HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EQUETRO safely and effectively. See full prescribing information for EQUETRO.

EQUETRO (carbamazepine) extended-release capsules, for oral use
Initial U.S. Approval: 1968

WARNING: SERIOUS DERMATOLOGIC REACTIONS and APLASTIC ANEMIA AND AGRANULOCYTOSIS
See full prescribing information for complete boxed warning.

Serious Dermatologic Reactions

- **Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), have occurred with EQUETRO (5.1)**
- **Patients of Asian ancestry have a 10-fold greater risk of TEN/SJS, compared to other populations. In genetically at-risk patients, test for the HLA-B*1502 allele prior to initiating EQUETRO (2.3, 5.1)**
- **Discontinue EQUETRO if these reactions occur (5.1)**

Aplastic Anemia and Agranulocytosis

- **Aplastic anemia and agranulocytosis occurred with EQUETRO (5.2)**
- **Obtain complete pretreatment hematological testing. Consider discontinuing EQUETRO if significant bone marrow depression develops (2.3, 5.2)**

----------RECENT MAJOR CHANGES----------
Contraindications, concomitant use with delavirdine or other non-nucleoside reverse transcriptase inhibitors (4, 5.9) ---------- 11/2012
Contraindications, concomitant use with nefazodone (4) ---------- 11/2012
Warnings and Precautions, drug reaction with eosinophilia and systemic symptoms (5.3) and hepatic porphyria (5.10) ---------- 11/2012

----------INDICATIONS AND USAGE----------
EQUETRO is a mood stabilizer indicated for the treatment of acute manic or mixed episodes associated with bipolar I disorder (**1**)

----------DOSAGE AND ADMINISTRATION----------
- Recommended initial dose of EQUETRO: 200 mg twice daily (2.1)
- Adjust dose in 200-mg increments to achieve optimal clinical response (2.1)
- When discontinuing treatment, reduce dose gradually (2.1, 5.7)
- Monitoring serum carbamazepine concentrations may be useful in dose selection and miniziming risk of toxicity (2.2)
- Take capsules whole or open capsules and sprinkle beads over food (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Extended-Release Capsules: 100 mg, 200 mg, and 300 mg (3)

----------CONTRAINDICATIONS----------
- Bone marrow depression (4)
- Known hypersensitivity to carbamazepine (4)
- Known hypersensitivity to tricyclic antidepressants (4)
- Concomitant use with monoamine oxidase inhibitors (MAOIs) or use within 14 days of discontinuing an MAOI (4)
- Concomitant use with delavirdine or other non-nucleoside reverse transcriptase inhibitors. EQUETRO decreases efficacy of these drugs (4, 5.9)
- Concomitant use of nefazodone (4)

----------WARNINGS AND PRECAUTIONS----------
- *Drug Reaction with Eosinophilia and Systemic Symptoms:* Monitor for hypersensitivity. Discontinue if another cause can not be established (5.3)
- *Suicidal Behavior and Ideation:* Monitor for depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior (5.4)
- *Embryofetal Toxicity:* Advise women of child-bearing potential of possible risks to the fetus (5.4, 8.1)
- *Abrupt Discontinuation and Risk of Seizure:* Taper the dose when discontinuing treatment (5.6).
- *Hyponatremia:* Consider discontinuing EQUETRO in patients with significant symptomatic hyponatremia (5.7).
- *Cognitive and Motor Impairment:* Advise patients not to drive or operate machinery until they have gained sufficient experience on EQUETRO to gauge whether it adversely affects these activities (5.8)
- *Hepatic Porphyria:* Avoid EQUETRO use in patients with hepatic porphyria: can cause acute episodes of porphyria (5.10)

----------ADVERSE REACTIONS----------
Most common (>5% and 2 times placebo) adverse reactions were dizziness, somnolence, nausea, vomiting, ataxia, constipation, pruritus, dry mouth, asthenia, rash, blurred vision, and speech disorder (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Validus Pharmaceuticals LLC at 1-866-9VALIDUS or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
Cytochrome (CYP) 3A4 inhibitors, epoxide hydrolase inhibitors, CYP3A4 inducers, drugs metabolized by CYP1A2 or CYP3A4 (oral contraceptives, delavirdine, nefazodone), phenytoin, CNS depressants, lithium, chloroquine, mefloquine (7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8)

----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Can cause fetal harm. (5.5, 8.1)
Nursing Mothers: Discontinue drug or discontinue nursing, taking into consideration importance of drug to mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: November 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS DERMATOLOGIC ADVERSE REACTIONS and APLASTIC ANEMIA AND AGRANULOCYTOSIS

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 occurred in patients treated with carbamazepine. These syndromes may be accompanied by mucous membrane ulcers, fever, or painful rash occur. 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 patients of Asian descent is estimated to be about 10 times higher. There is 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 that is found almost exclusively in patients with Asian ancestry. Test for HLA-B*1502, prior to initiating EQUETRO in patients with an increased likelihood of carrying this allele. Avoid use of EQUETRO in patients testing positive for the allele unless the benefit clearly outweighs the risk. Discontinue EQUETRO if you suspect that the patient has a serious dermatologic reaction *[see Warnings and Precautions (5.1)]*.

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis can occur during treatment with EQUETRO. The risk of developing these reactions with EQUETRO is 5-8 times greater than in the general population. However, the overall risk in the general population is low (6 cases in a population of one million per year for agranulocytosis and two cases in a population of one million per year for aplastic anemia). Obtain a complete blood count before beginning treatment with EQUETRO, and monitor CBC periodically. Consider discontinuing if EQUETRO if significant bone marrow depression develops *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

1.1 Acute Manic or Mixed Episodes associated with Bipolar I Disorder

EQUETRO is indicated for treatment of patients with acute manic or mixed episodes associated with bipolar I disorder.

The efficacy of EQUETRO in acute mania was established in 2 randomized, double-blind, placebo-controlled, 3-week studies in adult patients meeting DSM-IV criteria for bipolar I disorder who had an acute manic or mixed episode *[see Clinical Studies (14.1)]*. The effectiveness of EQUETRO for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use EQUETRO for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended initial dose of EQUETRO is 200 mg administered twice daily. The dose may be increased by 200 mg per day to achieve optimal clinical response. Doses higher than 1600 mg per day have not been studied in mania associated with bipolar disorder.

When discontinuing treatment, reduce the dose gradually and avoid abrupt discontinuation in order to decrease the risk of seizure *[see Warnings and Precautions (5.6)]*.

2.2 Monitoring Serum Carbamazepine Concentration

Monitoring serum carbamazepine concentrations may be useful for dose selection, minimizing toxicity, and verifying drug compliance, especially in clinical conditions in which alterations in EQUETRO metabolism can occur (e.g., drug interactions) *[see Drug Interactions (7)]*.

2.3 Laboratory Testing Prior to Dosing

Prior to initiating treatment with EQUETRO, test patients with ancestry in genetically at-risk populations for the presence of the HLA-B*1502 allele. The high resolution genotype test is positive if one or two HLA-B*1502 alleles are present. Avoid use of EQUETRO in patients testing positive for the allele, unless the benefit clearly outweighs the risk *[see Boxed Warning, Warnings and Precautions (5.1)]*.

Prior to initiating EQUETRO in all patients, obtain a pre-treatment complete blood count including platelets and differential. Monitor CBC periodically *[see Warnings and Precautions (5.2)]*.

2.4 Administration Instructions

The EQUETRO capsules may be taken orally or may be opened and the beads sprinkled over food, such as a teaspoon of applesauce. Do not crush or chew EQUETRO capsules. EQUETRO can be taken with or without meals.

3 DOSAGE FORMS AND STRENGTHS

EQUETRO (carbamazepine) extended-release capsules for oral administration is supplied in three dosage strengths:

- 100 mg — Two-piece hard gelatin capsule yellow opaque cap with bluish green opaque body printed with SPD417 on one end and SPD417 and 100 mg on the other in white ink
- 200 mg — Two-piece hard gelatin capsule yellow opaque cap with blue opaque body printed with SPD417 on one end and SPD417 and 200 mg on the other in white ink.
- 300 mg — Two-piece hard gelatin capsule yellow opaque cap with blue body printed with SPD417 on one end and SPD417 and 300 mg on the other in white ink.

4 CONTRAINDICATIONS

- Bone marrow depression *[see Warnings and Precautions (5.2)]*.
- Known hypersensitivity to carbamazepine, such as anaphylaxis or serious hypersensitivity reaction *[see Warnings and Precautions (5.3)]*.
- Known hypersensitivity to any of the tricyclic compounds (e.g., amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. Hypersensitivity reactions include anaphylaxis and serious rash.
- Concomitant use of delavirdine or other non-nucleoside reverse transcriptase inhibitors. EQUETRO can substantially reduce the concentrations of these drugs through induction of CYP3A4. This can lead to loss of virologic response and possible resistance to these medications. *[see Warnings and Precautions (5.9) and Drug Interactions (7.2)]*
- Concomitant use of monoamine oxidase inhibitors (MAOIs). Before beginning treatment with EQUETRO, MAOIs should be discontinued for a minimum of 14 days. Concomitant use can cause serotonin syndrome.
- Concomitant use of nefazodone. This may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Dermatologic Reactions

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with carbamazepine treatment. These syndromes may be accompanied by mucous membrane ulcers, fever, or painful rash occur. Over 90% of carbamazepine-treated patients who experienced SJS/TEN developed these reactions within the first few months of treatment. The risk of these reactions is estimated to be about 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. However, the risk in some Asian countries is estimated to be about 10 times higher. Discontinue EQUETRO if you suspect that the patient has a serious dermatologic reaction. If signs or symptoms suggest SJS/TEN, do not resume treatment with EQUETRO.

*SJS, TEN, and HLA-B*1502 Allele*

Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of the HLA-B*1502 allele (an inherited variant of the HLA-B gene). Prior to initiating EQUETRO therapy in patients at higher likelihood for this allele, perform testing for HLA-B*1502. The high resolution genotype test is positive if one or two HLA-B*1502 alleles are present. Avoid use of EQUETRO in patients positive for the HLA-B*1502 allele unless the benefits clearly outweighs the risks of serious dermatologic reactions. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN associated with carbamazepine treatment.

The prevalence of the HLA-B*1502 allele may be higher in Asian populations: Hong Kong, Thailand, Malaysia, and parts of the Philippines (> 15%); Taiwan (10%), North China (4%); south Asians, including Indians (2 to 4%); and Japan and Korea (< 1%). HLA-B*1502 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans). The accuracy of estimated rates of the HLA-B*1502 allele in these populations may be limited by wide variability in rates within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry.

The HLA-B*1502 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as maculopapular rash, or to predict Drug Reaction with Eosinophilia and Systemic Symptoms hypersensitivity syndrome or non-serious rash (maculopapular eruption [MPE]) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) *[see Warnings and Precautions (5.3)]*.

Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other anti-epileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable.

*Hypersensitivity Reactions and HLA-A*3101 Allele*

Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms *[see Warnings and Precautions (5.3)]*.

HLA-A*3101 is expected to be present in the following frequencies: greater than 15% in patients of Japanese and Native American ancestry; up to about 10% in patients of Han Chinese, Korean, European, and Latin American ancestry; and up to about 5% in African-Americans and patients of Indian, Thai, Taiwanese, and Chinese (Hong Kong) ancestry.

The risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for HLA-A*3101.

Hypersensitivity and Limitations of HLA Genotyping

Application of HLA-B*1502 genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many HLA-B*1502 positive Asian and HLA-A*3101

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