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ABSTRACT

Objective: To assess the effectiveness and safety of extended-release carbamazepine capsules (ERC-CBZ; SPD417) in the treatment of bipolar disorder.

Method: A chart review of 101 adult outpatients with DSM-IV bipolar disorder and treated with ERC-CBZ was conducted (mean age 32.8 ± 10.5 years; 71% female; 70% bipolar I, 18% bipolar II, 12% bipolar not otherwise specified). Charts of subjects who received ERC-CBZ in a private practice setting (LDG, Red Oak Psychiatry Associates, Houston, Tex) between October 1998 and August 2003 were reviewed. Treatment response was assessed with the Clinical Global Impression–Improvement (CGI-I) scale (1 = very marked improvement; 2 = moderate improvement). Relapse was defined as a mood change that occurs 4 weeks after initiation of medication or the return of symptoms from the original episode.

Results: Forty-four subjects (44%) taking ERC-CBZ had marked to moderate improvement (CGI-I score: 1, 23%; 2, 21%). No subjects experienced moderate to marked worsening. Twenty-six patients (26%) relapsed during ERC-CBZ treatment (mean time to relapse = 180 days). Mixed symptoms were the most common bipolar illness presentation. The mean ERC-CBZ dose was 666.1 ± 267.8 mg/d, and the mean serum concentration was 7.4 ± 2.3 µg/mL. Somnolence (9%) and nausea (8%) were the most frequently reported side effects.

Conclusion: Extended-release carbamazepine appears effective in the treatment of bipolar disorder and was well tolerated.

NOTE: Study protocol has changed since abstract submission.

[The following information concerns a use that has not been approved by the U.S. Food and Drug Administration.]

SAFETY AND EFFICACY OF EXTENDED-RELEASE CARBAMAZEPINE FOR ADULT BIPOLAR DISORDER PATIENTS

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INTRODUCTION

- Carbamazepine (CBZ) has been studied in at least 14 double-blind, controlled trials, in which it consistently demonstrated efficacy in acute mania comparable to lithium, with a pooled response rate of 52%.¹ However, these studies had limitations such as small patient populations or concomitant treatment with other medications, and all used immediate-release CBZ (IR-CBZ)
- IR-CBZ has been associated with numerous adverse effects and can require TID or QID dosing^{2,3}
- Extended-release (ER) formulations of CBZ have been developed in recent years to decrease daily fluctuations in serum CBZ concentration and improve dosing convenience. These formulations of CBZ have been associated with lower peak serum concentrations,⁴ decreased circadian toxicity,⁵ and decreased central nervous system side effects, such as sedation, diplopia, confusion, and ataxia⁶
- A novel ER formulation—beaded, extended-release CBZ capsules (ERC-CBZ; SPD417)—is filled with 3 different types of beads: 25% immediate release, 40% ER, and 35% enteric release
- ERC-CBZ monotherapy has been shown to be effective in the treatment of manic symptoms in patients with bipolar disorder in two 3-week, multicenter, randomized, double-blind, placebo-controlled trials.^{7,8} Based on the results of these 2 studies, a New Drug Application has been filed with the US Food and Drug Administration for an indication for ERC-CBZ in the treatment of bipolar disorder
- The objectives of this study were to evaluate the effectiveness, safety, and tolerability of ERC-CBZ in adult patients with bipolar disorder

METHODS

- This is an interim report of an ongoing retrospective chart review
- Records of patients with a DSM-IV diagnosis of bipolar disorder who were treated with ERC-CBZ at a private practice (LDG, Red Oak Psychiatry Associates, Houston, Tex) between October 1998 and January 2004 (n=248) were included in this study
- Charts were reviewed for relapse, adverse events, weight, scores on the Clinical Global Impression–Improvement (CGI-I) and Clinical Global Impression–Severity (CGI-S) scales, CBZ blood levels, and white blood cell count
- Patients were considered to have responded to therapy if they achieved a CGI-I score of ≤ 3. Patients were considered to have relapsed if they had a CGI-I of ≥ 4 after a response had been previously observed

Table 1. Study Population

Patients	Adult
Gender (% Female)	71%
Mean age (y ± SD)	34.7 ± 11.6
Age Range (y)	18 – 84
Mean ERC-CBZ dose* (mg/d)	617.0 ± 231.4
Mean ERC-CBZ blood level* (µg/mL)	7.1 ± 1.8
ERC-CBZ Monotherapy at initiation	49%
Patients dosed QD on ERC-CBZ	6%

CGI-I = Clinical Global Impression–Improvement scale.
ERC-CBZ = extended-release carbamazepine capsules.
*Mean dose and blood level are at patients' best CGI score.
Data on file, Lawrence D. Ginsberg, MD, Red Oak Psychiatry Associates.

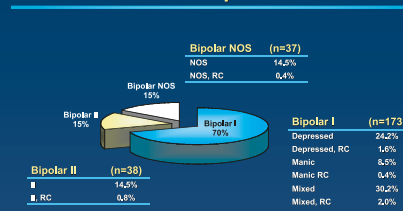
Table 2. Treatment-Emergent Adverse Events on ERC-CBZ

Event	(n=248)
Somnolence	11.3%
Nausea	8.1%
Dizziness	7.7%
Rash	4.8%
Headaches	3.2%
Increased appetite	2.4%
Vomiting	2.0%
Blurred vision	2.0%
Weight gain	2.0%

Adverse events reported with an incidence ≥ 2%.
Data on file, Lawrence D. Ginsberg, MD, Red Oak Psychiatry Associates.

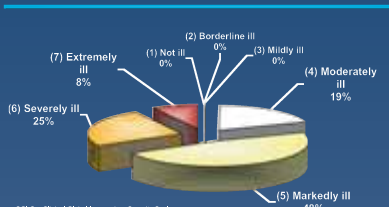
ERC-CBZ = extended-release carbamazepine capsules

Figure 1. Bipolar Subtype of Patient Population



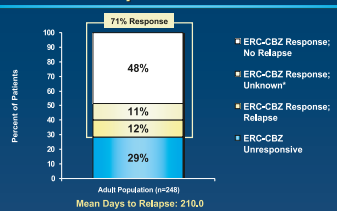
Data on file, Lawrence D. Ginsberg, MD, Red Oak Psychiatry Associates.
RC = relapsed; NOS = not otherwise specified.

Figure 2. Severity of Illness (CGI-S) at ERC-CBZ Initiation



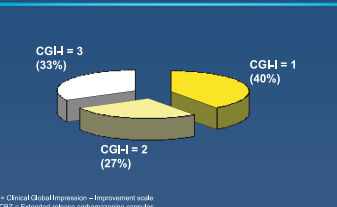
CGI-S = Clinical Global Impression–Severity Scale

Figure 3. Patient Response and Relapse on ERC-CBZ



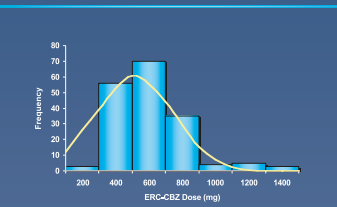
ERC-CBZ response is defined as achieving a CGI-I ≤ 3. Relapse is defined by a change in CGI-I to ≥ 4 after an observed ERC-CBZ response.
*Response unknown includes, but is not limited to, moved out of location, switched physicians, could not afford treatment, etc.
Data on file, Lawrence D. Ginsberg, MD, Red Oak Psychiatry Associates.

Figure 4. Analysis of ERC-CBZ Responders' CGI-I Scores



CGI-I = Clinical Global Impression–Improvement scale.
ERC-CBZ = extended-release carbamazepine capsules.

Figure 5. Dosage Distribution of ERC-CBZ at Best CGI-I



CGI-I = Clinical Global Impression–Improvement Scale

RESULTS

- Of the 248 patients reviewed in this study, 71% were female, and ages ranged from 18–84 years, with a mean age of 35 years. Forty-nine percent of patients were initiated on ERC-CBZ monotherapy, while 6% of patients were able to be maintained on a once-daily dose of ERC-CBZ (Table 1)
- Seventy percent of patients were diagnosed with bipolar I disorder, 15% with bipolar II disorder, and 15% with bipolar disorder not otherwise specified (Figure 1)
- The severity of bipolar illness at ERC-CBZ initiation was determined using the CGI-S scale. Eighty-one percent of patients were determined to be at least markedly ill, scoring ≥ 5 on the CGI-S (Figure 2)
- One hundred seventy-six patients (71%) responded to ERC-CBZ
- Of the responders, 48% did not relapse, 11% were lost to follow-up, and 12% relapsed. The mean time to relapse was 210 days (95% CI, 97–323) (Figure 3)
- Analysis of ERC-CBZ responders revealed 40% of patients having achieved a CGI-I score of 1, 27% a score of 2, and 33% a score of 3 (Figure 4)
- At patients' best CGI-I score, the mean ERC-CBZ dose was 617 ± 231.4 mg/d, and the mean ERC-CBZ blood level was 7.1 ± 1.8 µg/mL (Figure 5; Table 1)
- Common treatment-emergent adverse events included somnolence (11.3%), nausea (8.1%), and dizziness (7.7%) (Table 2)
- Mean weight changed from 174.2 ± 44.4 lbs at ERC-CBZ initiation to 172.0 ± 40.6 lbs at drug discontinuation. Mean change was –3.2 ± 11.9 lbs (n=30 [smaller sample size due to missing data])
- There was no evidence of agranulocytosis or aplastic anemia

CONCLUSIONS

- This large retrospective study shows that ERC-CBZ appears to be effective in the treatment of bipolar disorder with a response rate similar to previous ERC-CBZ trials
- ERC-CBZ was effective in a broad spectrum of bipolar disorder
- Dosage and CBZ blood levels were similar to previous trials as was a low incidence of side effects, with no evidence of agranulocytosis or aplastic anemia, and no associated weight gain

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