

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 minimizing 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

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APLASTIC ANEMIA AND AGRANULOCYTOSIS**

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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

positive patients treated with carbamazepine will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in HLA-B*1502-negative and HLA-A*3101-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

5.2 Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis have occurred in patients treated with carbamazepine. Data from a population-based case-control study suggest 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. Consider discontinuing EQUETRO if any evidence of significant bone marrow depression develops. Clinical features can include fever, dyspnea on exertion, fatigue, easy bruising, petechiae, epistaxis, gingival bleeding, and heavy menses.

5.3 Drug Reaction with Eosinophilia and Systemic Symptoms/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan hypersensitivity, have occurred with carbamazepine. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. This disorder is variable in its expression, and other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Equetro should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Hypersensitivity

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin, primidone, and phenobarbital. A history of hypersensitivity reactions should be obtained for patients and their immediate family members. If such history is present, benefits and risks should be carefully considered, and, if carbamazepine is initiated, the signs and symptoms of hypersensitivity should be carefully monitored.

In patients who have exhibited hypersensitivity reactions to carbamazepine, approximately 25 to 30% may experience hypersensitivity reactions with oxcarbazepine.

5.4 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 (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which

had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 presents the absolute and relative risk by indication for all evaluated AEDs.

Table 1 Risk of suicidal thoughts or behavior (reactions) for antiepileptic drugs by indication in the pooled analysis

	Placebo	Antiepileptic Drugs		
Indication	Reactions Per 1000 Patients	Reactions Per 1000 Patients	Relative Risk: Incidence of Reactions in AED Group/ Incidence of Reactions in Placebo Group	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing EQUETRO or any other AED must balance the risk of suicidal thought or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs 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, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.5 Embryofetal Toxicity

EQUETRO is a Category D drug [see *Use in Specific Populations (8.1)*].

EQUETRO can cause fetal harm when administered to a pregnant woman. Apprise women of childbearing potential of this risk. Use in pregnancy only if the potential benefits of treatment outweigh the risks

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30–60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10–25 times a human daily dosage of 1200 mg on a mg/kg basis or 1.5–4 times the human daily dosage of 1200 mg on a mg/m² basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg, and 4 of 119 offspring showed other anomalies at 650 mg/kg (cleft palate, 1; talipes, 1; anophthalmos, 2).

Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

To provide additional information regarding the effects of in utero exposure to Equetro, physicians are advised to recommend that pregnant patients taking Equetro enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>

5.6 Abrupt Discontinuation and Risk of Seizure

Do not discontinue EQUETRO abruptly, because of the risk of seizure and other withdrawal signs/symptoms. Patients with seizure disorder are at increased risk of developing seizure and status epilepticus with attendant hypoxia and threat to life.

5.7 Hyponatremia

Hyponatremia can occur as a result of treatment with EQUETRO. In many cases, the hyponatremia appears to be caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The risk of developing SIADH with EQUETRO treatment appears to be dose-related. Elderly patients and patients treated with diuretics are at greater risk of developing hyponatremia. Consider discontinuing EQUETRO in patients with symptomatic hyponatremia. Signs and symptoms of hyponatremia include headache, new or increased seizure frequency, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Consider discontinuing EQUETRO in patients with symptomatic hyponatremia.

5.8 Potential for Cognitive and Motor Impairment

EQUETRO has the potential to cause impairment in judgment, cognition, and motor function. Caution patients about operating hazardous machinery, including automobiles, until they are reasonably certain the EQUETRO does not affect them adversely. Adverse reactions in the clinical trials in bipolar disorder included (EQUETRO, N= 251 and Placebo, N= 248): somnolence (32% vs. 13%), ataxia (15% vs. 0.4%), dizziness (44% vs. 12%), vertigo (2% vs. 1%), thinking abnormal (2% vs. 0.4%), tremor 3% vs. 1%), and blurred vision (6% vs. 2%) [*see Adverse Reactions (6.1)*].

5.9 Decreased Antiviral Effect of Non-nucleoside Reverse Transcriptase Inhibitors with Concomitant use of EQUETRO

Coadministration of EQUETRO with non-nucleoside reverse transcriptase inhibitors, including delavirdine, may lead to loss of virologic response and possible resistance. Through induction of CYP3A4, EQUETRO can markedly decrease the concentrations of these drugs. Coadministration of delavirdine and EQUETRO can decrease delavirdine concentrations by 90% [*see Contraindications (4), Warnings and Precautions (5.9), and Drug Interactions (7.2)*].

5.10 Hepatic Porphyrria

The use of EQUETRO should be avoided in patients with a history of hepatic porphyria (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Acute attacks have been reported in such patients receiving carbamazepine therapy. Carbamazepine administration has also been demonstrated to increase porphyrin precursors in rodents, a presumed mechanism for the induction of acute attacks of porphyria.

5.11 Increased Intraocular Pressure

Carbamazepine has mild anticholinergic activity. In patients with a history of increased intraocular pressure, consider assessing intraocular pressure before initiating treatment and periodically during therapy.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Serious dermatologic reactions: Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome [*see Warnings and Precautions (5.1)*]
- Aplastic anemia/agranulocytosis [*see Warnings and Precautions (5.2)*]
- Drug reaction with eosinophilia and systemic symptoms/multiorgan hypersensitivity [*see Warnings and Precautions (5.3)*]
- Suicidal Behavior and Ideation [*see Warnings and Precautions (5.4)*]
- Embryofetal Toxicity [*see Warnings and Precautions (5.5)*]
- Abrupt Discontinuation and Seizure Risk [*see Warnings and Precautions (5.6)*]
- Hyponatremia [*see Warnings and Precautions (5.7)*]
- Cognitive and Motor Impairment [*see Warnings and Precautions (5.8)*]
- Drug Interaction with Non-Nucleoside Reverse Transcriptase Inhibitors [*see Warnings and Precautions (5.9)*]
- Hepatic Porphyria [*see Warnings and Precautions (5.10)*]
- Anticholinergic Reactions and Increased Intraocular Pressure [*see Warnings and Precautions (5.11)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most commonly reported adverse reactions ($\geq 5\%$ in the EQUETRO group and at least twice placebo) in the pooled 3-week placebo-controlled trials in patients with acute mania associated with Bipolar I Disorder (Studies 1 and 2) were dizziness, somnolence, nausea, vomiting, ataxia, constipation, pruritus, dry mouth, asthenia, rash, blurred vision, and speech disorder [*see Clinical Studies (14.1)*]. The EQUETRO doses used were 400 to 1600 mg per day.

Table 2. Common Adverse Reactions Reported in Bipolar Disorder Studies 1 and 2 (Incidence $\geq 2\%$ and greater than placebo)

Adverse Reactions	EQUETRO® (N = 251)	Placebo (N = 248)
Dizziness	44%	12%
Somnolence	32%	13%
Nausea	29%	10%

Vomiting	18%	3%
Ataxia	15%	0.4%
Constipation	10%	5%
Pruritus	8%	2%
Dry Mouth	8%	3%
Asthenia	8%	4%
Rash	7%	4%
Blurred vision	6%	2%
Speech Disorder	6%	0.4%
Hypertension	3%	0.4%
Paresthesia	2%	1%
Thinking abnormal	2%	0.4%
Tremor	3%	1%
Twitching	2%	1%
Vertigo	2%	1%

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of carbamazepine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System: confusion, diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, tinnitus.

Digestive System: gastric distress, abdominal pain, diarrhea, anorexia.

Other: lupus erythematosus-like syndrome

One case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

7. DRUG INTERACTIONS

7.1 Pharmacokinetic Effects of other Drugs on EQUETRO

Drugs that Inhibit Cytochrome P450 3A4 (CYP3A4)

EQUETRO is metabolized primarily by CYP3A4 to the active carbamazepine-10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Inhibitors of CYP 3A4 and/or epoxide hydrolase can increase plasma levels of EQUETRO and its active metabolites, increasing plasma concentrations of EQUETRO and the risk of adverse reactions. It may be necessary to reduce the EQUETRO dose if used concomitantly with inhibitors of CYP3A4 and/or epoxide hydrolase. The following drugs are CYP3A4 inhibitors:

Acetazolamide, azole antifungals, cimetidine, clarithromycin, dalfopristin, danazol, delavirdine, diltiazem, erythromycin, fluoxetine, fluvoxamine, grapefruit juice, isoniazid, itraconazole, ketoconazole, loratadine, nefazodone, niacinamide, nicotinamide, protease inhibitors, propoxyphene, quinine, quinupristin, troleandomycin, valproate, verapamil, zileuton.

Drugs that Inhibit Epoxide Hydrolase and CYP3A4

Clarithromycin, erythromycin, and valproate also inhibit epoxide hydrolase, resulting in increased levels of the active metabolite carbamazepine-10,11-epoxide.

Drugs that Induce CYP3A4

CYP3A4 inducers can decrease serum concentrations of EQUETRO and decrease its effectiveness. It may be necessary to increase the dose of EQUETRO if used concomitantly with a CYP3A4 inducer. Such drugs include the following:

Cisplatin, doxorubicin, felbamate, rifampin, phenobarbital, phenytoin, primidone, methsuximide, and theophylline.

7.2 Pharmacokinetic Effects of EQUETRO on other Drugs

EQUETRO decreases the concentrations of the following drugs through induction of their metabolism:

Oral Contraceptives (CYP3A4 Substrates)

EQUETRO is a strong inducer of CYP3A4. EQUETRO can increase the metabolism of certain oral contraceptives (through CYP3A4 induction), leading to significantly lower concentrations. This can cause contraceptive failure or breakthrough bleeding. Consider alternatives to oral contraceptives that are significantly affected by induction of CYP3A4; or consider alternatives to EQUETRO.

Delavirdine and other Non-Nucleoside Reverse Transcriptase Inhibitors (CYP3A4 Substrates)

Through induction of CYP3A4, EQUETRO increases the metabolism of delavirdine and other non-nucleoside reverse transcriptase inhibitors and significantly reduces the plasma concentrations of these drugs. This can cause inadequate antiviral activity, loss of virologic response, and possible resistance to delavirdine or other non-nucleoside reverse transcriptase inhibitors. Therefore, the use of EQUETRO with non-nucleoside reverse transcriptase inhibitors is contraindicated [see *Contraindications (4)* and *Warnings and Precautions (5.9)*]

Nefazodone (CYP3A4 Substrate)

The use of EQUETRO is contraindicated with the use of nefazodone because the concomitant use may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect of nefazodone.

Warfarin (CYP1A2 and CYP3A4 Substrate)

Through induction of CYP1A2 and CYP3A4, EQUETRO decreases the concentration of warfarin and decreases its anticoagulant effectiveness.

Other CYP1A2 and CYP3A4 Substrates

EQUETRO induces CYP1A2 and CYP3A4, leading to decreased concentrations of drugs metabolized by CYP3A4 or CYP1A2. It may be necessary to increase the doses of such drugs when used concomitantly with EQUETRO. Drugs metabolized by CYP3A4 or CYP1A2 include the following:

Acetaminophen, alprazolam, amitriptyline, bupropion, buspirone, citalopram, clobazam, clonazepam, clozapine, cyclosporin, delavirdine, desipramine, diazepam, dicumarol, doxycycline, ethosuximide, felbamate, felodipine, glucocorticoids, haloperidol, itraconazole, lamotrigine, levothyroxine, lorazepam, methadone, midazolam, mirtazapine, nefazodone, nortriptyline, olanzapine, oral contraceptives, oxcarbazepine, phenytoin, praziquantel, protease inhibitors, quetiapine, risperidone, theophylline, topiramate, tiagabine, tramadol, triazolam, trazodone, valproate, warfarin, ziprasidone, and zonisamide.

EQUETRO increases the plasma levels of the following drugs by inhibition of their metabolism:

Clomipramine, Phenytoin, and Primidone

EQUETRO can increase the concentrations of clomipramine, phenytoin, and primidone. If a patient has been titrated to a stable dosage on one of these agents in this category, and then begins treatment with EQUETRO, it may be necessary to decrease the dose of these drugs.

Phenytoin

Phenytoin levels have been reported to increase or decrease in the presence of carbamazepine. There are multiple pharmacokinetic mechanisms for changes in phenytoin levels when used concomitantly with EQUETRO. Monitor phenytoin serum levels carefully when used concomitantly with EQUETRO.

7.3 Pharmacodynamic Drug Interactions

Monoamine Oxidase Inhibitors

Concomitant treatment with EQUETRO is contraindicated during use of an MAOI or within 14 days after discontinuing an MAOI. Concomitant use can cause serotonin syndrome.

Lithium

Concomitant administration of EQUETRO and lithium can increase the risk of neurotoxic adverse reactions. Consider reducing the dose of lithium or EQUETRO when using these drugs concomitantly.

CNS Depressants

The concomitant use of EQUETRO and other CNS depressants can increase the risk of respiratory depression, profound sedation, hypotension, and syncope. CNS depressants include: alcohol, opioid analgesics, benzodiazepines, tricyclic antidepressants, sedative/hypnotics, anticonvulsants, antipsychotics, antihistamines, anticholinergics, alpha and beta blockers, general anesthetics, muscle relaxants, and illicit CNS depressants. Consider reducing the dose of CNS depressants or EQUETRO when using these drugs concomitantly.

Chloroquine and Mefloquine

The anti-malarial drugs chloroquine and mefloquine can antagonize the activity of EQUETRO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

EQUETRO can cause fetal harm when administered to a pregnant woman. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Adverse developmental effects were seen in animal reproduction studies with carbamazepine. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be apprised of the potential hazard to the fetus [*see Warning and Precautions (5.4)*].

Pregnancy Registry

Patients should be encouraged to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1888-233-2334. Information about the North American Drug Pregnancy Registry can be found at <http://www.massgeneral.org/aed/> [*see Warnings and Precautions (5.4)*].

Clinical Considerations

When treating a pregnant woman with EQUETRO, carefully consider both the potential risks and benefits of treatment and provide appropriate counseling. Tests to detect major congenital malformations using current accepted procedures should be considered a part of routine prenatal care in pregnant women receiving carbamazepine [see *Warnings and Precautions (5.4)*].

Human Data

Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

Transplacental passage of carbamazepine is rapid (30–60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal carbamazepine and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhea, and/or decreased feeding have also been reported in association with maternal carbamazepine use. These symptoms may represent a neonatal withdrawal syndrome.

Animal Data

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10–25 times a human daily dosage of 1200 mg on a mg/kg basis or 1.5–4 times the human daily dosage of 1200 mg on a mg/m² basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg, and 4 of 119 offspring showed other anomalies at 650 mg/kg (cleft palate, 1; talipes, 1; anophthalmos, 2).

8.2 Labor and Delivery

The effect of carbamazepine on human labor and delivery is unknown. Carbamazepine and its epoxide metabolite are transferred to breast milk during lactation. There is a potential for serious adverse reactions in nursing infants exposed to carbamazepine. Nursing mothers should consider the potential benefits and risks of treatment when deciding on whether to discontinue nursing or to discontinue treatment with EQUETRO, taking into account the importance of the drug to the mother.

8.3 Nursing Mothers

Carbamazepine and its epoxide metabolite are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants exposed to EQUETRO, a decision should be made whether to discontinue nursing or to discontinue treatment with EQUETRO, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of EQUETRO in pediatric and adolescent patients have not been established.

8.5 Geriatric Use

Clinical studies of EQUETRO did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

10.1 Human Experience

Lowest known lethal dose of carbamazepine: adults, >60 grams (39-year-old man). Highest known doses survived: adults, 30 grams (31-year-old woman); children, 10 grams (6-year-old boy); small children, 5 grams (3-year-old girl).

Signs and Symptoms: The first signs and symptoms of carbamazepine overdose appear after 1–3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 grams) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria, and acetonuria. ECG may show dysrhythmias.

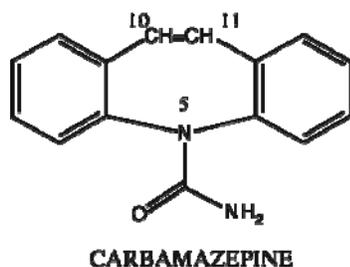
Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates, or hydantoin are taken at the same time, the signs and symptoms of acute poisoning with carbamazepine may be aggravated or modified.

10.2 Management of Overdosage

For the most up to date information on management of EQUETRO overdose, contact the certified poison center for your area by calling 1-800-222-1222 (or at www.poisson.org). In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

11 DESCRIPTION

EQUETRO (carbamazepine) is a mood stabilizer available for oral administration as 100 mg, 200 mg, and 300 mg extended-release capsules of carbamazepine, USP. Carbamazepine is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27. The chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and the structural formula is:



EQUETRO[®] is a multi-component capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice-daily dosing of EQUETRO[®].

Inactive ingredients: citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate, and other ingredients.

The 100 mg capsule shells contain gelatin-NF, FD&C Blue #2, Yellow Iron Oxide, and Titanium Dioxide, and are imprinted with white ink; the 200 mg capsule shells contain gelatin-NF, Yellow Iron Oxide, FD&C Blue #2, and Titanium Dioxide, and are imprinted with white ink; and the 300 mg capsule shells contain gelatin-NF, FD&C Blue #2, Yellow Iron Oxide, and Titanium Dioxide, and are imprinted with white ink.

12 Clinical Pharmacology

12.1 Mechanism of Action

Although numerous pharmacological effects of carbamazepine have been described in the published literature (e.g., modulation of ion channels [sodium and calcium], receptor-mediated neurotransmission [GABAergic, glutamatergic, and monoaminergic], and intracellular signaling pathways in experimental preparations), the contribution of these effects to the efficacy of carbamazepine in acute manic or mixed episodes associated with bipolar disorder is unknown.

12.3 Pharmacokinetics

Carbamazepine (CBZ)

Absorption: Following a single 200 mg oral extended-release dose of carbamazepine, peak plasma concentration was 1.9 ± 0.3 $\mu\text{g/mL}$ and the time to reach the peak was 19 ± 7 hours. Following repeat dose administration (800 mg every 12 hours), the peak levels were 11.0 ± 2.5 $\mu\text{g/mL}$ and the time to reach the peak was 5.9 ± 1.8 hours. The pharmacokinetics of extended-release carbamazepine is linear over the single dose range of 200–800 mg.

Carbamazepine is 76% bound to plasma proteins. Carbamazepine is primarily metabolized in the liver. Cytochrome P450 3A4 was identified as the major isoform responsible for the formation of carbamazepine-10,11-epoxide. Since carbamazepine induces its own metabolism, the half-life is also variable. The average half-life ranged from 35 to 40 hours following a single extended-release dose of carbamazepine and from 12 to 17 hours following repeated dosing. The apparent oral clearance was 25 ± 5 mL/min following a single dose and 80 ± 30 mL/min following multiple dosing.

Carbamazepine-10,11-epoxide (CBZ-E): Carbamazepine-10,11-epoxide is considered to be an active metabolite of carbamazepine. Following a single 200 mg oral extended-release dose of carbamazepine, the peak plasma concentration of carbamazepine-10,11-epoxide was 0.11 ± 0.012 $\mu\text{g/mL}$ and the time to reach the peak was 36 ± 6 hours. Following chronic administration of an extended-release dose of carbamazepine (800 mg every 12 hours), the peak levels of carbamazepine-10,11-epoxide were 2.2 ± 0.9 $\mu\text{g/mL}$ and the time to reach the peak was 14 ± 8 hours. The plasma half-life of carbamazepine-10,11-epoxide following administration of carbamazepine is 34 ± 9 hours. Following a single oral dose of extended-release carbamazepine (200–800 mg) the AUC and C_{max} of carbamazepine-10,11-epoxide were less than 10% of carbamazepine. Following multiple dosing of extended-release carbamazepine (800–1600 mg daily for 14 days), the AUC and C_{max} of carbamazepine-10,11-epoxide were dose-related, ranging from 15.7 $\mu\text{g}\cdot\text{hr/mL}$ and 1.5 $\mu\text{g/mL}$ at 800 mg/day to 32.6 $\mu\text{g}\cdot\text{hr/mL}$ and 3.2 $\mu\text{g/mL}$ at 1600 mg/day, respectively, and were less than 30% those of carbamazepine. Carbamazepine-10,11-epoxide is 50% bound to plasma proteins.

Food Effect: A high-fat meal diet increased the rate of absorption of a single 400 mg dose (mean T_{max} was reduced from 24 hours, in the fasting state, to 14 hours, and C_{max} increased from 3.2 to 4.3 $\mu\text{g/mL}$) but not the extent (AUC) of absorption. The elimination half-life remained unchanged between fed and fasting state. The multiple-dose study conducted in the fed state showed that the steady-state C_{max} values were within the therapeutic concentration range. The pharmacokinetic profile of extended-release carbamazepine was similar when given by sprinkling the beads over applesauce compared to the intact capsule administered in the fasted state.

Elimination: After oral administration of ^{14}C -carbamazepine, 72% of the administered radioactivity was found in the urine and 28% was found in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged carbamazepine

Metabolism: In vitro data indicate carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine-10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of carbamazepine is not known.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of carbamazepine is not known. Consider reducing the dosage in patients with hepatic impairment.

Effect of Age: Carbamazepine is more rapidly metabolized to carbamazepine-10,11-epoxide in young children than in adults. In children below the age of 15, there is an inverse relationship between CBZ-E/CBZ ratio and increasing age. The safety and effectiveness of EQUETRO[®] in pediatric and adolescent patients have not been established.

Effect of Gender: No difference in the mean AUC and C_{max} of carbamazepine and carbamazepine-10,11-epoxide was found between males and females.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity: Administration of carbamazepine to Sprague-Dawley rats for 2 years in the diet at doses of 25, 75, and 250 mg/kg/day (low dose approximately 0.2 times the human daily dose of 1200 mg on a mg/m² basis) resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Mutagenicity: Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results.

Impairment of Fertility: The effects of carbamazepine on male and female fertility have not been studied.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4–52 weeks at dosage levels of 50–400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis.

14 CLINICAL STUDIES

14.1 Bipolar I Disorder (Acute Manic or Mixed Episodes)

The efficacy of EQUETRO in the acute treatment of manic or mixed symptoms associated with bipolar I disorder was established in two 3-week, multicenter, randomized, double-blind, placebo-controlled, flexible-dose studies (Studies 1 and 2) in adult patients who met the DSM-IV criteria for bipolar I disorder, manic or mixed episode. In both studies, patients must have had a history of at least one previous manic or mixed episode. They must have had a Young Mania Rating Scale (YMRS) baseline score of at least 20. The YMRS is an 11-item instrument, ranging from 0 to 60 (greater score indicates a more severe manic disorder) that measures symptoms associated with a manic state: elevated mood, increased motor activity/energy, sexual interest, sleep, irritability, speech, language-thought disorder, content, disruptive/aggressive behavior, appearance, and insight.

In Studies 1 and 2, patients were hospitalized for at least one week. They received placebo during a 5-day lead-in period and subsequently were randomized to receive placebo or EQUETRO, initially at a dose of 200 mg twice daily (400 mg per day). If tolerated, the total daily dose could be increased by 200 mg once daily to a maximum dose of 800 mg twice daily (1600 mg/day). The mean EQUETRO dose during the last week was 952 mg/day in Study 1 and 726 mg/day in Study 2.

Patients were permitted to receive lorazepam for agitation or insomnia (up to 6 mg/day during the placebo-lead in period, up to 4 mg/day during the first week of controlled treatment, and up to 2 mg/day during the second week of

treatment; no lorazepam was permitted during the third week of treatment. They were permitted to continue their routine psychotherapy. Patients were not allowed to use antipsychotics, lithium, antidepressants, or sedatives/hypnotics (other than lorazepam) during the studies. There were no significant differences in lorazepam use between the EQUETRO and placebo groups in both studies.

In Studies 1 and 2, the primary endpoint was the mean change from baseline in the YMRS total score at Day 21. In both studies, treatment with EQUETRO was statistically significantly superior to placebo, as measured by the mean decrease in YMRS score at Day 21 (Table 3)

The key secondary efficacy endpoint in both trials was the change in Clinical Global Impression-Severity (CGI-S) Scale score. The CGI-S an investigator-rated global assessment of symptom severity that is scored on a 7-point scale (1 = normal, not ill); 7 = severely ill). In both studies, there was a statistically significant decrease from baseline in the mean CGI-S score at Day 21, compared to placebo (Table 3).

Table 3. Efficacy Results in the 2 Trials in Patients with Bipolar I Disorder – Change in mean YMRS score from baseline to Week 3 and change in mean CGI-S from baseline to Week 3

	Study 1		Study 2	
	EQUETRO (n=94)	Placebo (n=98)	EQUETRO (n=120)	Placebo (n=115)
Young Mania Rating Scale (YMRS)				
Baseline YMRS	26.6	27.3	28.5	27.9
Week 3 YMRS	17.9	22.1	13.4	20.8
LS mean change	-7.8	-4.8	-14.8	-7.0
LS mean difference from placebo*	-3.5	—	-8.0	—
p-value	P= 0.033		(< 0.0001	
Clinical Global Impression-Severity Scale (CGI-S)				
Baseline CGI-S	4.4	4.4	4.5	4.5
Week 3 CGI-S	3.7	4.1	3	3.9
Change from Baseline at Week 3	-0.7	-0.3	-1.5	-0.6
Difference (p-value)	-0.4 (0.025)_		-0.9 (< 0.0001_	

* Least squares mean for the difference defined as the change from baseline at Week 3 in the EQUETRO group minus that in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EQUETRO (carbamazepine) extended-release capsules are 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: Supplied in bottles of 120 NDC 30698-419-12
- 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: Supplied in bottles of 120 NDC 30698-421-12
- 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: Supplied in bottles of 120 NDC 30698-423-12

16.2 Storage

Store at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) [see USP controlled room temperature].

Protect from light and moisture

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients and caregivers that a Medication Guide is available. Instruct them to read the Medication Guide before taking EQUETRO.

- *Serious Dermatologic Reactions*
Inform patients and caregivers about the risk of potentially fatal, serious skin reactions and the signs and symptoms that may signal a serious skin reaction. Instruct patients to consult with their healthcare provider immediately if a skin reaction occurs during treatment with EQUETRO [see *Warnings and Precautions (5.1)*].
- *Agranulocytosis and Aplastic Anemia*
Inform patients and caregivers about the risk of potentially fatal agranulocytosis and aplastic anemia and the signs and symptoms that may signal these reactions. Instruct them to contact their healthcare provider immediately if symptoms occur [see *Warnings and Precautions (5.2)*].
- *Drug Reaction with Eosinophilia and Systemic Symptoms*
Inform patients of the early toxic signs and symptoms of a potential hematologic, dermatologic, hypersensitivity, or hepatic reactions. Advise patients that these signs and symptoms may signal a serious reaction and to report any occurrence immediately to their healthcare provider [see *Warnings and Precautions (5.3)*].
- *Suicidal Ideation and Behavior*
Counsel patients, their caregivers, and families that AEDs, including EQUETRO, may increase the risk of suicidal thinking and behavior and advise them of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Instruct patients, caregivers and families to report behaviors of concern immediately to healthcare providers [see *Warnings and Precautions (5.4)*].
- *Embryofetal Toxicity*
Advise women of childbearing potential that EQUETRO may cause fetal harm. Use in pregnancy only if the potential benefits of treatment outweigh the risks [see *Warning and Precautions (5.5)* and *Use in Specific Populations (8.1)*].

Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see *Warning and Precautions (5.5)* and *Use in Specific Populations (8.1)*].
- *Abrupt Discontinuation and Risk of Seizure*
Inform patients that abrupt discontinuation of EQUETRO can cause seizures or an increase in seizure frequency. Advise patients that the drug should be tapered when discontinued [see *Warnings and Precautions (5.6)*].
- *Hyponatremia*
Advise patients that EQUETRO may reduce serum sodium concentrations especially if they are taking other medications that can lower sodium. Advise patients to report symptoms of low sodium like nausea, tiredness, lack of energy, confusion, seizures, or more frequent or more severe seizures [see *Warnings and Precautions (5.7)*].

- *Potential for 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 their ability to drive or operate machinery.
Advise patients to exercise caution if alcohol is taken in combination with EQUETRO therapy, due to a possible additive sedative effect [see *Warnings and Precautions (5.8)*].
- *Decreased Antiviral Effect of Delavirdine or other Non-nucleoside Reverse Transcriptase Inhibitors*
Inform patients that EQUETRO can significantly decrease serum concentrations of these drugs.
Concomitant use of the drugs and EQUETRO are contraindicated [see *Warnings and Precautions (5.9)*].
- *Concomitant Use with other Carbamazepine Products*
Inform patients that Equetro contains carbamazepine and should not be used in combination with any other medications containing carbamazepine.

Manufactured for Validus Pharmaceuticals LLC, 119 Cherry Hill Road, Suite 310, Parsippany, NJ 07054,

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