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February 25, 2003

Rigardy Munoz, M.D.  
Carolina Treatment Associates  
419 Second Street NW  
Hickory, NC 28601

Dear Dr. Munoz:

Your Neuroscience Associate, Steve Mc Kee, has forwarded to us your request for information regarding Trileptal® (oxcarbazepine) and its use in the treatment of mania, bipolar, and aggression disorders.

Trileptal® (oxcarbazepine), a 10-keto analogue of carbamazepine (CBZ), is an antiepileptic drug indicated for use as monotherapy or adjunctive therapy for partial seizures in adults and as adjunctive therapy in children ages 4-16 years with epilepsy. Novartis received marketing clearance from the Food and Drug Administration (FDA) on January 14, 2000. In evaluating Trileptal for marketing clearance, the FDA reviewed results from 34 trials and a safety database that included more than 6,900 patients. Trileptal is not indicated for use in the treatment of aggressive, bipolar, and mania disorders and there is no FDA approved dosing regimen.

#### **Aggressive, Bipolar and Mania Disorders**

Retrospective reviews of 200 cases by **Reinstein et al. (2002)** (age range 11-83 years) showed positive findings with regards to improvement in manic symptoms in patient who had received oxcarbazepine (OXC) therapy. Of the 200 cases reviewed, 194 showed an improvement in psychiatric symptoms as documented/confirmed by resolution of admission criteria. The admission criteria were not provided. The dose range for OXC was 600-3000mg daily. None of the patients had to discontinue OXC therapy due to dose-related side effects or cognitive/neuropsychiatric adverse events, such as psychomotor slowing, impaired concentration, speech or language problems, somnolence, or fatigue, or coordination abnormalities including ataxia and gait disturbances. Of the 200 cases reviewed, 3 discontinued therapy due to hyponatremia (sodium <125mEq/L) within three days of initiating OXC treatment. Nineteen (19) patients were flagged for drug-drug interaction with their drug regimens. Of these, 3 patients discontinued therapy due to concomitant treatment with oral contraceptives. The other 16 patients all of whom received calcium channel blockers were evaluated for blood pressure irregularities. No significant blood pressure increases were measured and all 16 patients remained on OXC and their calcium channel blockers at the time of discharge.

**Nasr and Casper (2002)** reviewed the charts of 87 patients (ages 13-72 years) with mood disorders over a 9-month period. Seventy percent of the patients had previously failed to improve on other AEDs, which included clonazepam, valproate, carbamazepine, gabapentin, lamotrigine, and topiramate, or experienced intolerable adverse events. No information was provided on adverse events. Each patient was assessed using a computerized version of MiniScid and Psychosocial history, SCL-90, visual analogue scale (VAS), Carroll Depression Rating Scale

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(CRDS), and a CGI-Severity of Illness score. The mean dose of oxcarbazepine was 801mg/day ( $\pm$  359mg). The results showed a statistically significant improvement in mean CGI-S score for all patients ( $p < 0.0001$ ). Forty-one (47%) of the patients were rated as "much" to "very much" improved on the CGI-S scale at last observation. Bipolar patients reported significant improvement in their VAS score ( $p < 0.03$ ) and CDRS ( $p < 0.06$ ) compared to unipolar patients. The adverse events experienced by patients included, nausea ( $n=3$ ), weight gain ( $n=2$ ), intolerability ( $n=2$ ), edema ( $n=1$ ), headache ( $n=1$ ), hives/blisters ( $n=1$ ), rash ( $n=1$ ), and sedation ( $n=1$ ). The authors conclude that there is potential for using OXC in the treatment of mood disorders and OXC use in prospective, randomized, placebo, controlled studies are needed for further evaluation of this population.

In a prospective, single-center, open-label trial, **Munoz (2002)** investigated the mood stabilizing effects of OXC as adjunctive therapy in 30 patients (ages 18-65 years) with a DSM-IV diagnosis of bipolar disorder. Of the 28 patients who completed the study, 21 patients were manic and 7 patients were depressed at the time of enrollment. Patients who were receiving active treatment for their manic or depressive state had OXC added to their regimen for 12 weeks. During the titration of OXC, their current medication(s) were tapered if necessary. OXC was initiated at a dose of 300mg and increased to a maximum of 2400mg/day. The primary efficacy measures were the Young Mania Rating Scale (YMRS) and the Hamilton Rating Scale (HAM-D). The Scale for Affective Disorders and Schizophrenia (SADS) and the Global Assessment Schedule (GAS) were the other efficacy measures used for overall psychiatric functioning and daily self-reporting of mood, sleep, life events and medications. Responders were defined as manic patients with a  $> 50\%$  improvement in YMRS after 3 weeks, or as depressed patients with a 50% improvement in HAM-D after 6 weeks. The results of the study showed that of the 21 patients who were manic at the start of the study, 15 patients (71%) responded to OXC with  $\geq 50\%$  improvement in YMRS within 3 weeks of starting treatment. Of the 15 patients, 9 remained euthymic, 3 patients relapsed into mania, and 3 became depressed. All 7 patients who were depressed, responded with a  $\geq 50\%$  improvement within 6 weeks of starting treatment and remained euthymic. None of the 28 patients who completed the study discontinued OXC therapy due adverse events. Four patients experienced clinically significant hyponatremia (serum  $\text{Na}^+$  levels  $< 125\text{mEq/L}$ ), all of whom were receiving concomitant medications. Information on comedications was not provided. Other adverse events experienced were mood related ( $n=3$ ), drowsiness ( $n=2$ ), aspiration pneumonia ( $n=1$ ), asthma ( $n=1$ ), and nausea/vomiting ( $n=1$ ).

In a naturalistic, prospective study, **Reinstein et al. (2001)** evaluated the potential of OXC in the treatment of mania in 42 adults over a ten week period. The study compared efficacy and tolerability between oxcarbazepine (OXC) and divalproex sodium (VA). All 42 subjects were diagnosed with bipolar disorder or schizoaffective disorder and were receiving active treatment of VA; 23 of whom were switched to OXC at baseline. The authors suggest that OXC has comparable efficacy and tolerability to VA in the treatment of mania.

In a letter to the editor, **Teitelbaum (2001)**, discusses a case report on the use of OXC in a 6 year old patient who was diagnosed with bipolar I disorder. The patient had been hospitalized over the previous years due to episodic "out-of-control" behaviors, and had used medications which included lithium carbonate, lamotrigine, valproate, gabapentin, clonidine, risperidone, and quetiapine. OXC was initiated at 150mg twice daily in addition to a regimen of lithium carbonate 150mg three times daily and guanfacine 0.5mg two times daily for 3 months. The author states that the patient experienced "full mood stabilization" within six weeks. Social skills improved to an age-appropriate level, defiant behavior was vastly reduced, and all schoolwork was being completed. No property destruction, no aggression or outbursts were observed after 3 months of maintenance therapy. At 3 months, the lithium dose was reduced to 150mg bid while the guanfacine dosage did not change. Complete symptom remission was maintained for 7 months on OXC therapy without side effects.

**Tavormina (2000)**, in an open-label, comparative, naturalistic study evaluated the efficacy, safety, and tolerability of OXC versus CBZ as a mood regulator in 13 subjects. All subjects met the DSM-IV diagnostic criteria for bipolar disorder and were assessed by the "Global Assessment Scale" at the beginning of the treatment. CBZ therapy was initiated in nine of the subjects, while 4 were receiving OXC therapy for a duration of 6 weeks. The subjects were monitored periodically for any emergent adverse events. The results showed that all of the subjects obtained a score of > 90 points using the "Global Assessment Scale". All 9 subjects initially receiving CBZ therapy were converted to OXC therapy due to the hepatic, hematologic, cardiac and dermatologic effects experienced with CBZ. Side effects resolved after eight weeks of OXC treatment in these subjects. Details of the side effects were not provided.

**Emrich (1990)** reviewed the results of double-blind multicenter trials comparing OXC with haloperidol in 42 patients with acute mania, and with lithium in a further 58 acutely manic patients. Psychiatric symptoms were measured using BMRS over 15 days of therapy during which time various drugs were titrated to mean dosages of 2400mg/day or 1400mg/day of OXC (in trials vs haloperidol or lithium respectively), 42mg/day of haloperidol and 1100mg/day of lithium. A decline in mania rating scales values was observed. Although the average improvement with OXC was slower initially, the efficacy was comparable with either haloperidol or lithium by the second week. Haloperidol therapy, however, was associated with a 3.5 fold higher incidence of adverse effects than OXC. The investigator concluded that lithium on the other hand, seemed to be better tolerated than oxcarbazepine.

**Greil et al. (1985)**, in an open clinical trial, selected 13 patients, aged 35-63 years, with bipolar affective disorders (and schizoaffective psychoses in 2 cases). The majority of these patients were lithium non-responders. Nine patients were treated with OXC, dose range 600-1200mg for 2-11 months, while 4 patients were treated with carbamazepine (CBZ), dose range 400-600mg daily for 11-15 months. Despite lithium treatment the patients had suffered from at least one episode per year and 7 of them had experienced 4 or more episodes within the 12 months preceding study. The investigators observed that there was no reduction in frequency of the episodes during treatment with OXC or CBZ. However, there was a reduction in severity of symptoms in individual patients. There was some further evidence of efficacy since further hospitalization could be avoided in 3 of the 13 patients. Adverse effects noted were dizziness, drowsiness, fatigue and ataxia. Polyuria (lithium-induced) was reduced in 2 patients, and 1 patient dropped out after 2 months of OXC therapy due to dizziness, nausea and headache.

**Emrich et al. (1984)** investigated the use of oxcarbazepine (OXC) and Depakote (VPA) in patients with manic syndrome. In a double-blind controlled design, 5 pts were on VPA and 7 pts ages 17-34 years, were on OXC. The maximal dose ranges for VPA and OXC were 1.8g-3.9g, and 1.8-2.1g respectively. The results showed that efficacy was similar with both compounds. The average reduction in inpatient multidimensional psychiatric scale was 49.6% and 49.9% for VPA and OXC respectively. These effects were statistically significant.

**Velikonja et al. (1984)** in their open label study with OXC observed a decrease in psychotic symptoms. The open study was carried out in 10 pts with manic syndrome or schizoaffective psychosis. The eleventh patient dropped out because of an exanthema, probably due to OXC. Patients received 900mg of OXC daily in combination with haloperidol. All 10 patients showed a decrease of psychotic symptoms during the three (3) week trial. A positive response to OXC in patients with severe excitement and aggressive psychopathology was noted using the Friedman tests. In a matched control group at the same site, the average haloperidol dose was twice that of the OXC-treated group. It was evident that with OXC, haloperidol could be given at a lower dose to minimize the side effects. No adverse effects were monitored except for one (1) EEG with an increase of slow, generalized theta-waves. No other changes were observed.

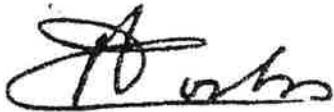
**Muller and Stoll (1984)** conducted two trials with OXC. The first trial was a multicenter pilot study with OXC used in 48 (age 17-61 years) patients with mania. Doses ranged from

600mg/day to 2100mg/day and in one case 3000mg/day. Good therapeutic results were observed in 83% of the patients. Adverse reactions such as double vision, dizziness, nausea, itching and increased restlessness were mentioned by only 3 patients. The second controlled double-blind clinical trial included 20 patients who were randomly assigned to either OXC or haloperidol. The duration of trial was 2 weeks. Dose range for OXC was 900-1200mg daily and 15-20mg daily for haloperidol. Psychiatric symptoms were measured according to the Bech-Rafaelson Mania Scale (**BMRS**) at Days 1, 3, 7, and 14. The results showed that the final mania scores decreased the same in both groups, but the onset of action seemed to be faster with OXC.

Views and opinions expressed by authors that may have been cited in this letter or listed in a bibliography do not necessarily represent those of Novartis. The use of Novartis products in any manner other than described in the accompanying full prescribing information is not recommended.

We hope this information proves useful. Thank you for your interest in Trileptal® (oxcarbazepine) and for the courtesy extended to your Neuroscience Associate, Steve Mc Kee.

Sincerely,



Alston Coombs Pharm.D.  
Medical Information Specialist  
Medical Information & Communication

AC:db:852432  
Enclosures

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