NOVARTIS

TEGRETOL® (carbamazepine)

200 mg tablet

200 mg and 400 mg controlled release, film-coated tablet

100mg/5 ml suspension

Professional Information

Document status: Final

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SCHEDULING STATUS: S3

1. NAME OF THE MEDICINAL PRODUCT

TEGRETOL® 200 Tablets

TEGRETOL® CR 200 Divitabs

TEGRETOL® CR 400 Divitabs

TEGRETOL® S Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TEGRETOL 200 Tablets: Each tablet contains 200 mg carbamazepine.

TEGRETOL CR 200 and TEGRETOL CR 400 Controlled release, film-coated divisible tablets: Each controlled-release tablet contains 200 mg and 400 mg carbamazepine respectively.

TEGRETOL S Suspension: 100 mg/5 ml carbamazepine with methylparaben 0,12 % m/v, propylparaben 0,03 % m/v and 0,1 % m/v sorbic acid as preservatives.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

TEGRETOL® 200

White, round tablet, flat on both sides, with slightly bevelled edges. Imprinted CG on one side, and G/K with a score on the other. Diameter approximately 9,0 mm. Thickness approximately 3,7 mm.

TEGRETOL® CR 200

Beige orange, ovaloid shaped, convex, film-coated tablets, scored on both sides. Imprinted C/G on one side and H/C on the other. Approximately 12,2 x 5,6 mm and approximately 5,0 mm thick.

TEGRETOL® CR 400

Brownish orange, ovaloid shaped, convex, film-coated tablets, scored on both sides. Imprinted CG/CG on one side and ENE/ENE on the other. Approximately 16,7 x 6,7 mm and approximately 6,0 mm thick.

TEGRETOL® S

A milky white, viscous suspension with the odour and taste of caramel.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy with motor and psychic manifestations:

- psychomotor or temporal-lobe epilepsy
- generalized tonic-clonic seizure
- mixed forms of seizures
- complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalisation.

Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.

Idiopathic trigeminal neuralgia.

Idiopathic glossopharyngeal neuralgia.

TEGRETOL is suitable for both monotherapy and combination therapy.

TEGRETOL is usually not effective in absences (petit mal) and myoclonic seizures. (See section 4.4).

4.2 Posology and method of administration

The TEGRETOL 200 tablets, TEGRETOL CR DIVITABS and the TEGRETOL S suspension (to be shaken before use) may be taken during, after, or between meals. The TEGRETOL CR DIVITABS should be swallowed whole with adequate amount of fluid.

TEGRETOL S suspension (one measure = 5 ml = 100 mg) is particularly suitable for infants and small children and for elderly patients as the liquid form affords easier and more flexible 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 S suspension produces higher peak levels than the same dose in tablet form, therapy should be started with low doses and should be increased slowly to avoid adverse reactions.

Dosage should be as low as is consistent with a satisfactory effect. Blood plasma levels can be used to help establish the optimum dose. In the treatment of epilepsy, the dose of TEGRETOL usually requires total plasma-carbamazepine concentrations of about 4 to 12 µg/ml (17 to 50 µmol/liter).

When the patient is transferred from another anticonvulsant medicine to TEGRETOL, the dosage of the first should be reduced gradually.

In switching patients from TEGRETOL tablets to suspension, the same daily dose should be given in smaller, more frequent doses. 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.

Due to interactions and different anti-epileptic medicine pharmacokinetics, the dosage of TEGRETOL should be selected with caution in elderly patients.

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.

Determination of plasma levels may help in establishing the optimum dosage.

When TEGRETOL is added to existing anti-epileptic therapy, this should be done gradually while maintaining, or if necessary, adapting the dosage of the other anti-epileptic(s) (see section 4.5).

Usual dosage for adults

Initially, 100 mg to 200 mg once or twice a day, followed by a slow increase until usually at a level of 400 mg twice or three times a day, the best response is obtained. In some instances 1 600 mg in 3 to 4 divided doses may be necessary. However, the maximum daily dose of Oral suspension is limited to 1 200 mg. Adult patients who require doses exceeding 1 200 mg up to 1 600 mg/ day of oral suspension, should be switched to alternative oral formulations of Tegretol, such as immediate release and prolonged release tablets.

Usual dosage for children

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, has been 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 - 20 mg/kg body weight daily in divided doses, e.g.: (1 medicine measure = 5 ml)

Age up to 1 year: 100 to 200 mg daily (= 5 to 10 ml = 1 to 2 measures of suspension)

1 to 5 years: 200 to 400 mg daily (=10 to 20 ml = 2 x 1 to 2 measures of suspension)

6 to 10 years: 400 to 600 mg daily (= 20 to 30 ml = 2 to 3 x 2 measures of suspension)

11 to 15 years: 600 to 1000 mg daily (= 30 to 50 ml = 3 x 2 to 3 measures of suspension)

>15 years of age: 800 to 1200 mg/day (same as daily dose in adults)

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, in some instances it may necessitate 1 600 mg daily). The dosage should then be gradually reduced to the lowest possible maintenance level. In elderly and particularly sensitive patients (see section 4.4) an initial dosage of 100 mg twice a day is recommended.

Acute mania and maintenance treatment of (bipolar) affective disorders

Dosage range:

Approximately 400 to 1 600 mg daily, the usual dosage being 400 to 600 mg daily given in 2 to 3 divided doses. However, the maximum daily dose of Oral suspension is limited to 1 200 mg. Adult patients who require doses exceeding 1 200 mg up to 1 600 mg/ day of oral suspension, should be switched to alternative oral formulations of TEGRETOL, such as immediate release and prolonged release tablets.

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.

4.3 Contraindications

- Known hypersensitivity to TEGRETOL, or structurally related medicines 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 porphyria (e.g. acute intermittent porphyria, variegate porphyria)
- The use of TEGRETOL is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of MAOIs (see section 4.5).
- The active substance of TEGRETOL passes into the breast milk (about 25 – 60 % of plasma concentration). Mothers taking TEGRETOL should not breastfeed their infants.
- Previous Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

4.4 Special warnings and precautions for use

Patients should be made aware of early toxic signs and symptoms of a potential haematological 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 haemorrhage appear, the patient should be advised to consult the medical practitioner immediately.

Medical supervision during treatment is essential.

Haematological effects

Aplastic anaemia and agranulocytosis have been reported. Transient or persistent decreased platelet or white blood cell counts may occur; in the majority of cases these effects prove transient. Complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a 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.

Serious dermatological reactions

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported with TEGRETOL. Patients with serious dermatological reactions may require hospitalisation, 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.

If signs and symptoms suggestive of severe skin reactions (e.g. SJS, TEN) appear, TEGRETOL should be withdrawn at once and alternative therapy should be considered (see section 4.3).

Immune-mediated ADR's

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.

*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, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (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, with a frequency between 5 – 15 %. A prevalence of 10 – 15 % has been estimated in some ethnic groups.
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.
The use of TEGRETOL should be avoided in patients who are found to be positive for HLA-A*3101.

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.
*HLA-B*1502 allele*
Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between SJS/TEN skin reactions associated with TEGRETOL 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 % and 6 % have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous people 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 “carrier frequency”) 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 should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with TEGRETOL.

The use of TEGRETOL should be avoided in tested patients who are found to be positive for HLA-B*1502. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic medicines associated with SJS/TEN. Consideration should therefore be given to avoiding use of other medicines 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 TEGRETOL therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with TEGRETOL will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. Similarly many patients positive for HLA-A*3101 and treated with TEGRETOL may not develop severe cutaneous side-effects and patients negative for this allele can still develop them.

The role of other possible factors in the development of, and morbidity from, these severe cutaneous side-effects, such as other anti-epileptic medicines dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for the Healthcare professionals

When testing for the presence of the HLA-B*1502 allele, high resolution “HLA-B*1502 genotyping”

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 presence of the HLA-A*3101 allele should be performed, high-resolution "HLA-A*3101 genotyping" 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

Skin reactions, e.g. macular or maculopapular exanthema, can also occur. However, since it may be difficult to differentiate the early signs of more serious skin reactions from less severe skin reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing TEGRETOL.

The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from TEGRETOL, 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 medicine 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, hepatosplenomegaly, 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, colon) (see section 4.8).

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

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

If signs and symptoms 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

Liver function tests should also be undertaken periodically. If allergic skin reactions occur, if the platelet count diminishes, if tests reveal deterioration in liver function, or if any serious adverse symptoms develop, TEGRETOL should be withdrawn.

Renal function

Baseline and periodic complete urinanalysis and blood urea determinations are recommended.

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 haematological reactions to other medicines, or interrupted courses of therapy with TEGRETOL.

Hyponatraemia

Hyponatraemia is known to occur with TEGRETOL. 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 TEGRETOL 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 hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

TEGRETOL 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 4.8).

Special excipients

TEGRETOL S suspension contains parahydroxybenzoates which may cause allergic reactions (possibly delayed). It also contains sorbitol and, therefore, should not be administered to patients with rare hereditary problems of fructose intolerance.

Other

Medical supervision during treatment is essential.

Abnormalities of liver function and jaundice have been associated with long-term treatment.

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 behavior have been reported in patients treated with antiepileptic medicines such as TEGRETOL in several indications. A meta-analysis of randomized placebo controlled trials of antiepileptic medicines has shown an increased risk of suicidal ideation and behavior. The mechanism of this risk is not known. Therefore patients should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behavior emerge.

Pregnancy and females of reproductive potential

TEGRETOL may be associated with foetal harm when administered to a pregnant woman (see section 4.6).

Adequate counselling should be made available to all pregnant women and women of childbearing potential, regarding the risks associated with pregnancy due to potential teratogenic risk to the foetus (see section 4.6).

Women of childbearing potential should use effective contraception unaffected by enzyme inducing medicines, during treatment with TEGRETOL and for a period of 28 days after discontinuation of treatment (see section 4.6).

Endocrinological effects

Breakthrough bleeding has been reported in women taking hormonal contraceptives; the reliability of hormonal contraceptives may be adversely affected by TEGRETOL, and women of childbearing age should be advised to consider using alternative forms of birth control while taking TEGRETOL.

Dose reduction and withdrawal effects

Tolerance may develop to some of the untoward effects of TEGRETOL. These effects can be minimised by gradual increase in dosage and adjustment to the lowest effective maintenance

dosage.

Abrupt withdrawal of TEGRETOL may precipitate seizures therefore carbamazepine should be withdrawn gradually over a 6-month period. If treatment with TEGRETOL has to be withdrawn abruptly in a patient with epilepsy, the change-over to the new anti-epileptic medicine should be made under cover of a suitable medicine (e.g. diazepam or phenytoin).

Falls

TEGRETOL treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 4.8) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term TEGRETOL treatment.

Interactions

Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with TEGRETOL can induce adverse reactions (increase of carbamazepine or carbamazepine-10,11 epoxide plasma concentrations respectively). The dosage of TEGRETOL should be adjusted accordingly and/or the plasma levels monitored.

Co-administration of CYP3A4 inducers with TEGRETOL may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of TEGRETOL may have to be adjusted.

TEGRETOL is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism (see section 4.5**)**.

Female patients of child-bearing potential should be warned that the concurrent use of TEGRETOL with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.5

and 4.6). Alternative non-hormonal forms of contraception are recommended when using TEGRETOL.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P4503A (CYP3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine-10,11-epoxide. Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations, which could induce adverse reactions. Co-administration of CYP 3A4 inducers might increase the rate of TEGRETOL metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

TEGRETOL is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolised by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11-epoxide. Coadministration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11-epoxide plasma concentrations. Such inhibitors are valproic acid, valpromide, valnoctamide and progabide.

Medicines that may raise carbamazepine plasma levels

Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of TEGRETOL should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below.

Analgesics, anti-inflammatory medicines: dextropropoxyphene, ibuprofen

Androgens: danazol

Antibiotics: macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin) and ciprofloxacin

Antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazadone, viloxazine

Antiepileptics: stiripentol, vigabatrin

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole

Antihistamines: terfenadine

Antipsychotics: olanzapine

Antituberculosis: isoniazid

Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir)

Carbonic anhydrase inhibitors: acetazolamide

Cardiovascular medicines: diltiazem, verapamil

Gastrointestinal medicines: cimetidine, omeprazole

Muscle relaxants: oxybutynin, dantrolene

Platelet aggregation inhibitors: ticlopidine

Other interactions: nicotinamide (only in high dosage), grapefruit juice

Medicines that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels

Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of TEGRETOL should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide, valpromide and brivaracetam.

Medicines that may decrease carbamazepine and/or carbamazepine-10,11-epoxide plasma levels

The dose of TEGRETOL may have to be adjusted when used concomitantly with the substances described below:

Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbitone, phensuximide, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 µg/ml before adding TEGRETOL to the treatment), primidone and, although the data are partly contradictory, possibly also clonazepam

Antineoplastics: cisplatin or doxorubicin

Antituberculosis: rifampicin

Bronchodilators or anti-asthma medicines: theophylline, aminophylline

Dermatological medicines: isotretinoin

Other interactions: herbal preparations containing St John's wort (*Hypericum perforatum*)

Effect of TEGRETOL on plasma levels of concomitant medicines

TEGRETOL may lower the plasma level, or diminish - or even abolish - the activity of certain medicines. The dosage of the following medicines may have to be adjusted to clinical requirements:

Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol (long-term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity)

Antibiotics: doxycycline, rifabutin

Anticoagulants: oral anticoagulants (e.g. warfarin, rivaroxaban and others e.g. dabigatran, apixaban, endoxaban)

Antidepressants: bupropion, citalopram, mianserin, nefazodone, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine). The use of TEGRETOL is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering TEGRETOL, MAOIs should be discontinued for a minimum of 2 weeks or longer, if the clinical situation permits. (See section 4.3).

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. There have been reports of an increase in plasma mephenytoin levels. To avoid phenytoin intoxication and subtherapeutic

concentrations of carbamazepine, it is recommended to adjust the plasma concentration of phenytoin to 13 µg/ml before adding TEGRETOL to the treatment.

Antifungals: itraconazole, voriconazole. Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole

Antihelmintics: praziquantel, albendazole

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus

Antipsychotics: clozapine, haloperidol and bromperidol, quetiapine, risperidone, ziprasidone, olanzapine, aripiprazole, paliperidone

Anxiolytics: alprazolam, midazolam

Bronchodilators or anti-asthma medicines: theophylline

Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered)

Cardiovascular medicines: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine

Corticosteroids: corticosteroids (e.g. prednisolone, dexamethasone)

Medicines used in erectile dysfunction: tadalafil

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus

Thyroid agents: levothyroxine

The level of serum folic acid should be observed during anticonvulsant therapy since TEGRETOL may enhance the metabolism of folic acid.

Combinations that require specific consideration

Concomitant use of TEGRETOL and levetiracetam has been reported to increase TEGRETOL-induced toxicity.

Concomitant use of TEGRETOL and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

Combined use of TEGRETOL and lithium, or metoclopramide on the one hand, and TEGRETOL and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of 'therapeutic plasma levels').

Concomitant medication with TEGRETOL and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

TEGRETOL may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium); their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

TEGRETOL may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol during treatment.

Concomitant use of TEGRETOL with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban, and edoxaban) may lead to reduced plasma concentrations of direct acting oral anticoagulants, which carries the risk of thrombosis. Therefore, if a concomitant use is necessary, close monitoring of signs and symptoms of thrombosis is recommended.

Interference with serological testing

TEGRETOL may result in false positive perphenazine concentrations in HPLC analysis due to interference.

Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarized immunoassay method.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety of TEGRETOL in pregnancy has not been demonstrated.

Patients should consult their doctor for guidance on the use of TEGRETOL during pregnancy.

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. There are reports of developmental disorders and malformations, including spina bifida and hypospadias in association with TEGRETOL.

Neurodevelopmental disorders have been reported among children born to women with epilepsy treated with carbamazepine alone or in combination with other antiepileptic medicines during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are contradictory and a risk cannot be excluded.

- If women receiving TEGRETOL become pregnant or plan to become pregnant, or if the need of initiating treatment with TEGRETOL arises during pregnancy, the medicine's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing potential TEGRETOL should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic medicines is greater than in those of mothers receiving the individual medicines as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific medicines used and may be higher in polytherapy combinations that include valproate.
- Minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range (4 to 12 µg/ml) provided seizure control is maintained. There is evidence to suggest that the risk of malformation with TEGRETOL may be dose-dependent, i.e. at a dose < 400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine.
- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

- During pregnancy, an effective antiepileptic treatment should not be interrupted, since aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention

Folic acid deficiency is known to occur in pregnancy. Anti-epileptic medicines have been reported to aggravate folic acid deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

In the neonate

In order to prevent bleeding disorders in the offspring, it is also recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

Cases of neonatal seizures and/or respiratory depression associated with maternal TEGRETOL and other concomitant anticonvulsant medicine use have been reported. Cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal TEGRETOL use. These reactions may represent a neonatal withdrawal syndrome.

Women with manic depressive (bipolar) disorders have an increased risk to relapse during pregnancy and/or the post partum period.

Lactation:

Carbamazepine passes into breast milk (about 25 to 60 % of plasma concentrations). Mothers on TEGRETOL should not breastfeed their infants.

Fertility:

There have been reports of impaired male fertility and/or abnormal spermatogenesis.

Contraception

Women of childbearing potential should use effective contraception during treatment with TEGRETOL and for 2 weeks after the last dose. Due to enzyme induction, TEGRETOL may result in a failure of the therapeutic effect of oral contraceptive medicines containing oestrogen and/or

progesterone. Therefore, women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with TEGRETOL.

4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired by the medical condition, resulting in seizures, and adverse reactions including dizziness, drowsiness ataxia, diplopia, impaired accommodation and blurred vision have been reported with TEGRETOL, especially at the start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Particularly at the start of treatment with TEGRETOL, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reactions occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.

Dose-related adverse reactions may abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels.

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000), including isolated reports.

Table 1

Blood and lymphatic system disorders	
Very common:	leukopaenia
Common:	thrombocytopaenia, eosinophilia

Rare:	leukocytosis, lymphadenopathy
Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia
Immune system disorders	
Rare:	a delayed multiorgan hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly and abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon)
Very rare:	anaphylactic reaction, angioedema, hypogammaglobulinaemia
Endocrine disorders	
Common:	oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusion, neurological disorders
Very rare:	galactorrhoea, gynaecomastia
Metabolism and nutrition disorders	
Rare:	folate deficiency, decreased appetite
Very rare:	porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda)

Psychiatric disorders	
Rare:	hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state
Very rare:	activation of psychosis

Nervous system disorders	
Very common:	dizziness, ataxia, somnolence
Common:	headache, diplopia
Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus
Rare:	dyskinesia, eye movement disorders, speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, peripheral neuropathy, paraesthesia, paresis
Very rare:	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia
Eye disorders	
Common	accommodation disorders (e.g. blurred vision)
Very rare:	lenticular opacities, conjunctivitis
Ear and labyrinth disorders	
Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception
Cardiac disorders	
Rare:	cardiac conduction disorders
Very rare:	arrythmia, atrioventricular block with syncope, bradycardia, congestive cardiac failure, aggravation of coronary artery disease
Vascular disorders	
Rare:	hypertension or hypotension
Very rare:	circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis
Respiratory, thoracic and mediastinal disorders	
Very rare:	pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia

Gastrointestinal disorders	
Very common:	nausea, vomiting
Common:	dry mouth
Uncommon:	diarrhoea, constipation
Rare:	abdominal pain
Very rare:	pancreatitis, glossitis, stomatitis
Hepatobiliary disorders	
Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice
Very rare:	hepatic failure, granulomatous liver disease
Skin and subcutaneous tissue disorders	
Very common:	allergic dermatitis, urticaria which may be severe
Uncommon:	exfoliative dermatitis
Rare:	systemic lupus erythematosus, pruritus
Very rare:	Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism
Musculoskeletal, connective tissue and bone disorders	
Rare	muscular weakness
Very rare:	bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms
Renal and urinary disorders	
Very rare:	tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and increased blood urea/azotaemia, urinary retention, urinary frequency
Reproductive system	
Very rare:	sexual dysfunction/erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility)

General disorders and administration site conditions	
Very common	fatigue
Investigations	
Very common:	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant
Common:	blood alkaline phosphatase increased
Uncommon:	transaminases increased
Very rare:	intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased
* In some Asian countries also reported as rare. See section 4.4.	

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following side-effects have been derived from post-marketing experience with TEGRETOL via spontaneous case reports and literature cases.

Infections and infestations

Reactivation of Human herpes virus 6 infection

Blood and lymphatic system disorders

Bone marrow failure

Injury, poisoning and procedural complications

Fall (associated with TEGRETOL treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4).

Nervous system disorders

Sedation, memory impairment

Gastrointestinal disorders

Colitis

Immune system disorders

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Skin and subcutaneous tissue disorders

Acute Generalised Exanthematous Pustulosis (AGEP), lichenoid keratosis, onychomadesis

Musculoskeletal and connective tissue disorders

Fracture

Investigations

Bone density decreased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, and respiratory systems.

Central nervous system

CNS depression, disorientation, depressed level of consciusness, somnolence, agitation, hallucination, coma, blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia, convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis

Respiratory system

Respiratory depression, pulmonary oedema

Cardiovascular system

Tachycardia, hypotension, at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest

Gastrointestinal system

Vomiting, delayed gastric emptying, reduced bowel motility

Musculoskeletal system

Cases of rhabdomyolysis have been reported in association with carbamazepine toxicity

Renal function

Retention of urine, oliguria or anuria, fluid retention, water intoxication due to an ADH-like effect

Laboratory findings

Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase

Treatment

No specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm TEGRETOL poisoning and to ascertain the size of the overdose.

Administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations

Charcoal haemoperfusion has been recommended. Haemodialysis is the effective treatment modality in the management of TEGRETOL overdose.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.5 Anticonvulsants, including anti-epileptics.

Therapeutic class: antiepileptic, neurotropic, and psychotropic agent; (ATC Code: N03 AF01).

Mechanism of action

Carbamazepine possesses both anticonvulsant and psychotropic properties.

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is absorbed relatively slowly from the tablet. Peak plasma concentrations are attained 4 to 24 hours after a single oral dose. The CR 200 tablets yield a mean peak plasma concentration of the carbamazepine within 24 hours, while for the suspension, mean peak plasma concentrations are attained within 2 hours.

There is no clinically relevant difference between the quantity of carbamazepine absorbed from the various dosage forms.

The CR tablets provide more stable plasma concentrations throughout the day, thereby allowing twice daily dosage.

Distribution

Carbamazepine is 70 – 80 % bound to plasma proteins. The concentration of carbamazepine in the saliva reflects the unbound fraction in the plasma (20 to 30 %).

Elimination

The elimination half-life of carbamazepine is approximately 36 hours after a single oral dose, whereas after repeated administration, which leads to auto induction of hepatic enzymes, it averages only 16 to 24 hours, depending on the duration of the medication. In patients receiving

concomitant treatment with other enzyme inducing anti-epileptic agents, half-life values averaging 9 to 10 hours have been found.

Only 2 to 3 % of the dose is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active carbamazepine-10,11-epoxide.

Biotransformation/metabolism

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the carbamazepine-10,11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 is responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine, while the microsomal epoxide hydrolase enzyme is responsible for the formation of the carbamazepine-10,11-transdiol derivative from carbamazepine-10,11-epoxide.

The steady-state plasma concentrations of carbamazepine considered as in the 'therapeutic range', vary considerably interindividually: for the majority of patients a range between 4 - 12 µg/ml corresponding to 17 - 50 µmol/l has been reported.

Special populations

Pediatric patients

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults.

Geriatric patients (65 years or above)

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

Patients with hepatic or renal impairment

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TEGRETOL® 200 Tablets:

Colloidal anhydrous silica, microcrystalline cellulose, magnesium stearate, sodium carboxymethylcellulose.

TEGRETOL® CR 200 and TEGRETOL® CR 400 Controlled release, film-coated divisible tablets:

Colloidal anhydrous silica, ethylcellulose aqueous dispersion, microcrystalline cellulose, polyacrylate dispersion, magnesium stearate, croscarmellose sodium, talc.

Coating: hypromellose, macrogolglycerol hydroxystearate, iron oxide red, iron oxide yellow, talc, titanium dioxide.

TEGRETOL® S Suspension:

Microcrystalline cellulose + sodium carboxymethylcellulose, caramel aroma 52929 A, methylparaben, hydroxyethylcellulose, propylene glycol, polyethylene glycol 400 stearate, propylparaben, saccharin sodium, sorbic acid, sorbitol solution, purified water.

6.2 Incompatibilities

None known.

6.3 Shelf life

TEGRETOL® 200: 2 years.

TEGRETOL® CR 200 and TEGRETOL® CR 400: 2 years

TEGRETOL® S: 3 years

6.4 Special precautions for storage

TEGRETOL® 200

Store at or below 30 °C and protect from moisture.

TEGRETOL® CR 200 and TEGRETOL® CR 400

Store at or below 30 °C and protect from moisture.

TEGRETOL® S

Store below 30 °C and protect from light.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

TEGRETOL® 200 is supplied as tablets in packs of 50.

TEGRETOL® CR 200 and TEGRETOL® CR 400 are supplied in packs of 30.

TEGRETOL® S is supplied in bottles of 250 ml.

7. MARKETING AUTHORISATION HOLDER

Novartis South Africa (Pty) Ltd

Magwa Crescent West,

Waterfall City, Jukskei View

Johannesburg, 2090

+2710 347 6600

8. REGISTRATION NUMBER:

TEGRETOL® 200	B1530 (Act 101/1965)
TEGRETOL® CR 200	V/2.5/321
TEGRETOL® CR 400	V/2.5/322
TEGRETOL® S	D/2.5/204

9. DATE OF FIRST AUTHORISATION

TEGRETOL® 200: Old medicine – B1530 (Act 101 of 1965)

TEGRETOL® CR 200 and 400: 18 February 1989

TEGRETOL® S: 16 March 1972

10. DATE OF REVISION OF THE TEXT

07 October 2024

Tegretol S	Botswana	BOT 0400641	S2	Delpharm Huningue S.A.S 26, rue de la Chapelle, 68330 Huningue, France
	Namibia	90/2.5/00728	NS2	
Tegretol CR 200	Botswana	BOT 0400643	S2	Novartis Pharma S.p.A Via Provinciale Schito 131, 80058 Torre Annunziata, Italy
	Namibia	90/2.5/00726	NS2	
Tegretol CR 400	Botswana	BOT 0400644	S2	
	Namibia	90/2.5/00727	NS2	
Tegretol 200	Botswana	BOT 0400642	S2	
	Namibia	08/2.5/0131	NS2	