

NEW ZEALAND DATA SHEET

TEGRETOL[®]

Carbamazepine

200 mg and 400 mg Tablets

200 mg and 400 mg CR Tablets

100 mg / 5 mL Syrup

Qualitative and quantitative composition

Active substance: 5H-dibenzo[b,f]azepine-5-carboxamide (carbamazepine)

Tablets: 200 mg and 400 mg carbamazepine.

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

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

For a full list of excipients, see List of excipients.

Pharmaceutical forms

1. Tablet containing 200mg carbamazepine. Round, white, flat tablet, 9mm in diameter, with bevelled edges. Imprinted CG on one side, and G/K on the scored side.
2. Tablet containing 400mg carbamazepine. White, flat, rod-shaped tablet with bevelled edges. 17mm in length and 5.5mm in width. Imprinted CG/CG on one side and LR/LR on the second side; both sides of the tablet are scored.
3. Controlled Release Tablet containing 200mg carbamazepine. Beige-orange, ovaloid-shaped, film-coated divisible tablet with slightly convex faces. Approximate length is 12.2mm, and approximate width is 5.6mm. Both sides are scored; one side is imprinted C/G, and the other side H/C.
4. Controlled Release Tablet containing 400mg carbamazepine. Brown-orange, ovaloid-shaped, film-coated divisible tablet, with slightly convex faces. Approximately 16.7mm in length, and approximately 6.6mm in width. Imprinted CG/CG on one side, and ENE/ENE on the other side; both sides are scored.
5. Syrup containing 100mg/5mL carbamazepine. A viscous white suspension with a caramel odour and taste. It contains sorbitol (875mg/5mL), which is converted slowly into glucose, making the syrup suitable for diabetics.

Clinical particulars

Therapeutic indications

- Epilepsy
 - Complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalization.
 - 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 Special warnings and precautions for use).
- 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 and method of administration

The tablets and the syrup (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.

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 Syrup 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 syrup: this should be done by giving the same number of mg per day in smaller, more frequent doses (e.g. Syrup 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.

Due to drug interactions and different antiepileptic drug 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 (see Special warnings and precautions for use).

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 Interaction with other medicinal products and other forms of interaction).

Adults

Oral forms

Initially, 100 to 200 mg once or twice daily; the dosage should be slowly raised until – generally at 400 mg 2 to 3 times daily – an optimum response is obtained. In some patients 1600 mg or even 2000 mg daily may be appropriate.

Children

Oral forms

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 mL to 10 mL)
- 1 to 5 years of age 200 to 400 mg daily (10 mL to 20 mL)
- 6 to 10 years of age 400 to 600 mg daily (20 mL to 30 mL)
- 11 to 15 years of age 600 to 1000 mg daily (30 mL to 50 mL)

Acute mania and maintenance treatment of bipolar affective disorders

Dosage range: about 400 to 1600 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.

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.

Trigeminal 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. In elderly patients, an initial dose of 100 mg twice daily is recommended.

Painful diabetic neuropathy

Average dosage: 200 mg 2 to 4 times daily.

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.

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, variegated porphyria, porphyria cutanea tarda)
- The use of Tegretol is not recommended in combination with monoamine-oxidase inhibitors (MAOIs) (see Interaction with other medicinal products and other forms of interaction).

Special warnings and precautions for use

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 haematological reactions to other drugs, or interrupted courses of therapy with Tegretol.

Haematological effects

Agranulocytosis and aplastic anaemia 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 anaemia.

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 anaemia 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 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 his physician immediately.

Serious dermatologic reactions

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN; also known as Lyell's 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. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, Tegretol should be withdrawn at once and alternative therapy should be considered.

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, 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. The frequency of this allele is estimated less than 5% in the majority of European, 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.

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, 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.

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese ancestry 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. 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 prevalence of the HLA-B*1502 allele in the

population. The prevalence of carriers of this allele in Asian populations is above 15% in the Philippines, Thailand, Hong Kong and Malaysia, around 10% in Taiwan, around 4% in North China, around 2 to 4% in South Asia including Indians, and less than 1% in Japan and Korea. The prevalence of the HLA-B*1502 allele is negligible in Caucasian, African, indigenous peoples of the Americas, and Hispanic populations sampled.

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 (see Information for 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.

Limitation of genetic screening

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 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.

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

Tegretol may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver (including intrahepatic bile ducts), haematopoietic

organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction (see Adverse effects).

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 phenytoin.

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.

Anticholinergic effects

Tegretol has shown mild anticholinergic activity. Patients with increased intraocular pressure should therefore be closely observed during therapy (see Adverse effects).

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

An analysis of reports of suicidality (suicidal behaviour or ideation) from placebo-controlled clinical studies of eleven medicines used to treat epilepsy as well as psychiatric disorders, and other conditions revealed that patients receiving anti-epileptic drugs had approximately twice the risk of suicidal behaviour or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behaviour and suicidal ideation was observed as early as one week after starting the anti-epileptic medicine and continued through 24 weeks. The results were generally consistent among the eleven medicines. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the medicines in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any anti-epileptic drug should be closely monitored for notable changes in behaviour that could indicate the emergence or worsening of suicidal thoughts or behaviour or depression.

Health Care Professionals should inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality. Prescribers should advise patients to seek medical advice immediately if they develop any symptoms suggestive of suicidality.

Endocrinological effects

Breakthrough bleeding has been reported in women taking Tegretol while using 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. Due to enzyme induction, Tegretol may cause failure of the therapeutic effect of drugs containing oestrogen and/or progesterone (e.g. failure of contraception).

Monitoring of plasma levels

Although correlations between dosage and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following situations: dramatic increase in seizure frequency/verification of patient compliance, during pregnancy, when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see Interaction with other medicinal products and other forms of interaction).

Dose reduction and withdrawal

Abrupt withdrawal of Tegretol may precipitate seizures. If treatment with Tegretol has to be withdrawn abruptly in a patient with epilepsy, the switch to the new antiepileptic compound should be made under cover of a suitable drug (e.g. diazepam i.v., rectal; or phenytoin i.v.).

Others

Tegretol Syrup 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.

Interaction with other medicinal products and other forms of interaction

Cytochrome P450 3A4 (CYP3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine-10,11-epoxide. Coadministration of inhibitors of CYP3A4 may result in increased carbamazepine plasma concentrations which could induce adverse reactions. Coadministration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels. Carbamazepine 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 comedications mainly metabolized 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. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

Agents 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 drugs: dextropropoxyphene, ibuprofen.

Androgens: danazol.

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

Antidepressants: possibly desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine.

Antiepileptics: stiripentol, vigabatrin.

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole).

Antihistamines: loratadine, terfenadine.

Antipsychotics: olanzapine.

Antituberculosis: isoniazid.

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

Carbonic anhydrase inhibitors: acetazolamide.

Cardiovascular drugs: diltiazem, verapamil.

Gastrointestinal drugs: possibly cimetidine, omeprazole.

Muscle relaxants: oxybutynin, dantrolene.

Platelet aggregation inhibitors: ticlopidine.

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

Agents 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 and valpromide.

Agents that may decrease carbamazepine 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 and fosphenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

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

Effect of Tegretol on plasma levels of concomitant agents

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

Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol, phenazone (antipyrine), tramadol.

Antibiotics: doxycycline.

Anticoagulants: oral anticoagulants (e.g. warfarin, phenprocoumon, dicoumarol and acenocoumarol).

Antidepressants: bupropion, citalopram, mianserin, nefazodone, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine). The use of Tegretol is not recommended 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 Contraindications).

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. Plasma phenytoin levels have

been reported both to be raised and to be lowered by carbamazepine, and there have been rare reports of an increase in plasma mephenytoin levels.

Antifungals: itraconazole.

Anthelmintics: praziquantel, albendazole.

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

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

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

Anxiolytics: alprazolam, midazolam.

Bronchodilators or anti-asthma drugs: theophylline.

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

Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin.

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

Drugs used in erectile dysfunction: tadalafil

Immunosuppressants: cyclosporin, everolimus, tacrolimus, sirolimus.

Thyroid agents: levothyroxine.

Other drug interactions: products containing oestrogens and/or progesterones.

Combinations that require specific consideration

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

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

Combined use of carbamazepine and lithium or metoclopramide on the one hand, and carbamazepine 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.

Carbamazepine may antagonize the effects of non-depolarizing 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.

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol.

Pregnancy and lactation

Pregnancy

In animals (mice, rats, rabbits) oral administration of carbamazepine during organogenesis led to increased embryonic mortality at daily doses which caused maternal toxicity (above 200 mg/kg body weight daily, i.e. 10 to 20 times the usual human dosage). In the rat there was also some evidence of abortion at 300 mg/kg body weight daily. Near-term rat foetuses showed growth retardation, again at maternally toxic doses. There was no evidence of teratogenic potential in the three animal species tested, but, in one study using mice, carbamazepine (40 to 240 mg/kg body weight daily, orally) caused defects (mainly dilatation of cerebral ventricles) in 4.7% of exposed foetuses as compared with 1.3% in controls. Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major antiepileptic

drugs, increases this risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However, developmental disorders and malformations, including spina bifida and also other congenital anomalies, e.g. craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with Tegretol.

Taking these data into consideration:

- Pregnant women with epilepsy should be treated with special care.
- If women receiving Tegretol become pregnant or plan to become pregnant, or if the problem of initiating treatment with Tegretol arises during pregnancy, the drug's potential benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing age 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 drugs is greater than in those of mothers receiving the individual drugs as monotherapy.
- Minimum effective doses should be given and monitoring of plasma levels is recommended.
- 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 must not be interrupted, since the 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. Antiepileptic drugs 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 has also been recommended that vitamin K1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few 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.

Lactation

Carbamazepine passes into the breast milk (about 25 to 60% of plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking Tegretol may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).

Fertility

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

Effects on ability to drive and use machines

The patient's ability to react may be impaired by dizziness and drowsiness caused by 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.

Adverse 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 reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), and allergic skin reactions. The dose-related adverse reactions usually 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 plasma levels.

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

Table 1

Blood and lymphatic system disorders	
Very common:	leukopenia.
Common:	thrombocytopenia, eosinophilia.
Rare:	leukocytosis, lymphadenopathy, folic acid deficiency.
Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia.
Immune system disorders	
Rare:	a delayed multiorgan hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and <u>vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts)</u> , occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).
Very rare:	aseptic meningitis, with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioneurotic oedema.
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, confusional state, neurological disorders.
Very rare:	Blood prolactin increased with or without clinical manifestations such as galactorrhoea, gynecomastia, abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol), leading to osteomalacia/osteoporosis, increased blood cholesterol, including HDL cholesterol, and triglycerides.
Psychiatric disorders	
Rare:	hallucinations (visual or auditory), depression, anorexia, restlessness, aggression, agitation, confusional state.
Very rare:	activation of psychosis.
Nervous system disorders	
Very common:	dizziness, ataxia, drowsiness, fatigue.
Common:	headache, diplopia, accommodation disorders (e.g. blurred vision).
Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus.

Rare:	orofacial dyskinesia, eye movement disturbances, speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis.
Very rare:	taste disturbances, neuroleptic malignant syndrome.
Eye disorders	
Very rare:	lenticular opacities, conjunctivitis, intraocular pressure increased.
Ear and labyrinth disorders	
Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac disorders	
Rare:	cardiac conduction disorders; hypertension or hypotension.
Very rare:	bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thromboembolism (e.g. pulmonary embolism).
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; with suppositories, rectal irritation may occur.
Uncommon:	diarrhoea, constipation.
Rare:	abdominal pain.
Very rare:	glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders	
Very common:	increased gamma-GT (due to hepatic enzyme induction), usually not clinically relevant.
Common:	increased blood alkaline phosphatase.
Uncommon:	increased transaminases.
Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, <u>vanishing bile duct syndrome</u> , jaundice.
Very rare:	granulomatous hepatitis, hepatic failure.
Skin and subcutaneous tissue disorders	
Very common:	dermatitis allergic, urticaria which may be severe.
Uncommon:	exfoliative dermatitis and erythroderma.
Rare:	systemic lupus erythematosus, pruritus.
Very rare:	Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhidrosis, hair loss, hirsutism.
Musculoskeletal, connective tissue and bone disorders	
Rare	muscular weakness
Very rare:	arthralgia, muscle pain, muscle spasms.
Renal and urinary disorders	
Very rare:	interstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and blood urea increased/azotemia), urinary frequency, urinary retention.
Reproductive system	
Very rare:	sexual dysfunction/impotence, spermatogenesis abnormal (with decreased sperm count and/or motility).
Investigations	
Very rare:	hypogammaglobulinaemia.

- In some Asian countries also reported as rare. See also Special warnings and precautions for use.

"Emergence or worsening of existing depression, suicidal behaviour and suicidal ideation have been reported in patients treated with antiepileptic agents in several indications. The frequency of these events is unknown."

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

The following adverse drug reactions have been derived from post-marketing experience with Tegretol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Immune system disorders: Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Skin and subcutaneous tissue disorders: Acute Generalized Exanthematous Pustulosis (AGEP)

Overdose**Signs and symptoms**

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

Central nervous system

CNS depression; disorientation, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, 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.

Renal function

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

Laboratory findings

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

Management

There is no specific antidote.

Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose.

Evacuation of the stomach, gastric lavage, and 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

Hypotension: administer dopamine or dobutamine i.v.

Disturbances of cardiac rhythm: to be handled on an individual basis.

Convulsions: administer a benzodiazepine (e.g. diazepam) or another antiepileptic, e.g. phenobarbitone (with caution because of increased respiratory depression), or paraldehyde.

Hyponatraemia (water intoxication): fluid restriction and slow and careful NaCl 0.9% infusion i.v. These measures may be useful in preventing brain damage.

Charcoal hemoperfusion has been recommended. Forced diuresis, haemodialysis, and peritoneal dialysis have been reported to be not effective.

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

Pharmacological properties

Pharmacodynamic properties

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

Dibenzazepine derivative.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalization; generalized tonic-clonic seizures, as well as combinations of these types of seizures.

In clinical studies Tegretol given as monotherapy to patients with epilepsy - in particular children and adolescents - has been reported to exert a psychotropic action, including a positive effect on symptoms of anxiety and depression as well as a decrease in irritability and aggressiveness. As regards cognitive and psychomotor performance, in some studies equivocal or negative effects, depending also upon dosages administered, were reported. In other studies, a beneficial effect on attentiveness, cognitive performance/memory was observed.

As a neurotropic agent Tegretol is clinically effective in a number of neurological disorders, e.g. it prevents paroxysmal attacks of pain in idiopathic and secondary trigeminal neuralgia; in addition, it is used for the relief of neurogenic pain in a variety of conditions, including tabes dorsalis, post-traumatic paresthesia, and post-herpetic neuralgia; in alcohol-withdrawal syndrome it raises the lowered convulsion threshold and improves withdrawal symptoms (e.g. hyperexcitability, tremor, impaired gait); in diabetes insipidus centralis, Tegretol reduces the urinary volume and relieves the feeling of thirst.

As a psychotropic agent Tegretol proved to have clinical efficacy in affective disorders, i.e. as treatment for acute mania as well as for maintenance treatment of (manic-depressive) bipolar affective disorders, when given either as monotherapy or in combination with neuroleptics, antidepressants, or lithium, in excited schizo-affective disorder and excited mania in combination with other neuroleptics, and in rapid cycling episodes.

The mechanism of action of carbamazepine, the active substance of Tegretol, has only been partially elucidated. Carbamazepine stabilizes hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarized neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

Whereas reduction of glutamate release and stabilization of neuronal membranes may account mainly for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

Pharmacokinetic properties

Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets and the chewable tablets yield mean peak plasma concentrations of the unchanged substance within 12 and 6 hours, respectively, following single oral doses. With

the Syrup, mean peak plasma concentrations are attained within 2 hours, and with the suppositories within a mean of 12 hours. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400 mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5 micrograms/mL.

When CR tablets are administered singly and repeatedly, they yield about 25% lower peak concentrations of active substance in plasma than the conventional tablets; the peaks are attained within 24 hours. The CR tablets provide a statistically significant decreased fluctuation index, but not a significant decreased C_{min} at steady state. The fluctuation of the plasma concentrations with a twice-daily dosage regimen is low. The bioavailability of Tegretol CR tablets is about 15% lower than that of the other oral dosage forms.

Steady-state plasma concentrations of carbamazepine are attained within about 1 to 2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pretreatment status, dosage, and duration of treatment. The steady-state plasma concentrations of carbamazepine considered as 'therapeutic range' vary considerably interindividually: for the majority of patients a range between 4 to 12 micrograms/mL corresponding to 17 to 50 micromol/L has been reported. Concentrations of carbamazepine-10,11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Tegretol.

Distribution

Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Carbamazepine crosses the placental barrier.

Carbamazepine is bound to serum proteins to the extent of 70 to 80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in the plasma (20 to 30%). Concentrations in breast milk were found to be equivalent to 25 to 60% of the corresponding plasma levels.

Biotransformation

Carbamazepine is metabolized in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10,11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of the pharmacologically active carbamazepine-10,11 epoxide from carbamazepine. 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. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway. Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16 to 24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other liver-enzyme inducing

drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9 to 10 hours have been found.

The mean elimination half-life of the 10,11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10,11-epoxide metabolite.

Characteristics in patients

Children

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

Elderly

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.

Preclinical safety data

In rats treated with carbamazepine for 2 years, the incidence of tumors of the liver was found to be increased. The significance of these findings relative to the use of carbamazepine in humans is unknown at present. Bacterial and mammalian mutagenicity studies yielded negative results.

Pharmaceutical particulars

List of excipients

Tablets: Aerosil 200 (silica, colloidal anhydrous), Avicel PH 101 (cellulose) magnesium stearate, Nymcel ZSB-10 modified (carmellose sodium, low substituted)

CR tablets: Aerosil 200 (silica, colloidal anhydrous), Ethylcellulose aqueous dispersion, Avicel PH 102 (cellulose), Eudragit ED solid (copolymer based on polyacrylic / methacrylic esters), magnesium stearate, sodium CMC XL, talc. Coating: Cellulose -HP- M 603 (hydroxypropyl methylcellulose), Cremophor RH 40 (glyceryl polyoxyethylene glycol stearate), iron oxide red, iron oxide yellow, talc, titanium dioxide.

Syrup: Avicel RC 581 (cellulose + sodium CMC), caramel aroma 52929 A, methylparaben, Natrosol 250 G (hydroxyethyl cellulose), propylene glycol dist., polyethylene glycol 400 stearate, propylparaben, saccharin sodium cryst., sorbic acid, sorbitol solution, water deionized.

Incompatibilities

None known.

Shelf life

Tablets: 5 years.

CR tablets: 3 years.

Syrup: 3years.

Special precautions for storage

Tablets: store below 25°C and protect from moisture.

CR tablets: store below 25°C and protect from moisture.

Syrup: protect from heat (store below 30°C) and protect from light.

Tegretol must be kept out of the reach and sight of children.

Nature and contents of the container

Tablets: 200mg: blister packs of 100 tablets
400mg: blister pack of 100 tablets

CR Tablets: blister packs of 100 tablets

Syrup: 250ml bottle, 100mg/5ml

Instructions for use/handling

There is no specific instruction for use/handling.

Information for the Healthcare professionals

If testing for the presence of the HLA-B*1502 allele should be performed, 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 the 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.

Medicine classification

Prescription medicine

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