SHERI SPIRT

PSYCHIATRY

16 East 96th Street Unit 1A

(212) 595 6901

SSDR18@aol.com

TEGRETOL (one formulation branded as equetro)

## Pharmacology

### Mechanism of Action

Stabilizes inactivated state of sodium channels, thereby making neurons less excitable

May reduce activity of nucleus ventralis of the thalamus or decrease synaptic transmission or summation of temporal stimulation leading to neuronal discharge

### Absorption

Bioavailability: 85% (oral suspension)

Peak serum time: 4.5 hr (immediate-release tablets); 3-12 hr (extended-release tablets); 1.5 hr (oral suspension)

### Distribution

Protein bound: 75-90%

Vd: 1.5 L/kg (neonates); 1.9 L/kg (children); 0.59-2 L/kg (adults)

### Metabolism

Via hepatic CYP3A4

Metabolites: Carbamazepine 10,11-epoxide

Enzymes induced: CYP1A2, CYP2C9, CYP3A4

### Elimination

Half-life: 25-65 hr (initial dosing); decreases to 10-20 hr after autoinduction; 35-40 hr (extended release)

Excretion: Urine (72%); feces (28%)

### Pharmacogenomics

HLA-B\*1502

* It is estimated that 1 in 20 patients with HLA-B\*1502 will have a severe dermatologic reaction (eg, TEN, SJS) when taking carbamazepine
* This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including Han Chinese, Filipinos, Malaysians, South Asian Indians, and Thais

HLA-A\*3101

* 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 HLAA\*3101, an inherited allelic variant of the HLA-A gene, in patients using carbamazepine; these hypersensitivity reactions include Stevens Johnson syndrome and toxic epidermal necrolysis
* HLA-A\*3101 is expected to be carried by more than 15% of patients of Japanese, Native American, Southern Indian (eg, Tamil Nadu) and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American, and other Indian ancestry; and up to about 5% in African-Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry

Genetic testing laboratories

* The following companies provide genetic testing for HLA variants
* Kashi Clinical Laboratories (www.kashilab.com)
* LabCorp (http://www.labcorp.com/)
* Specialty Laboratories (http://www.specialtylabs.com)
* Quest (http://www.questdiagnostics.com)

### Dosage Forms & Strengths

tablet, chewable (Epitol)

* 100mg

tablet, immediate-release (Tegretol)

* 200mg

### Indications

### Epilepsy

Indicated for the treatment of partial seizures with complex symptomatology (eg, psychomotor, temporal lobe), generalized tonic-clonic seizures (grand mal), and mixed seizure patterns, which include the seizure types listed here or other partial or generalized seizures

Maintenance dose range: 800-1200 mg/day PO in divided doses

Therapeutic range: 4-12 mg/L (16.9-50.8 micromoles/L)

Maximum dose of 1600 mg/day recommended (rarely, some patients have required 1.6-2.4 g/day)

Tablet (immediate-release)

* Initial: 200 mg PO q12hr
* Increase qWeek by 200 mg/day divided PO q6-8hr

Tablet/capsule (extended-release)

* Initial: 200 mg PO q12hr
* Increase qWeek by 200 mg/day PO divided q12hr

Oral suspension

* Initial: 10 mL (200 mg) PO q6hr
* Increase qWeek by up to 200 mg/day PO divided q6-8hr

IV solution

* Indicated as replacement therapy in adults for PO carbamazepine formulations, when PO administration is temporarily not feasible
* Approved as temporary use (ie, ≤7 days) for the following seizure types
	+ Partial seizures with complex symptomatology
	+ Generalized tonic-clonic seizures
	+ Mixed seizure patterns which include the above, or other partial or generalized seizures
* Dose
	+ The total daily dose of carbamazepine IV is 70% of the total daily PO dose from which patients are being
	+ Equally divide the total daily dose of the IV in four 30-minute infusions, separated by 6 hr
	+ Patients should be switched back to oral carbamazepine administration at their previous total daily oral dose and frequency of administration as soon as clinically appropriate
	+ IV administration has not been studies for >7 days

Limitations of use

* Not indicated for absence seizures (including atypical absence); carbamazepine has been associated with increased frequency of generalized convulsions in these patients

### Trigeminal Neuralgia

Indicated for pain associated with trigeminal neuralgia; beneficial results have also been reported in glossopharyngeal neuralgia; carbamazepine is not a simple analgesic and should not be used for the relief of trivial aches or pains

Maintenance dose range: 400-800 mg/day PO in divided doses; attempts to reduce or discontinue the drug should be made at least every 3 months throughout the treatment period

Maximum dose of 1200 mg/day recommended

Tablet (immediate-release)

* Initial: 200 mg/day on day 1 divided q12hr
* Increase by up to 200 mg/day in increments of 100 mg q12hr, to dose range of 400-800 mg/day divided twice daily; not to exceed 1200 mg/day

Tablet/capsule (extended-release)

* Initial (XR tablet): 200 mg/day PO on day 1 divided q12hr
* Initial (XR capsules): 200 mg PO once on the first day; may increase dose by up to 200 mg/day using increments of 100 mg q12hr to reach an effective/tolerated dose; not to exceed 1200 mg/day
* Increase by up to 200 mg/day in increments of 100 mg q12hr, to dose range of 400-800 mg/day divided twice daily; not to exceed 1200 mg/day

Oral suspension

* Initial: 200 mg PO on day 1 divided q6hr
* Increase by up to 200 mg/day in increments of 50 mg q6hr, to dose range of 400-800 mg/day divided twice daily; not to exceed 1200 mg/day

### Bipolar Mania

Equetro

* Indicated for treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
* Initial: 200 mg PO q12hr
* Increase by increments of 200 mg/day; not to exceed 1600 mg/day

### Dosage Modifications

Renal impairment

* Glomerular filtration rate <10 mL/min: Administer 75% of dose and monitor
* Peritoneal dialysis and hemodialysis: Administer 75% of dose and monitor

Hepatic impairment

* Use caution; drug is metabolized primarily in the liver

### Restless Legs Syndrome (Off-label)

100-600 mg PO qHS for up to 5 weeks

### Schizophrenia (Off-label)

200-1300 mg/day for 2.5-8 weeks

### Postherpatic Neuralgia

100-200 mg PO qDay; may increase slowly to 1200 mg/day

### Intravenous Carbamazepine (Orphan)

Orphan designation for treatment of epilepsy patients who cannot take anything by mouth

Orphan sponsor

* Lundbeck, LLC; Four Parkway North; Deerfield, IL 60015

**Contraindications**

#### Contraindicated (40)

* apixaban
* artemether/lumefantrine
* atazanavir
* boceprevir
* cariprazine
* cobimetinib
* daclatasvir
* darunavir
* delavirdine
* dienogest/estradiol valerate
* efavirenz
* elbasvir/grazoprevir
* elvitegravir/cobicistat/emtricitabine/tenofovir df
* etravirine
* isocarboxazid
* ledipasvir/sofosbuvir
* linezolid
* lumacaftor/ivacaftor
* lumefantrine
* lurasidone
* naloxegol
* nefazodone
* nevirapine
* ombitasvir/paritaprevir/ritonavir
* ombitasvir/paritaprevir/ritonavir & dasabuvir
* panobinostat
* phenelzine
* pirfenidone
* praziquantel
* procarbazine
* regorafenib
* rilpivirine
* roflumilast
* selegiline
* selegiline transdermal
* telaprevir
* telithromycin
* tranylcypromine
* vandetanib
* voriconazole

## Adverse Effects

### >10%

Ataxia (15%)

Dizziness (44%)

Drowsiness (32%)

Nausea (29%)

Vomiting (18%)

### 1-10%

Dry mouth (8%)

### Rare

MI

Stevens-Johnson syndrome

Hepatic failure

Punctate cortical lens opacities

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

### Frequency Not Defined

Hemopoietic system: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, anemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda

Skin: Toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) (see Black Box Warnings), pruritic and erythematous rashes, urticaria, photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, diaphoresis, generalized exanthematous pustulosis, and onychomadesis

Cardiovascular system: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis; very rare cases of hepatic failure

Pancreatic: Pancreatitis

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence (rare reports of impaired male fertility and/or abnormal spermatogenesis)

Laboratory: Albuminuria, glycosuria, elevated BUN, decreased plasma calcium, and microscopic deposits in the urine, decreased values of thyroid function tests

Nervous system: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, hyperacusis, isolated cases of neuroleptic malignant syndrome

Digestive system: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis, and stomatitis, liver damage

Eyes: Scattered punctate cortical lens opacities, increased intraocular pressure as well as conjunctivitis

Musculoskeletal system: Aching joints and muscles, and leg cramps

Metabolism: Fever and chills; SIADH; cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion; decreased levels of plasma calcium leading to osteoporosis

Other: Multiorgan hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases, signs or symptoms may include fever, skin rashes, vasculitis, lymphadenopathy, disorders mimicking lymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly and abnormal liver function tests

## Warnings

### Black Box Warnings

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with carbamazepine; studies in patients of Chinese ancestry found a strong association between the risk of developing SJS/TEN and the presence of HLA-B\*1502, an inherited allelic variant of the HLA-B gene; HLA-B\*1502 is found almost exclusively in patients of Asian ancestry, with populations across broad areas of Asia producing such descendants; patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk; patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B\*1502 prior to initiation of treatment with carbamazepine

Aplastic anemia and agranulocytosis reported; patients with a previous history of adverse hematologic reaction to any drug may be at increased risk

### Contraindications

Documented hypersensitivity

History of bone marrow suppression

Administration of MAO inhibitors within last 14 days

Coadministration with nefazodone; carbamazepine decreases plasma levels of nefazodone and its active metabolite

Coadministration with NNRTIs (eg, delavirdine, efavirenz, etravirine, nevirapine, rilpivirine); carbamazepine induces CYP3A4 and may substantially reduce NNRTI serum concentration

Jaundice, hepatitis

Pregnancy (especially first trimester: risk of fetal carbamazepine syndrome)

### Cautions

Monitor for notable changes in behavior that might indicate suicidal thoughts or depression and notify healthcare provider immediately if behavioral changes observed

Discontinue if significant bone marrow depression occurs

Withdraw gradually

Increased risk of agranulocytosis and aplastic anemia

May cause ECG abnormalities; use caution in patients with conduction abnormalities; AV heart block, including second and third degree block, reported following carbamazepine treatment; effect occurred generally, but not solely, in patients with underlying EKG abnormalities or risk factors for conduction disturbances

May exacerbate absence seizures; in the event of allergic or hypersensitivity reaction, more rapid substitution of alternative therapy may be necessary

Bipolar mania: Efficacy inconsistent; APA recommends use after failure of or if there is resistance to lithium and valproate

May cause psychosis/confusion/agitation; elderly patients are at greater risk

May render oral contraceptives ineffective

Higher risk of potentially fatal skin reactions (SJS/TEN) in patients of Asian ancestry (genetic testing recommended); increased risk of developing hypersensitivity reactions with presence of HLAA\*3101 or HLA-B\*1502, inherited allelic variants of the HLA-A and HLA-B gene (see Pharmacogenomics in the Pharmacology section);

Hyponatremia may occur and appears to be a result of SIADH; may be dose-related and elderly individuals are at greater risk

Associated with hypotension, bradycardia, AV block, and signs and symptoms of HF

Fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), reported

Not a simple analgesic; do not use to relieve minor aches and pains

Tegretol suspension contains sorbitol; not for administration to patients with rare hereditary problems of fructose intolerance

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

Mild anticholinergic activity; use caution in patients with snesitivity to anticholinergic effects

Hepatic effects

* Hepatic effects reported ranging from slight elevations in liver enzymes to rare cases of hepatic failure
* In some cases, hepatic effects may progress despite discontinuation
* Rare instances of vanishing bile duct syndrome reported; consists of a variable clinical course ranging from fulminant to indolent, involving the destruction and disappearance of the intrahepatic bile ducts
* Some cases associated other immunoallergenic syndromes (eg, multiorgan hypersensitivity [DRESS syndrome], serious dermatologic reactions)
* As an example there has been a report of vanishing bile duct syndrome associated with Stevens-Johnson syndrome, and in another case an association with fever and eosinophilia
* Baseline and periodic evaluations of liver function, particularly in patients with history of liver disease, must be performed during treatment with this drug since liver damage may occur; drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease

## Pregnancy & Lactation

Pregnancy category: D

Lactation: Enters breast milk; not recommended (AAP states compatible with nursing; however, adverse reactions in breastfeeding infant are possible; take into account the importance of the drug to the mother before deciding to discontinue breastfeeding or the drug)

### Pregnancy Categories

A:Generally acceptable. Controlled studies in pregnant women show no evidence of fetal risk.

B:May be acceptable. Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk.

C:Use with caution if benefits outweigh risks. Animal studies show risk and human studies not available or neither animal nor human studies done.

D:Use in LIFE-THREATENING emergencies when no safer drug available. Positive evidence of human fetal risk.

X:Do not use in pregnancy. Risks involved outweigh potential benefits. Safer alternatives exist.

NA:Information not available.

**WARNING: SERIOUS DERMATOLOGIC ADVERSE REACTIONS and APLASTIC ANEMIA AND AGRANULOCYTOSIS**

**Serious Dermatologic Reactions and HLA-B\*1502 Allelle**

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 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, Laboratory Tests)].

**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)].

**CONTRAINDICATIONS**

EQUETRO is contraindicated in patients with bone marrow depression, known hypersensitivity to carbamazepine, such as anaphylaxis or serious hypersensitivity reaction, or known hypersensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. Hypersensitivity reactions include anaphalyxis and serious rash. Concomitant use of delaviridine or other non-nucleoside reverse transcriptase inhibitors is contraindicated. 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 is contraindicated. Before administration of EQUETRO, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits. Concomitant use can cause serotonin syndrome.

Coadministration of EQUETRO with nefazodone is contraindicated. Coadministration of carbamazepine and nefazodone may result in insufficient plasma concentrations of nefazodone and its active metabolite to achieve a therapeutic effect.

**WARNINGS**

**Serious Dermatologic Reactions**

Discontinue EQUETRO if you suspect that a patient has a serious dermatologic reaction. If signs or symptoms suggest SJS/TEN, do not resume treatment with EQUETRO.

**Drug Reaction with Eosinophilia and Systemic Symptoms/Multiorgan Sensitivity**

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. 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.

**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.

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.

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.

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.

**Abrupt Discontinuation and Risk of Seizure**

Do not discontinue EQUETRO abruptly, because of the risk of seizure and other withdrawal signs/symptoms.

**Usage in Pregnancy**

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. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of potential harm to the fetus.

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 America 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" \t "_blank).

**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.

**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.

**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.

**General**

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk of bone marrow depression.

In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life.

**Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.**

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of latent psychosis, and in elderly patients, of confusion or agitation, should be considered.

Co-administration of EQUETRO and delavirdine may lead to loss of virologic response and possible resistance to the class of non-nucleoside reverse transcriptase inhibitors.