Bipolar I Therapy for the Mind and Body: Reducing Acute Manic & Mixed Symptoms of Bipolar I Disorders$^{1,2}$

Equetro® (carbamazepine) Extended - Release Capsules

PLEASE SEE ENCLOSED FULL PRESCRIBING INFORMATION INCLUDING CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND BLACK BOXED WARNING FOR ADDITIONAL SAFETY INFORMATION ON EQUETRO.
Equetro® Is Effective In Treating Patients With Manic or Mixed Episodes – 53% Mean Change From Baseline YMRS Scores by Day 21²

The YMRS scale reveals that Equetro® (carbamazepine) Extended-Release Capsules significantly reduces manic and mixed symptoms¹
- Onset of action as early as 7th Day¹
- 53% mean change from baseline YMRS scores by 21st day²

Primary endpoint was change in YMRS Score from Baseline to Day 21.

The YMRS scale is a measure for manic and mixed symptoms. The data shows a significant reduction in YMRS scores, indicating the efficacy of Equetro® in treating manic or mixed episodes.

3. Calculated from data on file [303], Validus Pharmaceuticals LLC

WARNING

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Equetro®. Patients testing positive for the allele should not be treated with Equetro® unless the benefit clearly outweighs the risk (see Warnings and Precautions, Laboratory Tests).

APLASTIC ANEMIA AND AGRANULOCYTOSIS

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data from a population-based case-control study demonstrate that the risk of developing these reactions is 5-8 times greater than in the general population. However, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia.

Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. However, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis.

Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormality. Nonetheless, complete pretreatment hematologic testing should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Please see enclosed full prescribing information including contraindications, warnings and precautions, and black boxed warning for additional safety information on Equetro®.

3. Data on file [301/302], Validus Pharmaceuticals, LLC
4. Calculated from data on file [303], Validus Pharmaceuticals LLC
Durable Safety and Tolerability Established During Extended Study

IN A 6-MONTH, OPEN-LABEL EXTENSION STUDY (n=92)*

- Adverse events were generally mild to moderate
- The most frequently reported adverse events were headache, dizziness, and rash
- No serious rash was reported

Minimal effect on weight as observed in two 3-week pivotal trials (n=208)4,5

TWO 3-WEEK PIVOTAL TRIALS (n=208)3

<table>
<thead>
<tr>
<th></th>
<th>Equetro</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in weight</td>
<td>+2.3 lb*</td>
<td>0.1 lb</td>
</tr>
</tbody>
</table>

- Low percentage of patients with clinically significant weight gain (Equetro 5.3%**, placebo 0.95%)

* p<0.001 vs. placebo
** p= 0.0112 vs. placebo
† Study completers, n =24. Clinically significant weight gain was defined as increase from baseline of ≥7%.
Reported data reflect weight change at endpoint (LOCF).

Additional Warnings and Precautions

WARNINGS
Suicidal Behavior and Ideation
Antiepileptic drugs (AEDs), including Equetro®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk of suicidal thinking or behavior compared to patients randomized to placebo.

Patients, their caregivers, and families should be informed that AEDs (and Bipolar Disorder in general) increase the risk of suicidal thoughts and behaviors and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behaviors, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Usage in Pregnancy
Carbamazepine can cause fetal harm when administered to a pregnant woman.

Nursing Mothers: Carbamazepine and its epoxide metabolite are transferred to breast milk during lactation. Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Drug Interactions: The potential exists for interaction between carbamazepine and any agent that induces or inhibits CYP3A4 or any agent that is metabolized by CYP3A4 or CYP1A2.

PLEASE SEE FULL PRESCRIBING INFORMATION INCLUDING CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, RECOMMENDED LABORATORY TESTS, CLINICALLY MEANINGFUL DRUG INTERACTIONS, AND BOXED WARNING FOR ADDITIONAL SAFETY INFORMATION ON EQUETRO® (CARBAMAZEPINE) EXTENDED-RELEASE CAPSULES.

Please advise your patients to read the Medication Guide thoroughly for additional information.


REMINDER: Equetro® contains carbamazepine. Please ensure patient is not taking any other form of carbamazepine.
### Before Considering an Atypical Anti-Psychotic, Evaluate the Benefits of **Equetro** (carbamazepine) Extended-Release Capsules

Most Common Adverse Events Reported in **Double-Blind, Placebo-Controlled** Trials (Incidence ≥ 5% and At Least Twice Placebo)*

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>EQUETRO® (n=251)</th>
<th>Placebo (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIZZINESS</td>
<td>44%</td>
<td>12%</td>
</tr>
<tr>
<td>SOMNOLENCE</td>
<td>32%</td>
<td>13%</td>
</tr>
<tr>
<td>NAUSEA</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>VOMITING</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>ATAXIA</td>
<td>15%</td>
<td>0%</td>
</tr>
<tr>
<td>PRURITIS</td>
<td>8%</td>
<td>0%</td>
</tr>
<tr>
<td>DRY MOUTH</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>AMBLYOPIA†</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>SPEECH DISORDER</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* Source: Table 1 of Equetro Full Prescribing Information
† Reported as blurred vision

### WARNING

**SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE**

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and stevens-johnson syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly caucasian populations, but the risk in some asian countries is estimated to be about 10 times higher. studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Equetro. patients testing positive for the allele should not be treated with Equetro unless the benefit clearly outweighs the risk (see warnings and precautions, laboratory tests).

**APLASTIC ANEMIA AND AGRANULOCYTOSIS**

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. data from a population-based case-control study demonstrate that the risk of developing these reactions is 5-8 times greater than in the general population. however, the overall risk of these reactions in the untreated general population is low, approximately six patients per one million population per year for agranulocytosis and two patients per one million population per year for aplastic anemia.

Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in association with the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. however, the vast majority of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulocytosis.

Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hematologic changes observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormality. nonetheless, complete pretreatment hematologic testing should be obtained as a baseline. if a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Please see enclosed full prescribing information including contraindications, warnings and precautions, and black boxed warning for additional safety information on Equetro®.
**Post-Hoc Analysis** Showed a Decrease in the Most Frequently Reported Adverse Events Over Time\(^8\)

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**Additional Warnings and Precautions**

**PRECAUTIONS AND POTENTIAL ADVERSE EFFECTS**

The most frequently observed adverse effects, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting.

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression. In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. **Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.** Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered. Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to RESPICITOR or to the class of non-nucleoside reverse transcriptase inhibitors. Before initiating therapy, a detailed history and physical examination should be made. Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

**CONTRAINDICATIONS**

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, and nefazodone. Likewise, on theoretical grounds, its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

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WARNING

SERIOUS DERMATOLOGIC REACTIONS AND HLA-B*1502 ALLELE

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APLASTIC ANEMIA AND AGRANULOCYTOSIS

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

PLEASE SEE ENCLOSED FULL PRESCRIBING INFORMATION INCLUDING CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, AND BLACK BOXED WARNING FOR ADDITIONAL SAFETY INFORMATION ON EQUETRO®.
12-Hour Consistent Release of Carbamazepine

- **25% immediate-release beads** release carbamazepine when swallowed for rapid absorption
- **40% extended-release beads** dissolve gradually over 8 to 12 hours
- **35% enteric-release beads** with pH-sensitive coating release carbamazepine slowly in the GI tract

* Tegretol® and Tegretol® XR are registered trademarks of Novartis Pharmaceuticals Corporation
Arrangement and color of beads in mechanism illustrations does not reflect actual placement or color within capsules

**Please see accompanying Full Prescribing Information.**

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**Additional Warnings and Precautions**

**WARNINGS**

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**Usage in Pregnancy**

Carbamazepine can cause fetal harm when administered to a pregnant woman.

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WARNING

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**Additional Warnings and Precautions**

**PRECAUTIONS AND POTENTIAL ADVERSE EFFECTS**
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Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression. In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy. Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered. Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to RESCRIPTOR or to the class of non-nucleoside reverse transcriptase inhibitors. Before initiating therapy, a detailed history and physical examination should be made. Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

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Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, and nefazodone. Likewise, on theoretical grounds, its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

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Please advise your patients to read the Medication Guide thoroughly for additional information.
Prescribe **Equetro® (carbamazepine) Extended-Release Capsules** as first-line therapy

- **Equetro®** is the first and only carbamazepine indicated for the treatment of the Acute Manic and Mixed Episodes of Bipolar 1 Disorders

- Minimal effect on weight as observed in two 3-week pivotal trials (n=208)

- Can be taken with or without food

- Tolerability and safety studied over time

**STARTING DOSAGE**

The recommended initial dose of Equetro® is 200 mg twice daily, given in divided doses

Available in 100, 200, and 300 mg capsules

Capsules shown actual size

**WARNING**

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