EQUETRO® LETTER OF MEDICAL NECESSITY

Equetro® (carbamazepine) Extended-Release Capsules 100 mg • 200 mg • 300 mg

PATIENT INFORMATION

Patient's Name _____ Date of Birth ____ /____ /_____

Patient's Address _____ Apt. _____

City _____ State _____ Zip Code _____

Payer Name _____ Patient's Member ID _____

DIAGNOSIS

☐ Bipolar 1 Disorder ☐ Epilepsy ☐ Pain of Trigeminal Neuralgia ☐ ICD-10 Code _____

PRESCRIPTION

☐ EQUETRO _____ mg BID

RATIONALE FOR REQUEST OF MEDICAL NECESSITY (Check all that apply)

☑ No AB-rated generic of EQUETRO® has been approved by the FDA. There is no substitute drug product.

☑ EQUETRO® is the only oral dosage form of carbamazepine that the FDA has approved for Bipolar I Disorder with Acute Manic or Mixed Episodes. Substituting any other drug product constitutes off-label use of that drug product.

☐ Patient has trouble swallowing and the sprinkle option is necessary. Only EQUETRO® is appropriate for sprinkling.

☐ Patient started and maintained on EQUETRO®. Destabilization or hospitalization may occur if patient switched to another formulation of carbamazepine.

☐ Other _____

PRESCRIBER INFORMATION

Name _____ Date ____ /____ /_____

NPI/DEA # _____

Address _____ Suite _____

City _____ State _____ Zip Code _____

Office Contact Name _____

Office Contact Email Address _____

Office Contact Phone Number _____

PHYSICIAN CERTIFICATION: By signing below, I certify that I am prescribing EQUETRO for the patient named above and that the above therapy is medically necessary and alternative therapy should not be dispensed. I also certify that I have received the necessary authorizations, including those required by state law and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), to release the above-referenced information and other health and medical information to any pharmacies or others involved in the authorization for payment or fulfillment of this medication.

Prescriber's Signature: _____ Date ____ /____ /_____

Please see additional Important Safety Information on back.

IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS DERMATOLOGIC 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. 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. 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.

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 EQUETRO if significant bone marrow depression develops.

INDICATIONS AND USAGE

EQUETRO is:

1. A mood stabilizer indicated for the treatment of acute manic or mixed episodes associated with bipolar I disorder.
2. Indicated for the treatment of the pain associated with trigeminal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.
3. An anti-epileptic drug (AED) indicated for the treatment of partial seizures with complex symptomatology, generalized tonic-clonic seizures, and mixed seizures.

Limitations of Usage: EQUETRO is not indicated for the treatment of absence seizures (petit mal). Carbamazepine has been associated with increased frequency of generalized convulsions in these patients.

ADMINISTRATION

Prior to initiating treatment with EQUETRO, genetically at-risk patients should be tested for the presence of the HLA-B*1502 allele. Avoid use of EQUETRO in patients testing positive for the allele unless the benefit clearly outweighs the risk.

A complete blood count and eye examination should be obtained as a baseline and periodically evaluated.

See full Prescribing Information for additional administration information, including recommendations for pretreatment screening.

CONTRAINDICATIONS

- Bone marrow depression.
- Known hypersensitivity to carbamazepine, such as anaphylaxis or serious hypersensitivity reaction.
- 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 that are substrates for CYP3A4. 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.
- 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.

WARNINGS AND PRECAUTIONS

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. 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 EQUETRO 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. Avoid use of EQUETRO in patients positive for the HLA-B*1502 allele unless the benefits clearly outweigh 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.

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

Hypersensitivity and Limitations of HLA Genotyping: Application of HLA genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management.

See full Prescribing Information for additional information on pretreatment genotype screening.

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis have occurred in patients treated with carbamazepine. 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.

Drug Reaction with Eosinophilia and Systemic Symptoms/Multiorgan Hypersensitivity

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multiorgan Hypersensitivity, has occurred with carbamazepine. Some of these events have been fatal or life-threatening. 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.

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 should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. 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.

(Continued)

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.

Embryofetal Toxicity

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

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/

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. However, in the event of an allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary.

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.

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.

Potential for Loss of Virologic Response to Non-nucleoside Reverse Transcriptase Inhibitors that are substrates for CYP3A4 with Concomitant use of EQUETRO

Coadministration of EQUETRO with non-nucleoside reverse transcriptase inhibitors, including delavirdine, is contraindicated because it may lead to loss of virologic response and possible resistance. Coadministration of delavirdine, an NNRTI and a substrate of CYP3A4, and EQUETRO can decrease delavirdine concentrations by 90%.

Liver Damage

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure, have been reported. In some cases, hepatic effects may progress despite discontinuation of the drug. In addition, rare instances of vanishing bile duct syndrome have been reported. Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

AV Heart Block

AV heart block, including second and third degree block, have been reported following carbamazepine treatment. This condition occurred generally, but not solely, in patients with underlying EKG abnormalities or risk factors for conduction disturbances.

Hepatic Porphyria

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.

Increased Intraocular Pressure

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

ADVERSE REACTIONS

In EQUETRO, the most commonly reported adverse reactions observed in the pivotal trials in patients with acute mania associated with bipolar I disorder were dizziness, somnolence, nausea, vomiting, ataxia, constipation, pruritus, dry mouth, asthenia, rash, blurred vision, speech disorder, hypertension, paresthesia, thinking abnormal, tremor, twitching, and vertigo.

During post-marketing, the following additional adverse reactions were identified:

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

Digestive System: gastric distress, abdominal pain, diarrhea, anorexia. *Laboratory Tests:* thyroid function tests (decreased values for T3 and T4). *Other:* lupus erythematosus-like syndrome.

To report SUSPECTED ADVERSE REACTIONS, contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch or Validus Pharmaceuticals LLC at 1-866-982-5436 or info@validuspharma.com. See full Prescribing Information for additional adverse reactions associated with carbamazepine.

DRUG INTERACTIONS

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; the potential exists for interaction between EQUETRO and any agent that affects CYP3A4 and/or epoxide hydrolase. EQUETRO is also an inducer of CYP1A2, 2B6, and 2C9/19 and may therefore reduce plasma concentrations ofco-medications mainly metabolized by CYP 1A2, 2B6, 2C9/19, and 3A4, through induction of their metabolism. When used concomitantly with EQUETRO, monitoring of concentrations or dosage adjustment of these agents may be necessary. See Full Prescribing Information for Potential Drug Interactions.

SPECIFIC POPULATIONS

Pregnancy and Lactation: EQUETRO can cause fetal harm when administered to a pregnant woman. Pregnancy registry and epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including neural tube defects and malformations involving other body systems (e.g., craniofacial defects and cardiovascular malformations). 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.

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, considering the importance of the drug to the mother.

Females and Males of Reproductive Potential: EQUETRO can increase metabolism of certain hormonal contraceptives (through CYP3A4 induction) such as oral and subdermal implant contraceptives, leading to significant lower plasma concentrations of hormones. This can cause contraceptive failure or breakthrough bleeding.

Pediatric: The safety and effectiveness of EQUETRO have not been established in pediatric patients for indications other than epilepsy.

Geriatric: 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.

DOSAGE FORM

EQUETRO is available as oral capsules containing 100 mg, 200 mg, and 300 mg of carbamazepine.

EQUETRO is available only by prescription.

Please see Full Prescribing Information at www.equetro.com.

Validus PHARMACEUTICALS