULTS

A total of 67 patients were randomized at 10 centers in the United States. The following chart displays patient flow in the trial (taken from Dr. Hershkowitz' Table 5, page 29):

	Drug	Placebo
Randomized	32	35
Met Exit Criterion	21	30
Median Time to Sz	11.7 (days)	3.2 (days)
Seizure Free	7	4

The logrank test of the primary outcome variable (Time to Exit Criterion) yielded a p-value of 0.046. In an additional analysis, data from one center was excluded because the sponsor concluded that the investigator had deviated from good clinical practice; when this center's patients were excluded, the resultant p-value was 0.03.

The following results were obtained for the secondary variable, 28 Day Seizure Frequency, presented as medians (results were unaffected by examining means, but the data were not normally distributed):

	Drug	Placebo	P-value
Baseline Frequency	5	5.5	
On Treatment	0.7	3.5	
Percent Change from Baseline	-89	-37.4	0.03

This analysis was based on an imputation of 0 seizures for 1 placebo and 4 drug treated patients who left the trial before their first seizure. If these patients are removed from the analysis, the resultant p-value is 0.85.

Analyses of the Percent of patients seizure free yielded p-values from 0.07-0.26, depending upon assumptions made for patients who left the trial early (some patients who left early were treated with open-label drug).

Study 026

This was a randomized, double blind, parallel group trial in which patients were randomized to receive either low dose (300 mg/day) or high dose (2400 mg/day) oxcarbazepine. Patients who were receiving 800-1600 mg/day of carbamazepine and were experiencing 2-40 seizures/month during a 56 day baseline period were switched to oxcarbazepine monotherapy during a 28 day open label conversion phase. During this phase, carbamazepine was removed by Day 21, and the target dose of 2400 mg/day of oxcarbazepine was reached. Patients were then maintained on this dose of OXC during a 56 day open label baseline phase.

After this Baseline phase, patients were randomized to receive either 300 mg or 2400 mg/day of OXC. During the first 56 days of this Double Blind phase, patients randomized to low dose had their dose decreased to 300 mg/day; patients randomized to high dose simply maintained their dose. The subsequent Maintenance Phase was to last 70 days, or until a patient met one of the following exit criteria:

1) Two-fold increase in the 28 day seizure frequency compared to baseline
2) Two-fold increase in the highest consecutive 2 day frequency seen at baseline
3) A single generalized seizure if none had occurred during baseline, or
4) A prolonged generalized seizure

The primary endpoint was Time to Exit Criteria.

RESULTS

A total of 96 patients at 12 centers in the United States were randomized to study treatment. The following chart describes patient flow (taken from Dr. Hershkowitz' Table 10, page 43):

	2400 mg/d	300 mg/d
Randomized	51	45
Met Exit Criteria	30	40
Completed Treatment	16	0

The results of the logrank analysis of the primary outcome variable, Time to Exit Criteria, was highly significant in favor of high dose ($p=0.0001$). The median time to reach exit criteria on high dose was 68 days and 28 days for the low dose (see Kaplan-Meier curve, page 45 of Dr. Hershkowitz' review).

Study 028

This was a randomized, double blind, parallel group trial in which patients were randomized to receive either low dose (300 mg/day) or high dose (2400 mg/day) OXC. Patients who were receiving one or 2 concomitant AEDs entered a 56 day Baseline period. After this phase, patients were randomized to receive either low or high dose OXC. Patients randomized to high dose were started on 1200 mg/day, and were titrated up to 2400 mg/day by Day 15. Patients randomized to 300 mg/day received that dose on Day 1.

Patients' concomitant AEDs were begun to be withdrawn on Day 1 of the Double blind treatment. The primary AED was completely withdrawn by Day 43; the secondary AED was withdrawn on Day 1. The Maintenance Phase was considered to have been from Days 28-126. Note that concomitant AED was still being taken from days 28-42, during this phase.

The trial lasted until day 126, or until a patient met one of the exit criteria previously described for Study 26. The primary outcome was the percentage of patients meeting an exit criterion. Time to Exit Criteria was a secondary outcome.

RESULTS

A total of 87 patients were randomized at 9 centers in the United States. The following chart displays patient flow in the trial (taken from Dr. Hershkowitz' Table 12, page 55):

	High Dose	Low Dose
Randomized	41	46
Met Criteria	14	42
Completed trial	20	30

The analysis of the primary outcome Percentage of Patients Reaching an Exit Criterion yielded a highly significant p-value in favor of high dose ($p<0.0001$).

Analysis of the secondary outcome, Time to Exit Criteria, also yielded a highly significant difference favoring high dose ($p<0.0001$). The median time to endpoint was 26 days for low dose and could not be computed for the high dose (see Kaplan-Meier curve, page 59 of Dr. Hershkowitz' review).

Adjunctive Studies

Study OT/PE1

This was a randomized, double blind, parallel group placebo and multiple fixed dose trial in which patients who were receiving up to 3 concomitant AEDs were randomized to receive either placebo, 600 mg/day, 1200 mg/day, or 2400 mg/day OXC (given BID). In an 8 week baseline period, patients were required to have had at least 4 seizures/month in order to be randomized to study drug. Maximum dose was to be achieved during a 2 week Titration Phase, followed by a Maintenance Phase of 26 weeks.

The primary outcome measure in this trial was Percent Change from Baseline in 28 Day Seizure Frequency. Secondary variables included 28 Day Seizure Frequency, Percent of Patients experiencing a 50% in 28 day seizure frequency, Time Between Seizures, and various scales assessing various subjective responses (seizure severity, etc.).

According to the protocol, effectiveness was to be assessed by pairwise comparisons of the 2400 mg and 1200 mg/day groups to placebo, with appropriate corrections for multiple comparisons.

RESULTS

A total of 694 patients were randomized at 60 centers in 11 countries (Canada, Argentina, New Zealand, South Africa, Hungary, Austria, France, Germany, UK, Italy, and Switzerland) The following chart displays the patient flow in this trial (taken from Dr. Hershkowitz' Table 18, page 69):

	600 mg/d	1200 mg/d	2400 mg/d	Placebo
Randomized	169	178	174	173
Completed Trial	130	97	46	124
Intent-to-Treat	168	177	174	173
Withdrawn Due to ADR	20	64	116	15

The following chart displays the results of analyses of the primary outcome, Percent Change from Baseline in 28 Day Seizure Frequency, evaluated in the Intent-to-Treat population (taken from Dr. Hershkowitz' Table 25, page 72):

	600 mg/d N=168	1200 mg/d N=177	2400 mg/d N=174	Placebo N=173
Median Baseline 28 Day Frequency	9.6	9.8	10.0	8.6
Median Treatment 28 Day Frequency	8.2	6.9	4.7	9.3
Median Percent Change	-13.4	-20.9	-34.2	-7.6
P-value	0.0001	0.0001	0.0001	

Similarly robust findings were seen for all doses on the secondary variables 28 Day Seizure Frequency and Percent of Patients with a 50% Reduction in 28 Day Seizure Frequency.

The most common adverse events leading to early discontinuation in the high dose group were vomiting, diplopia, ataxia, dizziness, and nausea (ranging from 19%-27%).

While there appeared to be some changes in concomitant AED levels (e.g., mean increase of 40% in phenytoin levels in a total of 18/352 mid and high dose patients), the changes were generally small and in a few patients, suggesting that these changes had no important effect on the outcome (indeed, as noted by Dr. Hershkowitz, an analysis that excluded patients receiving concomitant phenytoin yielded similar results).

Study 11

This was a randomized, double blind, placebo controlled, parallel group study in which children 4-17 years old treated with 1-2 concomitant AEDs were randomized to receive placebo or OXC, the dose dependent on weight. After a 56 day Baseline Phase, patients were randomized to receive placebo or one of the following doses:

Weight	Dose
20-29 kg	900 mg/day
29.1-39 kg	1200 mg/day
>39 kg	1800 mg/day

These doses were achieved during a 14 Day Titration Phase, after which patients entered the 98 Maintenance Phase.

The primary outcome measure was the Percent Change From Baseline in 28 Day Seizure Frequency. Secondary measures included 28 Day Seizure Frequency and Percent of Patients Experiencing a 50% Decrease in 28 Day Seizure Frequency.

RESULTS

A total of 267 patients were enrolled in 47 centers in Canada (7 centers), Argentina (10 centers), Israel (3 centers), Australia (4 centers), and the US (23 centers) The following chart displays patient flow in this study (taken from Dr. Hershkowitz' Table 29, page 83):

	Drug	Placebo
Randomized	138	129
Completed Trial	117	119
Intent-to-Treat	136	128

The following table displays the results of the analysis of the primary outcome measure, Percent Change From Baseline in 28 Day Seizure Frequency:

	Drug	Placebo
Median Baseline 28 Day Frequency	12.5	13.1
Median Treatment 28 Day Frequency	7.9	14.3
Median Percent Change	-34.8	-9.4
P-value	0.0001	

Results of analysis of secondary outcomes 28 Day Seizure Frequency and Percent of Patients Experiencing a 50% Decrease in 28 Day Seizure Frequency were similarly strongly positive (p=0.002 and 0.0005, respectively).

Of note, as discussed by Dr. Yan (page 45-46), the positive findings in this study seem to arise from patients aged 8-17 years. In the 61 patients in the younger age groups, the placebo patients had a slightly numerically superior response compared to the drug treated patients, with a p-value of 0.92.

SAFETY

A total of 2390 subjects were exposed to OXC in what the sponsor refers to as the primary database. While there were additional exposures to OXC (for example, Named Patient Program, etc.), these other data sources did not contain complete or adequate records which would conform to current Good Clinical Practices. The experience in the 2390 subjects represented about 2600 patient-years of exposure.

A total of 1712 patients received OXC in controlled trials in epilepsy, and a total of 2224 received OXC in all epilepsy trials (including open exposure). Of these patients, 1456 received treatment for at least 6 months, and 1096 received treatment for at least 1 year.

A total of 511 patients received a mean dose of at least 1800 mg/day, with 331 receiving this dose for at least 6 months, and 249 of these receiving this dose for at least 1 year.

DEATHS

There were a total of 29 deaths in the primary database, 22 in patients within 30 days of their last dose of OXC. Dr. Boehm presents mortality rates for OXC and comparator treatments for 2 different groups of studies: 1) adjunctive and monotherapy substitution trials, and 2) initiation of monotherapy trials (the view being that the patients in the former grouping are reasonably comparable and different from the latter patients).

For the adjunctive and monotherapy substitution patients, the mortality on drug was 17.2/1000 patient years, compared to 14.6/1000 patient years for placebo. The rates for carbamazepine and phenobarbital were 0 (but with about 1/10-1/5 the exposure compared to placebo). In the initiation of monotherapy cohort, the mortality was 4.5/1000 patient years on drug, with a combined rate of 9.1/1000 patient years for all other comparators.

A separate analysis of Study OT/PE1 (the fixed dose response add-on trial) revealed no difference in mortality between treatment and placebo.

Mortality in the open and extension experience was 6.5/1000 patient years.

Dr. Boehm has performed a detailed review of the deaths. Many were sudden and attributed to seizures, and details were often inadequate.

There were additional deaths in the other pre-marketing databases (total of 19) for which the data were even less adequate. There were also 9 post-marketing deaths. Of interest in this latter cohort was a 63 year old woman who had elevated LFTs 2 months after initiation of treatment with OXC. Drug was stopped, and 4 days later her ALP was 358, AST 2995, and LDH 4125. A laparotomy revealed hepatomegaly and ascites. She died after a rupture of her wound and sepsis.

SERIOUS ADVERSE EVENTS (SAE)

A total of 295/2224 (13.3%) of OXC treated epilepsy patients experienced an SAE. The largest number (129) were related to CNS events; of these 129, 92 were related to "convulsive" disorder.

In adjunctive and monotherapy substitution controlled trials, the rate of SAEs was 19.7/100 patient years for OXC treated patients, and 15.6/100 patient years for placebo treated patients, and 16.5/100 patient years for carabamazepine treated patients. For the initiation of monotherapy cohort, the rate for SAEs for OXC treated patients was 9/100 patient years, compared to 29/100 patient years for placebo, 6.5/100 patient years for phenytoin, and 9/100 patient years for valproate.

Dr. Boehm has described a number of categories of SAEs worthy of further attention.

Skin

A total of 13 serious dermatologic events in the primary database were identified. There were 11 rashes. A number of these were described as maculopapular. One patient developed edema of the lips in association with an extensive maculopapular rash, one patient developed angioedema and was hospitalized (this patient apparently continued in the study), and another patient developed an extensive pruritic erythematous rash with myalgias, arthralgias, and throat tightness; this patient was also hospitalized. One other patient was treated in an emergency room. Although follow-up was not complete in all cases, it appeared that most rashes resolved with discontinuation and/or treatment.

Liver

The sponsor reported 5 SAEs related to the liver (including 2 cases of cholelithiasis). Of note was a 49 year old male on multiple AEDs who had the following LFTs after 32 days of treatment (and several GTC seizures): OT-1186, PT-1623, Bili-3.3. No other cause was determined (Hepatitis A, B, C titers negative). Apparently, the patient was discharged one month after discontinuation of treatment with normal LFTs.

Blood

Two cases of granulocytopenia and 1 case of pancytopenia were reported. All were confounded and none were extremely worrisome.

DISCONTINUATIONS

In the adjunctive and monotherapy substitution studies, 36% of OXC treated patients discontinued treatment (22% due to ADRs) compared to 17% of placebo patients (5% due to ADRs), 35% of CBZ treated patients (12% due to ADRs), and 19% of phenobarbital treated patients (6% due to ADRs). In the initiation of monotherapy studies, 36% of OXC treated patients discontinued (9 due to ADRs), compared to 23% of placebo patients (8% due to ADRs), 40% of phenytoin patients (14% due to ADRs), and 34% of valproate patients (10% due to ADRs).

The sponsor's Exhibit 6.4.1.-1. (reproduced on page 28 of Dr. Boehm's review) displays the ADRs leading to discontinuation. The single most common ADR leading to discontinuation was Dizziness (4.7%), followed by diplopia (4.1%), ataxia (3.9%), vomiting (3.9%), nausea (3.7%), and somnolence (3.1%). This ordering was also seen in the adjunctive and monotherapy substitution trials, with these events occuring substantially more frequently than in the comparator groups. In the initiation of monotherapy studies, only rach occurred in more than 1% of patients (2.3%) with a relative risk greater than 2 compared to placebo.

In addition to these more common events, several of the SAEs described earlier also resulted in discontinuation of treatment.

ADVERSE EVENTS

Dizziness, nausea, diplopia, vomiting, ataxia, abnormal vision, vertigo, and dyspepsia were the most commonly occurring dose related ADRs in the adjunctive and monotherapy substitution studies. In the initiation of monotherapy studies, most of the same ADRs were dose related, but here headache, somnolence, diarrhea, apathy, weight gain, arthralgia, acne, tremor, alopecia, and trauma were also common (at least 5% in the high dose group) and dose related.

LABORATORY DATA

In general, there were no important mean changes in routine laboratory data associated with OXC treatment. However, in the adjunctive and monotherapy substitution studies, the percentage of patients who met criteria for outliers was greater on drug compared to placebo for 3 tests: serum sodium (less than 125-3.2% on drug, 0% on placebo); T4 (<LLN-30.2% on drug, 20% on placebo); and uric acid (<89 mcmol/L-5.5% on drug, 2.3% on placebo).

In the initiation of monotherapy studies, these differences were not as pronounced (the uric acid signal reversed in these studies), but the percentage of outliers on drug was greater than on placebo for LDH (>500 U/L-8.8% on drug, 0 % on placebo).

Other lab abnormalities of note are described earlier in the section on Serious Adverse Events.

Dr. Boehm conducted an additional search for all OXC treated patients with LFTs >3XULN or bilirubin >2 mg/dL. He found 24 patients who met the LFT criteria. None of them had a bilirubin >1 mg/dL (3 patients did not have bilirubin values recorded). In these patients, the highest recorded AST was 354 U/L, and the highest ALT was 228 U/L. Most resolved with continued treatment or dose reduction, but for 4 patients, the abnormal value was the last value recorded.

A total of 4 patients had elevations in bilirubin; the highest recorded bilirubin was 2.8 mg/dL. In 3 patients, the elevation was isolated and normal at the next recording. In a fourth patient, the elevation was the last value recorded.

VITAL SIGNS, EKG

There appeared to be no systematic abnormalities of vital signs or EKG, although the EKG assessment performed (comparison of baseline and end of study pooled data) is not likely to identify potentially important changes in EKG parameters, as noted by Dr. Boehm.

Dr. Boehm has provided a Review of Systems (see page 49 of his review). As he notes, 2 cardiovascular events (hypertension and syncope) were reported in greater than 1% of OXC treated patients (1.5% and 1.1%, respectively). There was a slight excess of these events in the adjunctive/monotherapy substitution studies compared to placebo, but only for hypertension in the initiation of monotherapy studies. While there were a number of cardiovascular reported events in the database, as well as several sudden deaths for which we have little useful information, many of these cases were confounded, and there does not appear to be a well documented systematic effect of OXC on the cardiovascular system.

Similarly, many CNS events were noted, some reported as SAEs, others as reasons for discontinuation of treatment or simply ADRs. Other events (e.g., death due to status epilepticus) have also been reported from data sources other than the primary dataset. While it is difficult to conclude that OXC was the cause of many of these events, it is clear that OXC is associated with CNS toxicity, similar to that of many other AEDs.

Regarding dermatologic effects, the important events in the primary database have been described above. Dr. Boehm describes 1 case of diagnosed Stevens-Johnson syndrome in the Named Patient Program, in a patient recently started on several new medications, although he reports that the patient improved coincident with discontinuation of OXC (I do not know if other meds were also discontinued). Skin related events were the most commonly reported post-marketing event (about 1/3). In this group, there were 3 reports of erythema multiforme, 2 reports each of Stevens-Johnson and exfoliative dermatitits, and 1 report of TEN (Dr. Boehm describes the estimate of post-marketing exposure as about 157,000 patient years).

In the GI system, the important events in the primary dataset have been described above. In the Named Patient Program, 1 patient developed pancreatitis. There were 2 such reports from the post-marketing experience, with 1 of the latter confounded, and the other apparently improved with continued treatment. There was also a post-marketing report of a 6 year old with hepatic failure who was also taking valproate, and a patient with SGPT 727U/L, SGOT 332U/L, and GGT 280U/L 1 month and 5 months after starting OXC and valproate, respectively. The tests returned to normal 1 week after withdrawal from both drugs.

While there was no systematic increased percentage of patients with hematologic abnormalities on drug compared to placebo in the controlled trials, there were a number of reports of leukopenia. Dr. Boehm has reviewed these cases (page 57 of his review); in only 1 of the 7 cases he describes did the WBC fall below 2. This was a patient being treated with 1500 mg/day, other concomitant AEDs, and a baseline WBC of 2.7. Her lowest recorded WBC was 1.8.

In the Named Patient Program, a woman with a history of marrow suppression experienced a low WBC count of 1.7, and a 16 year old woman developed pancytopenia 1 year after treatment initiation, which resolved on discontinuation. A bone marrow biopsy found decreased red and white cell and platelet lines. Another patient from other secondary datasources developed pancytopenia and pneumonia after 20 months of treatment; her counts apparently normalized upon treatment discontinuation.

Hyponatremia

In the primary database, a total of 14 patients were reported to have SAEs related to hyponatremia. Dr. Boehm describes these patients in detail in his review (page 25). Most of these patients had a minimum serum sodium of about 120-125mEq/L, but 2 had levels below 120 (both had a level of 115 mEq/L). Some of these patients were asymptomatic, and some were reported to have had increased seizure activity associated with the hyponatremia. Of the 2 patients with the lowest recorded sodium, one had slow thinking, increased seizures, drowsiness and dizziness, and the other had several seizures and was lethargic (post-ictal?). In most cases, the serum sodium increased with drug discontinuation.

Although there were no important mean changes in serum sodium in the controlled trials, the mean serum sodium did generally decrease in a dose related fashion (see table, page 37 of Dr. Boehm's review). The decrease seemed to be most prominent in the first few weeks following initiation of treatment (see section 4.11.3, Dr. Boehm's review, page 42), although decreases did persist out in time.

As noted earlier, 3.2% of patients in the adjunctive/monotherapy substitution trials had at least one measured serum sodium < 125 mEq/L, compared to 0 at baseline and 0 in the placebo group. In the entire primary database, 9.1% were below 135 mEq/L (I do not have the figures for below 125 in the entire primary database). According to an expert

report on hyponatremia commissioned by the sponsor, about 22% of almost 2000 OXC exposed patients had a serum sodium <135 mEq/L, and about 2.7% had a serum sodium < 125 mEq/L.

The sponsor's consultant described the results of 2 studies designed to examine the effects of OXC on serum sodium.

In one study, 11 patients and 10 healthy volunteers were given a water load prior to and during exposure to a maximally tolerated dose of OXC. After dosing, 1 patient developed a sodium of 121 mEq/L before the water load and 2 volunteers had levels of 124 and 119 mEq/L during the load. During drug exposure and water load, 17/19 subjects could not excrete at least 80% of the water load (the normal response). Patients excreted a mean of 32% of the load; normals, 54%. The consultant concluded that these results implied severe impairment of water excretion, which should have been reflected, in his view, in more significant hyponatremia than was actually seen in the NDA database. A second study comparing carbamazepine to OXC revealed no drop in serum sodium in patients treated with CBZ and given a water load.

COMMENTS

The sponsor has submitted the results of 6 controlled trials that are capable, by design, of providing substantial evidence of effectiveness of Trileptal as a treatment of partial seizures in adults and children. In addition, they have provided an amount of safety data which meets or exceeds ICH guidelines for exposure.

I have concluded that the evidence supports the conclusion that Trileptal is effective as adjunctive and monotherapy for partial seizures in adults. I acknowledge, as does Dr. Hershkowitz, that there are concerns raised by some of the designs used in the monotherapy trials (potential withdrawal and/or residual effects of concomitant AEDs, etc.), but these are minor for the reasons he states, and not all of the studies suffer from these flaws. In particular, the sponsor has provided evidence that supports the conclusion that Trileptal is effective as monotherapy whether the monotherapy represents the initial treatment for the patient's seizures, or whether monotherapy is achieved by converting a patient from other concomitant AEDs.

The data establish doses of 1200 mg/day and 2400 mg/day as effective as monotherapy in adults, although the evidence of effectiveness is more robust for the high dose. The data for 1200 mg/day arise from the initiation of monotherapy study, and the evidence for 2400 mg/day comes from studies in which patients were converted to Trileptal. While it is reasonable to assume that these 2 populations would be different in terms of severity of their seizure disorder, the evidence also suggest that they were. For example, the median number of seizures/28 days at baseline in the initiation study was 5; the mean number of seizures/28 days at baseline in the 2 long term substitution studies ranged from 9-13 (and was much higher in the short term pre-surgical study). It is difficult, for this reason, to conclude with great certainty that 1200 mg/day will be an effective dose as monotherapy for patients being converted to Trileptal. Nonetheless, I believe it is reasonable in the

Dosage and Administration section of labeling to not strictly limit the dose recommended in either of these 2 settings.

While the evidence supports the effectiveness of Trileptal as adjunctive treatment in adults, the question of the effective dose is raised. The adjunctive therapy trial examined 3 doses: 600, 1200, and 2400 mg/day. While the protocol specified an analysis of only the 2 higher doses, the evidence strongly supports the effectiveness of the 600 mg/day dose as well. However, the large number of dropouts (about 2/3) due to adverse events in the 2400mg/day dose suggests that this dose, at least as it was achieved in the trial, is not well tolerated in this population. Indeed, questions can be raised about whether any analysis can appropriately be performed that could adequately assess the effectiveness of this dose in the face of such large numbers of dropouts. Having said this, however, I do believe that this dose has been shown to be effective, but I do not believe that it should be a recommended dose in labeling.

I have also concluded that the evidence supports the conclusion that Trileptal is effective as adjunctive therapy in children, based on the single trial performed in this population and the findings in adults. I also believe it is reasonable to conclude (based on the findings in adults and the adjunctive trial in pediatrics) that Trileptal is likely an effective agent as monotherapy in the pediatric population.

However, in my view, the sponsor has not submitted sufficient evidence that would permit us to identify a dose that can be considered to be safe and effective as monotherapy in the pediatric population. For this reason, I do not believe that the drug can be indicated for use as monotherapy in the pediatric population at this time.

We have reason to believe, based on the adult data, that at least some doses shown to be effective as monotherapy are not tolerated when given as adjunctive therapy. Similarly, there is a question about whether the doses that are tolerated as adjunctive therapy are effective as monotherapy (a dose of 1200 mg/day in adults does appears to be effective and tolerated in both settings, although about 1/3 of the patients at this dose discontinued treatment due to adverse events, and only about ½ of the patients completed the study at this dose; further, as noted above, the efficacy is less robust at 1200 mg/day than is the evidence for 2400 mg/day as monotherapy). Nonetheless, we have no evidence that any of the specific doses shown to be tolerated (and effective) in the pediatric population as adjunctive therapy will be effective if given as monotherapy. The fact that at least one such dose could be considered to have been identified in adults provides no specific information about whether or not this is true for the pediatric population. It is true that some pediatric patients were included in the monotherapy studies, but only a very small number in the controlled trials that we consider adequately designed (N=18 on drug, 13 on control, with 15 on drug between the ages of 12-17).

One could, of course, simply include language in labeling that instructs practitioners to titrate pediatric patients to a tolerated dose as monotherapy. Such a maneuver, however, in my view, does not guarantee that an effective dose will be reached for at least 2 reasons. First, it is possible that the maximally tolerated dose achieved may not be

effective as monotherapy. Second, it is difficult to know clinically that an effective dose has been reached, especially in an initiation monotherapy setting, because the number of seizures expected in these patients without treatment may be very small for any given period after treatment initiation. For this reason, practitioners may falsely conclude that the dose given is effective when, in fact, it is not.

For these reasons, I am recommending that the label indicate Trileptal in the pediatric population only as adjunctive treatment, and that we explain our reasonoing in our action letter. The sponsor should present its arguments for approving the drug as monotherapy in pediatrics in their response.

Further, I am recommending that the lower age limit be increased to 8 years of age. This is based on the results of Dr. Yan's analyses that demonstrated that the effect of Trileptal was limited to patients 8 years of age and older. While this subset analysis was retrospective, and is subject to criticism on this basis, it is supported by the view that younger children have an increased clearance of the drug and its active metabolite (which is responsible for most of the anti-seizure effect of the drug), and therefore the lack of effectiveness seen in this age group might well be related to effective systematic underdosing. While we could indicate the drug at increased doses in this lower age group, I would prefer to see empirical evidence that these higher doses are effective and safe in this pediatric sub-group.

The sponsor has submitted sufficient safety data to support an approvable action at this time. There are, of course, some areas of concern, most notably hyponatremia, which will require additional work by the sponsor to be better understood (for example, the sponsor asserts that this has been asymptomatic, but increased seizure activity reported in some of these patients suggests that this might not be so), but I believe that these potential risks can be adequately described in labeling, and that language can be drafted that can reasonably ensure that the drug can be used safely (even given that we know that practitioners do not always manage patients according to labeling). In addition, there are several other safety issues that need to be further addressed by the sponsor (e.g., possible cases of aplastic anemia, further clarification of CNS and hepatic toxicity); we will ask for these additional analyses in the action letter. Based on the sponsor's responses to these requests, the labeling may ultimately look considerably different than the draft labeling we are forwarding. Given what we know about these events at the moment, I do not believe that they pose a bar to ultimate approval.

I have not been able to determine the exact number of patients exposed to doses of 2400 mg/day and greater, and the sponsor should be asked for this information.

There have been a total of 581 patients below the age of 17 exposed in the database, 81 below the age of 6. Of the total 581, 319 have been exposed for at least 1 year. I do not know what the exposure by dose (either absolute dose or on a mg/kg basis) for the pediatric population is, and, therefore, we cannot be certain of the number exposed for various durations to an effective dose. We will ask the sponsor for this information in our action letter.

The safety experience in pediatric patients, as described, also poses no bar to ultimate approval; the sponsor will be asked to adequately describe this experience in labeling.

One final point is worth a comment.

Oxcarbazepine is very similar structurally to carbamazepine. One could, simply on the basis of this similarity, include language in labeling raising the question of OXC's potential to be associated with various of the toxicities known to be associated with carbamazepine. In particular, labeling for carbamazepine includes a Black Box warning about agranulocytosis and aplastic anemia, 2 events not definitively reported in association with OXC. However, of course, the extent of experience with OXC is not sufficient to expect that a case of either would have been seen, if, for example, the true rate of either was similar to what is currently believed to be the rate with carbamazepine. Further, carbamazepine is labeled as Pregnancy Category D, based on its known association with birth defects, most notably spina bifida. Of course, there is no such human signal at this time for OXC.

OXC is, of course, a different drug than carbamazepine, and it cannot be stated with any assurance that it will be associated with these specific toxicities. For example, carbamazepine is a CYP 3A4 substrate and is metabolized to an epoxide; this is not true for OXC. Whether this distinction is relevant for this purpose is, of course, unknown. It is true that the drugs appear to act very similarly pharmacologically, the toxicities seen in animals are quite similar (including teratogenicity), and there are suggestions of similar clinical toxicities (most notably hyponatremia and, at least potentially for OXC, aplastic anemia). However, many of these findings are non-specific, and are true of other drugs not chemically related to either OXC or carbamazepine.

Given these considerations, I do not believe that it is necessary at this time to include in labeling a separate section highlighting the similarity of OXC to carbamazepine and suggesting that the toxicities are likely similar. We have, however, added a sentence to the Pregnancy Category section of labeling (we are calling OXC a Category C drug, whereas carbamazepine is Category D) noting the structural similarity and raising the possibility of an increased risk of teratogenicity. As far as the potential for any other comparisons to carbamazepine in labeling, these should be considered pending the sponsor's response (for example, we might add statements in labeling about aplastic anemia and OXC; it might be appropriate at that time to include language about the structural similarity to carbamazepine).

RECOMMENDATIONS

For the reasons given above, I recommend that the attached Approvable letter and draft labeling be issued.

/S/

Russell Katz, M.D.

Cc:
NDA 21-014
HFD-120
HFD-120/Katz/Hershkowitz/Burkhart/Boehm/Fitzgerald/Fisher/Malandrucco/
HFD-120/Christodoulou/Guzewska
HFD-860/Sekar/Sahajwalla
HFD-710/Yan/Jin

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1041	120	TRILEPTAL	Oxcarbazepine Film-Coated Tablets, 150 mg and 300 mg, 600 mg

ATTENTION: MELINA MALANDRUC

A. Look-alike/Sound-alike

	Potential for confusion:		
TRIAVIL	XXX Low	____ Medium	____ High
TRILEVLEN	XXX Low	____ Medium	____ High
PLETAL	XXX Low	____ Medium	____ High
	____ Low	____ Medium	____ High
	____ Low	____ Medium	____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

____ Satisfactory

XXX Unsatisfactory/Reason

"FILM-COATED" SHOULD NOT BE INCLUDED IN THE NAME

Recommended Established Name

OXCARBAZEPINE TABLETS

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 9/3/98

SECTION 4. Categorical Exclusion

A claim for categorical exclusion from the requirement to prepare an Environmental Assessment under 21 CFR 25.31(b) - Action on an NDA, abbreviated application, or a supplement to such applications, or action on an OTC monograph - if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be [redacted]

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be [redacted] "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation has filed a New Drug Application (NDA) 21-014 for the new molecular entity, oxcarbazepine, and certifies that this submission qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the concentration of oxcarbazepine will be significantly [redacted]

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

Malandrucco

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA #:	21-014
DATE:	23-JUL-99
PRODUCT NAME:	TRILEPTAL™ (oxcarbazepine) Tablets
FIRM NAME:	Novartis
SUBJECT:	Clarification on site, packaging, and stability data
CONVERSATION WITH:	Dr. Joyce Ann Sinno
TELEPHONE #:	973-781-5542

21-MAY-99 I contacted Dr. Sinno of Novartis to clarify:

1. Whether the facility will be performing drug substance stability, and its full address.
2. Which sites will be conducting drug product post-approval stability testing.

09-JUN-99

1. listed in DMF
2. Which used for (DMF
3. What s used in the
4. What s used for the
5.

21-MAY-99 Dr. Sinno responded:

1. Address of the facility was faxed
04-JUN-99 2. Addresses of were faxed.
11-JUN-99 1-5. It was clarified that the provides the desired DMF in primary stability studies are intended for commercial use. This information was faxed.

The faxed Novartis responses were also provided as an amendment, June 14, 1999.

/S/

D. Christodoulou, Ph.D., Chemist

cc. Orig. NDA 21-014
HFD-120/Division File
HFD-120/DChristodoulou
HFD-120/MMalandrucco
HFD-120/MGuzewska
R/D Init. by: MG 7.26.99
/S/

Filename: N21014t1.doc

IN

MEMORANDUM OF MEETING/TELEPHONE CONVERSATION

NDA #: [redacted]
DATE: 15-JUL-99
PRODUCT NAME: TRILEPTAL™ (oxcarbazepine) Tablets
FIRM NAME: Novartis
SUBJECT: Clarification on formulations
CONVERSATION WITH: Dr. Joyce Ann Sinno
TELEPHONE #: 973-781-5542

APPEARS THIS WAY ON ORIGINAL

15-JUL-99 I contacted Dr. Sinno of Novartis to clarify:

1. Why the same formulation F codes, appear in multiple strengths, Table 3-1, Vol. 1.6, p. 3-14 (e.g., F.3 for 150, 300, 600 mg tablets).
2. F.3 formulation for 150 mg strength, to be marketed in the US, is absent from Table 2-3.3, Vol. 1.8, p. 3-333.

15-JUL-99 Dr. Sinno responded:

1. Identification of formulations is indicated by code "F" and strength; i.e., the same F-code is used for multiple strengths.

16-JUL-99 2. She confirmed the F.3, 150 mg formulation to be marketed in the US is absent from Table 2-3.3, Vol. 1.8. (The formulations to be marketed in the US, F.3, F.9, and F.5 have not been tested in clinical trials; however the bioequivalence of F.9 and F.5 has been demonstrated. Formulations F.9 and F.5 are included in Table 2-3.3).

APPEARS THIS WAY ON ORIGINAL

/S/

D. Christodoulou, Ph.D., Chemist

cc. Orig. NDA 21-014
HFD-120/Division File
HFD-120/DChristodoulou
HFD-120/MMalandrucco
HFD-120/MGuzewska
R/D Init. by: MC /S/ 7.19.99

Filename: N21014t.doc