NOVARTIS

Tegretol®

Antiepileptic, neurotropic, and psychotropic agent

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Tablets: 200 mg carbamazepine.

CR tablets (modified-release film-coated tablets, divisible): 200 mg and 400 mg carbamazepine.

Oral Suspension: 5 mL (= 1 measure) contain 100 mg carbamazepine.

Active substance

Carbamazepine.

Certain dosage strengths and dosage forms may not be available in all countries.

INDICATIONS

- Epilepsy
  - ï Complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalization.
  - ï Generalized tonic-clonic seizures. Mixed forms of seizures.

  Tegretol is suitable for both monotherapy and combination therapy.

  Tegretol is usually not effective in absences (petit mal) and myoclonic seizures (see section WARNINGS AND PRECAUTIONS).
- Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
- Alcohol-withdrawal syndrome.
- Idiopathic trigeminal neuralgia and trigeminal neuralgia due to multiple sclerosis (either typical or atypical). Idiopathic glossopharyngeal neuralgia.
- Painful diabetic neuropathy.
- Diabetes insipidus centralis. Polyuria and polydipsia of neurohormonal origin.

DOSAGE REGIMEN AND ADMINISTRATION

Method of administration

The tablets and the oral suspension (to be shaken before use) may be taken during, after, or between meals. Tablets should be taken with a little liquid.

The CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid. The oral suspension (one measure = 5 mL = 100 mg; half a measure = 2.5 mL = 50 mg) is particularly suitable for patients who have difficulty in swallowing tablets or need initial careful adjustment of the dosage.

As a result of slow, controlled release of the active substance from the CR tablets, these are designed to be taken in a twice-daily dosage regimen.

Since a given dose of Tegretol oral suspension will produce higher peak levels than the same dose in tablet form, it is advisable to start with low doses and increase them slowly so as to avoid adverse reactions.

Switching patients from Tegretol tablets to oral suspension: this should be done by giving the same number of mg per day in smaller, more frequent doses (e.g., oral suspension three times a day (t.i.d.) instead of tablets twice a day (b.i.d)).

Switching patients from conventional tablets to CR tablets: clinical experience shows that in some patients the dosage in the form of CR tablets may need to be increased.

Epilepsy

When possible, Tegretol should be prescribed as monotherapy.

Treatment should be initiated with a low daily dosage, to be slowly increased until an optimal effect is obtained.

The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre) (see section WARNINGS AND PRECAUTIONS).

When Tegretol is added to existing antiepileptic therapy, this should be done gradually while maintaining, or if necessary, adapting the dosage of the other antiepileptic(s) (see sections INTERACTIONS AND CLINICAL PHARMACOLOGY - PHARMACOKINETICS).

General target population / Adults

Dosage in Epilepsy

Initially, 100 to 200 mg once or twice daily; the dosage should be slowly raised until ï generally at 400 mg 2 to 3 times daily ï an optimum response is obtained. In some patients 1,600 mg or even 2,000 mg daily may be appropriate.

Dosage in Acute mania and maintenance treatment of bipolar affective disorders

Dosage range: about 400 to 1,600 mg daily, the usual dosage being 400 to 600 mg daily given in 2 to 3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for maintenance therapy of bipolar disorders in order to ensure optimal tolerability.

Dosage in Alcohol-withdrawal syndrome

Average dosage: 200 mg 3 times daily. In severe cases, it can be raised during the first few days (e.g., to 400 mg 3 times daily). At the start of treatment for severe withdrawal manifestations, Tegretol should be given in combination with sedative-hypnotic drugs (e.g., clomethiazole, chlordiazepoxide). After the acute stage has abated, Tegretol can be continued as monotherapy.

Dosage in Trigeminal neuralgia and glossopharyngeal neuralgia

The initial dosage of 200 to 400 mg should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1,200 mg/day. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

Dosage in Painful diabetic neuropathy

Average dosage: 200 mg 2 to 4 times daily.

Dosage in Diabetes insipidus centralis

Average dosage for adults: 200 mg 2 to 3 times daily. In children the dosage should be reduced proportionally to the child's age and body weight.

Special populations

Patients with hepatic or renal impairment

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

Pediatric patients (below 18 years)

Dosage in Epilepsy

For children aged 4 years or less, a starting dose of 20 to 60 mg/day, increasing by 20 to 60 mg every second day, is recommended. For children over the age of 4 years, therapy may begin with 100 mg/day, increasing at weekly intervals by 100 mg.

Maintenance dosage: 10 to 20 mg/kg body weight daily in divided doses, e.g.,

Up to 1 year of age	100 to 200 mg daily (= 5 to 10 mL = 1 to 2 measures of oral suspension)
1 to 5 years of age	200 to 400 mg daily (= 10 to 20 mL = 2× 1 to 2 measures of

	oral suspension)
6 to 10 years of age	400 to 600 mg daily (= 20 to 30 mL = 2 to 3× 2 measures of oral suspension)
11 to 15 years of age	600 to 1,000 mg daily (= 30 to 50 mL = 3× 2 to 3 measures of oral suspension (plus an extra measure of 5 mL in case of administration of 1,000 mg))
>15 years of age:	800 to 1,200 mg daily (same as adult dose).

Maximum recommended dose

Up to 6 years of age: 35 mg/kg/day 6

to 15 years of age: 1,000 mg/day

>15 years of age: 1,200 mg/day.

Dosage in Diabetes insipidus centralis

In children the dosage should be reduced proportionally to the child's age and body weight. Average dosage for adults: 200 mg 2 to 3 times daily.

Geriatric patients (65 years of age or above)

Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of Tegretol should be selected with caution in elderly patients.

Dosage in Trigeminal neuralgia

In elderly patients, an initial dose of 100 mg twice daily is recommended. The initial dosage of 100 mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1,200 mg/day. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

CONTRAINDICATIONS

- Known hypersensitivity to carbamazepine or structurally related drugs (e.g., tricyclic antidepressants) or any other component of the formulation
- Patients with atrioventricular block
- Patients with a history of bone-marrow depression
- Patients with a history of hepatic porphyrias (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda)
- The use of Tegretol is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs) (see section INTERACTIONS).

WARNINGS AND PRECAUTIONS

Tegretol should be given only under medical supervision. Tegretol should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse hematological reactions to other drugs, or interrupted courses of therapy with Tegretol.

Hematological effects

Agranulocytosis and aplastic anemia have been associated with Tegretol; however, due to the very low incidence of these conditions, meaningful risk estimates for Tegretol are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anemia.

Transient or persistent decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Tegretol. However, in the majority of cases these effects prove transient and are unlikely to signal the onset of either aplastic anemia or agranulocytosis. Nonetheless, complete pretreatment blood counts, including platelets (and possibly reticulocytes and serum iron), should be obtained at baseline, and periodically thereafter.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored. Tegretol should be discontinued if any evidence of significant bone-marrow depression appears.

Patients should be made aware of early toxic signs and symptoms of a potential hematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage appear, the patient should be advised to consult the physician immediately.

Serious dermatologic reactions

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN; also known as Lyellôs syndrome) and Stevens-Johnson syndrome (SJS), have been reported very rarely with Tegretol. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with Tegretol. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g., SJS, Lyellôs syndrome/TEN) appear, Tegretol should be withdrawn at once and alternative therapy should be considered.

Pharmacogenomics

There is growing evidence of the role of different HLA alleles, including HLA-B*1502 and HLA-A*3101, in predisposing patients to immune-mediated adverse reactions.

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese ancestry and Thai origin found a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. The frequency of

HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations and is about 8% in Thai populations. Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g., Taiwan, Malaysia, and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the population (e.g., above 15% in the Philippines and some Malaysian populations). Allele frequencies up to about 2%, 6%, and 12% have been reported in Korea, India, and Singapore, respectively. The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (<1%).

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e., the ñcarrier frequencyò) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of HLA-B*1502 allele is highly recommended prior to the initiation of carbamazepine therapy in new patients of Asian ancestry (see below Information for the Healthcare professionals). The use of Tegretol should be avoided in tested patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore 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. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low. Screening is generally not recommended for any current Tegretol users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Association with HLA-A*3101

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash. Retrospective genome-wide studies in Japanese and Northern European populations reported association between severe skin reactions (SJS, TEN, DRESS, AGEP and maculopapular rash) associated with carbamazepine use and the presence of the HLA-A*3101 allele in these patients.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population. The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations, with some exceptions within 5-12%. Prevalence above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10%-15% in other native ethnicities in these same regions.

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a

copy of the allele on at least one of their two chromosomes (i.e., the ñcarrier frequencyò) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with Tegretol (see below INFORMATION FOR THE HEALTHCARE PROFESSIONALS). The use of Tegretol should be avoided in patients who are found to be positive for HLA-A*3101 unless the benefits clearly outweigh the risks. Screening is generally not recommended for any current Tegretol users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

Limitation of genetic screening

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many patients positive for HLA-B*1502 and treated with Tegretol will not develop SJS/TEN. In populations in which HLA-B*1502 is common, these reactions rarely occur in HLA-B*1502-negative patients. Many patients positive for HLA-A*3101 and treated with Tegretol will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for the healthcare professionals

If testing for the presence of the HLA-B*1502 allele is performed, high-resolution ñHLA-B*1502 genotypingò is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected. Similarly, if testing for the presence of the HLA-A*3101 allele is performed, high-resolution ñHLA-A*3101 genotypingò respectively is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected and negative if no HLA- A*3101 alleles are detected.

Other dermatologic reactions

Mild skin reactions, e.g., isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.

The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine and may predict the risk of these reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However, the HLA-B*1502 allele has not been found to predict the risk of these

aforementioned skin reactions.

Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been reported with Tegretol. If a patient develops these reactions after treatment with Tegretol, the drug must be discontinued, and an alternative treatment started.

Tegretol may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g., lungs, kidneys, pancreas, myocardium, and colon). (See section ADVERSE DRUG REACTIONS).

The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopapular rash.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30 % of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal®).

Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g., phenytoin, primidone, and phenobarbital).

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Tegretol should be withdrawn immediately.

Seizures

Tegretol should be used with caution in patients with mixed seizures, which includes absences, either typical or atypical. In all these conditions, Tegretol may exacerbate seizures. In the event of exacerbation of seizures, Tegretol should be discontinued.

Hepatic function

Baseline and periodic evaluations of hepatic function must be performed during treatment with Tegretol, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.

Renal function

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hyponatremia

Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-

lowering medicinal products (e.g., diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatremia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy.

Anticholinergic effects

Tegretol has shown mild anticholinergic activity. Patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy (see section ADVERSE DRUG REACTIONS).

Psychiatric effects

The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic drugs has shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known.

Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Pregnancy and females of reproductive potential

Carbamazepine may be associated with fetal harm when administered to a pregnant woman (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL). Tegretol should be used during pregnancy only if the potential benefit justifies the potential risks.

Adequate counselling should be made available to all pregnant women and women of chto w Tm0 0.000s reF2 12 aQq1 0 0 1 85.104 368.214(o000MCID 7>> BDC q0.000006d)-29e to all p