NOVARTIS

Tegretol®

Composition

Active substances

Carbamazepine

Excipients

1 scored tablet contains: Microcrystalline cellulose, carmellose sodium equivalent to 0.23 mg sodium, magnesium stearate, colloidal anhydrous silica

1 scored CR Divitab contains: Tablet coating: Microcrystalline cellulose, croscarmellose sodium equivalent to 2 mg sodium (200 mg Divitabs) or 3 mg sodium (400 mg Divitabs), 30% polyacrylate dispersion, ethylcellulose, talc, colloidal anhydrous silica, magnesium stearate
Film coating: Hypromellose, talc, 0.22 mg macrogoglycerol hydroxystearate (200 mg Divitabs) or 0.44 mg macrogoglycerol hydroxystearate (400 mg Divitabs), E171, E172 (yellow and red)

5 ml (= 1 measuring spoon) of oral suspension contains: Macrogol 8 stearate (type I), saccharin sodium, hydroxyethylcellulose, microcrystalline cellulose, carmellose sodium, 1.25 g liquid sorbitol (non-crystallising), 125 mg propylene glycol, 6 mg methyl parahydroxybenzoate, 1.5 mg propyl parahydroxybenzoate, sorbic acid (E200), flavouring agents (caramel), purified water, 0.6 mg sodium.
The oral suspension contains 875 mg sorbitol/5 ml, which is slowly converted to glucose. The oral suspension is suitable for diabetics.

Pharmaceutical form and quantity of active substance per unit

Tablets containing 200 or 400 mg carbamazepine (divisible).

CR Divitabs (divisible, controlled-release, film-coated tablets) containing 200 or 400 mg carbamazepine.

Oral suspension containing 100 mg carbamazepine per 5 ml (= 1 measuring spoon).

Indications/Potential uses

- Epilepsy
  - Partial seizures (simple or complex, with or without loss of consciousness), with or without secondary generalisation.
  - Generalised tonic-clonic seizures.

- Mixed forms of seizures.
- Tegretol is suitable for both monotherapy and combination therapy.
- Tegretol is not normally effective in absence (petit mal) or in myoclonic seizures (see “Warnings and precautions”).

- Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
- Alcohol-withdrawal syndrome.
- Idiopathic trigeminal neuralgia and trigeminal neuralgia secondary to multiple sclerosis (typical or atypical).
- Idiopathic glossopharyngeal neuralgia.

Dosage/Administration

Dosage in special clinical situations

Elderly patients

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

An initial dose of 100 mg twice daily is recommended.

*Patients who are potential carriers of the HLA-A*3101 allele because of their ancestry*

Before initiating treatment with Tegretol it is recommended that patients at risk of certain adverse skin/hypersensitivity reactions because of their ancestry be tested for the presence of the HLA-A*3101 allele to improve risk assessment (see “Warnings and precautions”).

Epilepsy

Tegretol should be prescribed as monotherapy whenever possible.

Treatment should be initiated with a low daily dosage, slowly increasing until an optimum effect is achieved.

Particularly in the case of combination therapy, the therapeutic dose should be based both on a determination of plasma levels and on efficacy. Experience has shown that therapeutic levels of carbamazepine lie between 4 and 12 µg/ml.

When Tegretol is added to existing antiepileptic therapy, this should be done gradually while maintaining, or if necessary adapting, the dosage of the other drug(s) (see “Interactions”).

Adults

Oral forms: Initially 100-200 mg once or twice daily, slowly increasing until an optimum response is achieved – generally with 400 mg two or three times daily (corresponding to 800-1200 mg). In some patients, 1600 mg or even 2000 mg daily may be appropriate, although these high doses should be avoided due to a greater incidence of adverse effects.

Children and adolescents

Oral suspension: 10-20 mg carbamazepine per kg bodyweight per day, in divided doses, i.e.*

- Up to 1 year of age: 100-200 mg/day (= 5-10 ml = 1-2 measuring spoons)
- 1-5 years of age: 200-400 mg/day (= 10-20 ml = 2 × 1-2 measuring spoons)
- 6-10 years of age: 400-600 mg/day (= 20-30 ml = 2-3 × 2 measuring spoons)
- 11-15 years of age: 600-1000 mg/day (= 30-50 ml = 3 × 2-3 measuring spoons)
- >15 years of age: 800-1200 mg/day (same as daily dose in adults)

* 1 measuring spoon contains 100 mg of carbamazepine in 5 ml of suspension.

Maximum recommended daily dose:

- Up to 6 years of age: 35 mg/kg/day
- 6-15 years of age: 1000 mg/day
- >15 years of age: 1200 mg/day

A starting dose of 20-60 mg/day, increasing by 20-60 mg every second day, is recommended in children 4 years of age or younger. In children over 4 years of age, treatment may be started at 100 mg/day, increasing by 100 mg at weekly intervals.

Trigeminal neuralgia

The starting dose of 200-400 mg/day (in elderly patients, 100 mg twice daily) should be gradually increased until freedom from pain is achieved (normally with 200 mg three to four times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. The maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Alcohol-withdrawal syndrome

Patients should be given 200 mg three to four times daily on the first two days of treatment. In severe cases, the dosage may be increased to 1200 mg/day during the first few days of treatment. The dosage should subsequently be reduced slowly, and treatment gradually withdrawn (see *Discontinuation of treatment* under “Warnings and precautions”).

Acute mania and maintenance treatment of bipolar affective disorders

Dosage range: approx. 400-1600 mg daily. The normal daily dose is 400-600 mg, given in 2-3 divided doses. The dosage should be increased fairly rapidly in acute mania, whereas small increments are recommended for maintenance therapy of bipolar disorders to ensure optimal tolerability.

Further dosage instructions

Tegretol tablets

The tablets (either as whole tablets or – if prescribed – half tablets) should be swallowed without chewing with a small amount of liquid. The tablets may be taken during, after or between meals with a small amount of liquid.

Tegretol Divitabs

The CR Divitabs (either as whole tablets or – if prescribed – half tablets) should be swallowed without chewing with a small amount of liquid.

CR Divitabs can normally be administered twice daily owing to the slow, controlled release of active substance from the tablets.

Tegretol oral suspension

The oral suspension (to be shaken before use) may be taken during, after or between meals with a small amount of liquid.

The oral suspension (1 measuring spoon = 5 ml = 100 mg; ½ measuring spoon = 2.5 ml = 50 mg) is particularly suitable for patients who have difficulty swallowing tablets. The oral suspension is also suitable for patients who require careful initial dose titration.

Since higher peak plasma concentrations are reached with a given dose of oral suspension than the same dosage in tablet form, it is advisable to start the oral suspension at a low dosage, which should then be increased slowly to avoid adverse effects.

Switching dosage forms

- Switching from Tegretol tablets to Tegretol oral suspension: This should be done by giving the same daily dose, but in smaller, more frequent doses (e.g. oral suspension three times daily, instead of tablets twice daily).
- Switching from standard tablets to CR Divitabs: Clinical experience shows that the dosage may need to be increased in some patients when administering CR Divitabs.

Contraindications

- Known hypersensitivity to carbamazepine and oxcarbazepine, to structurally related drugs (e.g. tricyclic antidepressants) or to any of the other components of the formulation.
- Patients with atrioventricular (AV) block, bone-marrow depression or a history of hepatic porphyria (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).
- Use of Tegretol in combination with monoamine oxidase inhibitors (MAO inhibitors) is not recommended (see “Interactions”). MAO inhibitors should be discontinued a minimum of two weeks before initiating use of Tegretol – and even earlier if the clinical situation permits.
- Tegretol 2% oral suspension contains sorbitol and is thus unsuitable for persons with fructose intolerance (hereditary problems of fructose intolerance).
- In addition, it must not be used in persons hypersensitive to parabens (E200, E216, E218).

Warnings and precautions

General

Tegretol should only be used under medical supervision.

Tegretol should be prescribed only after critical risk-benefit assessment and under close monitoring in the following situations:

- Prior or existing haematological disease, history of haematological adverse reactions to other drugs
- Impaired sodium metabolism
- Patients with current or previous heart, liver or kidney disease (see “Adverse effects”)

after interruptions of treatment with Tegretol, or patients who have previously discontinued treatment with carbamazepine.

Haematological events

Agranulocytosis and aplastic anaemia have been associated with Tegretol but their very low frequency makes it difficult to derive a meaningful risk estimate. There are estimates that the incidence is not much higher with Tegretol than that calculated for the untreated general population, in which the probability of occurrence is 4.7 cases per million per year for agranulocytosis and 2.0 cases per million per year for aplastic anaemia.

Slightly decreased platelet or white blood cell counts are uncommon to common in association with Tegretol treatment. However, in the majority of cases they are transient and are unlikely to

signal the onset of aplastic anaemia or agranulocytosis.

Nonetheless, complete blood counts, including platelets, reticulocytes and serum iron, should be determined at baseline and at regular intervals thereafter.

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

Patients should be informed about the signs of incipient intoxication and the symptoms of possible haematological complications, as well as about the symptoms of cutaneous or hepatic hypersensitivity reactions. They should be instructed to consult their doctor immediately in the event of reactions such as fever, sore throat, perineal infection, exanthema, mouth ulcers, easy bruising, petechiae or idiopathic thrombocytopenic purpura.

Serious dermatological reactions

There have been rare reports of severe dermatological reactions, including toxic epidermal necrolysis (TEN, or Lyell syndrome) and Stevens-Johnson syndrome (SJS) following administration of Tegretol. The patients concerned may require hospitalisation, as these conditions may be life-threatening or fatal. Most cases of SJS/TEN were reported in the first few months of treatment with Tegretol. These dermatological reactions are estimated to occur in 1 to 6 per 10,000 new patients in countries with mainly Caucasian populations. In some Asian countries, however, the risk is estimated to be around ten times greater.

Tegretol must be withdrawn at once, and alternative therapy considered, as soon as signs or symptoms of severe skin reactions are ascertained.

There is growing evidence that different HLA alleles play a role in connection with immune-mediated adverse reactions in predisposed patients.

*Association with HLA-A*3101 allele*

The human leukocyte antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse reactions such as SJS/TEN, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and maculopapular rash.

Retrospective genetic studies in the Japanese and Northern European populations showed an association between severe skin reactions (SJS/TEN, DRESS, AGEP) and maculopapular rashes associated with carbamazepine use and the presence of the HLA-A*3101 allele.

The frequency of this allele varies widely in different ethnic populations. Its frequency is about 2 to 5% in European populations and about 10% in the Japanese population. The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North

American populations. For Western European populations the frequency of the HLA-A*3101 allele is estimated at up to approximately 6.7%, depending on geographic region. There are some exceptions with a frequency of 5-12%. Frequencies are estimated to be above 15% in the following ethnic groups: South America (Argentina and Brazil), North America (US Navajo and Sioux, and Seri Indians in Sonora, Mexico) and Southern India (Tamil Nadu).

The allele frequencies listed here represent the percentage of chromosomes in the specified populations that carry the allele concerned. 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 thus nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Before initiating treatment with Tegretol it is recommended that patients at risk because of their ancestry (e.g. patients from Japan, Caucasians and the indigenous population of America, patients of Spanish or Portuguese descent, and patients of South Indian or Arab descent) be tested for the presence of the HLA-A*3101 allele (see “Dosage/Administration”). Tegretol should not be used in patients who test positive unless the benefits clearly outweigh the risks. Screening for HLA-A*3101 is generally not recommended for patients who have already used Tegretol for a prolonged period, as SJS/TEN, AGEP, DRESS and maculopapular rash usually occur only during the first few months of therapy.

*Association with HLA-B*1502 allele*

Retrospective studies in patients of Han Chinese and Thai 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. The frequency of this allele ranges from 2 to 12% in Han Chinese populations and is about 8% in Thailand. Higher rates of SJS (“uncommon” rather than “rare”) are reported in Asian countries (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele. The frequency of carriers of this allele is over 15% in the Philippines and some Malay populations. Allele frequencies of up to 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in the Caucasian population, Africans, indigenous peoples of the Americas, Japanese, and Hispanic populations (<1%).

The allele frequencies listed here represent the percentage of chromosomes in the specified populations that carry the allele concerned. 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 thus nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

Patients at risk because of their ancestry should be tested before initiating treatment with Tegretol to determine if they are carriers of the HLA-B*1502 allele. Tegretol should not be used in patients who test positive unless the benefits clearly outweigh the risks. When assessing risk, it should be borne in mind that HLA-B*1502 is also a risk factor for other antiepileptic drugs. Screening for HLA-B*1502 is not required in populations with a low allele frequency. Similarly, screening is not appropriate in patients who have already used Tegretol for prolonged periods, as SJS/TEN usually occurs only during the first few months of therapy.

The identification of carriers of the HLA-B*1502 allele, and thus avoidance of carbamazepine therapy in such patients of Han Chinese descent, led to a decrease in the incidence of carbamazepine-induced SJS/TEN.

Genetic screening cannot substitute for close patient monitoring because many patients who are carriers of HLA-B*1502 do not develop SJS/TEN, while other patients not at genetic risk may develop SJS/TEN anyway. The situation is similar for carriers of the HLA-A*3101 allele who are treated with Tegretol. These patients do not necessarily develop SJS/TEN, DRESS, AGEP or maculopapular rash. However, patients who are not carriers of HLA-A*3101 may nevertheless develop serious adverse skin reactions. No studies have thus far been made of the extent to which other factors (such as dose, compliance, comedication and comorbidity) promote the development of such serious adverse skin reactions.

Other skin reactions

Mild cutaneous reactions, such as isolated macular or maculopapular eruptions, are frequently transient and not dangerous. They usually resolve within a few days or weeks, either despite continued treatment or following dose reduction. However, since it is difficult to differentiate the signs of mild and transient dermatological reactions from the early signs of severe dermatological reactions, close monitoring is required, and the product should be withdrawn immediately if the patient's condition worsens or if there are any signs of a systemic hypersensitivity reaction.

The HLA-B*1502 allele has no effect on the risk of mild dermatological reactions to carbamazepine.

An association has been shown between the presence of the HLA-A*3101 allele and mild adverse reactions associated with carbamazepine use. The HLA-A*3101 allele is thus a risk factor for developing severe hypersensitivity syndrome or mild maculopapular rash during carbamazepine treatment.

Hypersensitivity reactions

Tegretol may trigger hypersensitivity reactions that can occur in various combinations, 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). Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) (see “Adverse effects”).

Approximately 25-30% of patients with a hypersensitivity reaction to carbamazepine show a cross-reaction with oxcarbazepine (Trileptal®). A cross-reaction can also occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).

Tegretol should be withdrawn at once if there are signs or symptoms suggestive of a hypersensitivity reaction.

Epileptic seizures

As carbamazepine may cause or exacerbate absences, Tegretol should not be used in patients with absences or mixed seizures, which include typical and atypical absences. In all these conditions, Tegretol may exacerbate seizures. If this happens, Tegretol should be discontinued.

Hepatic function

Baseline and periodic evaluations of hepatic function must be performed before and during Tegretol therapy, particularly in patients with a history of liver disease and in elderly patients. Tegretol should be discontinued immediately if hepatic function deteriorates or active hepatitis develops.

Renal function

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hyponatraemia

Hyponatraemia can occur with carbamazepine treatment. In patients with pre-existing renal conditions associated with low sodium, or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors (use of diuretics, drug-related hyponatraemia, or patients with concussion, pre-existing low sodium values) must especially be taken into account for elderly patients. If hyponatraemia is observed, water restriction is an important countermeasure if clinically indicated.

Hypothyroidism

Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction. This may make it necessary to increase the dose of hormone replacement therapy in patients with hypothyroidism. Thyroid function monitoring is therefore recommended in order to determine the dosage of hormone replacement therapy.

Anticholinergic effects

Tegretol shows slight anticholinergic activity and patients with increased intraocular pressure (glaucoma) and urinary retention should therefore be closely monitored during therapy (see “Adverse effects”).

Psychiatric reactions

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

Suicidal ideation and suicidal behaviour

Suicidal ideation and suicidal behaviour have been reported in patients treated with antiepileptic agents in a wide variety of indications. A meta-analysis of placebo-controlled studies has shown a slightly increased risk in this respect. The underlying mechanism is not known.

Patients should therefore be monitored for suicidal ideation and behaviour, and appropriate treatment should be initiated if necessary. Patients and/or their caregivers should be told that they should seek medical advice in such situations.

Pregnancy and women of childbearing potential

Congenital malformations may occur if carbamazepine is used during pregnancy. For the treatment of epilepsy during pregnancy Tegretol should therefore only be taken if the potential benefit justifies the potential risks. For psychiatric indications and neuropathic pain carbamazepine should not be used and patients should instead be switched to more suitable alternative treatments.

Pregnant women and women of childbearing potential should be adequately advised on pregnancy risks due to the potential teratogenic risk for unborn infants.

Women of childbearing potential should use reliable contraception during treatment with carbamazepine and for 2 weeks after the last dose.

Hormonal contraceptives

Breakthrough bleeding has been reported in women using hormonal contraceptives. The efficacy of hormonal contraceptives may be adversely affected by Tegretol. Women of childbearing

potential should therefore be advised to use alternative, non-hormonal methods of contraception during Tegretol therapy.

Endocrinological effects

There have been isolated reports of impaired male fertility and/or abnormal spermatogenesis; a causal relationship has not been established.

Interactions

Due to enzyme induction, Tegretol may abolish the therapeutic effect of drugs containing oestrogens and/or progesterones (e.g. failure of contraception).

Coadministration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can increase carbamazepine or carbamazepine-10,11 epoxide plasma concentrations, which may induce adverse effects. The dosage of Tegretol should thus be adjusted accordingly, and plasma levels monitored.

Coadministration of CYP3A4 inducers may increase Tegretol metabolism, thereby decreasing carbamazepine serum levels and potentially reducing the therapeutic effect. Discontinuation of a CYP3A4 inducer may reduce carbamazepine metabolism, thereby increasing carbamazepine serum levels. The dosage of Tegretol may therefore have to be adjusted.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzymes in the liver, and may therefore reduce plasma concentrations of comedications mainly metabolised by CYP3A4 (see “Interactions”).

Concomitant use of carbamazepine with direct-acting oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) may lead to reduced plasma concentrations of direct-acting oral anticoagulants and thus increase the risk of thrombosis. Therefore, if concomitant use is necessary, close monitoring for possible signs and symptoms of thrombosis is recommended.

Monitoring of plasma levels

Although correlations between dosage and plasma concentrations of carbamazepine, and between plasma concentrations and clinical efficacy or tolerability, are rather tenuous, monitoring of plasma concentrations may be useful in the following circumstances: conspicuous increase in seizure frequency; verification of patient compliance; during pregnancy; in the treatment of children or adolescents; if an absorption disorder is suspected; if toxic effects are suspected in patients concomitantly using several medicinal products (see “Interactions”).

Change of treatment

Abrupt withdrawal of Tegretol may lead to seizures, therefore carbamazepine should be withdrawn gradually over a 6-month period. Epilepsy patients who have to switch from Tegretol therapy must not change abruptly, but transfer to treatment with another antiepileptic while tapering off Tegretol.

If Tegretol therapy has to be withdrawn abruptly in epilepsy patients, the switch to an alternative antiepileptic should be made under cover of a suitable drug (e.g. diazepam i.v. or rectal, phenytoin i.v.).

Falls

Tegretol treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional states or sedation (see “Adverse effects”), 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 for falls should be regularly considered during long-term Tegretol treatment.

Others

During treatment with carbamazepine, patients should protect themselves from intense sunlight due to the risk of photosensitisation.

Tegretol tablets
Tegretol tablets contain less than 1 mmol (23 mg) of sodium per tablet, making them practically “sodium-free”.

Tegretol Divitabs
Tegretol Divitabs contain less than 1 mmol (23 mg) of sodium per tablet, making them practically “sodium-free”.
Tegretol Divitabs macrogolglycerol hydroxystearate. May cause stomach upset and diarrhoea.

Tegretol oral suspension

Tegretol oral suspension contains less than 1 mmol (23 mg) of sodium per 5 ml (= 1 measuring spoon), making it practically “sodium-free”.

Tegretol oral suspension contains 125 mg propylene glycol per 5 ml (= 1 measuring spoon). Concomitant use with a substrate of alcohol dehydrogenase such as ethanol may cause severe adverse effects in neonates.

Tegretol oral suspension contains parahydroxybenzoates, which may cause allergic reactions (possibly delayed).

Tegretol oral suspension contains 875 mg sorbitol per 5 ml (= 1 measuring spoon) and therefore should not be administered to patients with the rare hereditary problem of fructose intolerance.

The additive effect of co-administered medicinal products containing sorbitol (or fructose) and the dietary intake of sorbitol or fructose must be taken into consideration. The sorbitol content of oral medicinal products may affect the bioavailability of other co-administered oral medicinal products.

Interactions

Cytochrome P450 3A4 (CYP3A4) is the main enzyme catalysing the formation of the active metabolite carbamazepine-10,11 epoxide. Coadministration of CYP3A4 inhibitors may result in increased plasma levels of carbamazepine, which could induce adverse effects. Coadministration of CYP3A4 inducers may increase Tegretol metabolism, leading to a decrease in serum carbamazepine and, possibly, a reduction in the therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the metabolism of carbamazepine, leading to an increase in carbamazepine serum levels.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzymes in the liver, and may therefore reduce plasma concentrations of comedications mainly metabolised by CYP3A4.

Human microsomal epoxide hydrolase is considered 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 (e.g. valproic acid) may result in elevated blood levels of carbamazepine-10,11 epoxide.

Agents that may raise plasma levels of carbamazepine

Elevated plasma levels of carbamazepine may result in adverse effects (e.g. dizziness, drowsiness, ataxia, diplopia), and the dosage of Tegretol should therefore be adjusted accordingly, and/or plasma levels monitored, if Tegretol is used concomitantly with the following agents:

Antitubercular agents: isoniazid.

Cardiovascular agents: verapamil, diltiazem.

Analgesics, anti-inflammatory agents: dextropropoxyphene, ibuprofen.

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

Gastrointestinal agents: possibly cimetidine, omeprazole.

Carbonic anhydrase inhibitors: acetazolamide.

Androgens: danazol.

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

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

Antihistamines: terfenadine, loratadine.

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

Antiepileptics: stiripentol, vigabatrin.

Antipsychotic agents: loxapine, olanzapine, quetiapine.

Muscle relaxants: oxybutynin, dantrolene.

Platelet aggregation inhibitors: ticlopidine.

Other: grapefruit juice, nicotinamide (only at high doses).

Agents that may raise plasma levels of carbamazepine-10,11-epoxide

Elevated plasma levels of carbamazepine-10,11-epoxide may cause adverse effects (e.g. dizziness, drowsiness, ataxia, diplopia), and the dosage of Tegretol should therefore be closely monitored, and adjusted where required, if Tegretol is given concomitantly with any of the following agents: brivaracetam, loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Agents that may lower plasma levels of carbamazepine

The dose of Tegretol may have to be adjusted if Tegretol is used concomitantly with the following agents:

Antiepileptics: phenobarbital, primidone, methsuximide, felbamate, oxcarbazepine, 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 commencing carbamazepine treatment), fosphenytoin, clonazepam.

Cytostatics: cisplatin, doxorubicin.

Antitubercular agents: rifampicin.

Bronchodilators or antiasthmatics: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

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

Effect of Tegretol on plasma levels of concomitantly administered agents

Carbamazepine may lower plasma levels of certain drugs, and diminish – or even abolish – their activity. The dosage of the following drugs may have to be adjusted to meet clinical requirements:

Analgesics, anti-inflammatory agents: buprenorphine, methadone, fentanyl, paracetamol (long-term administration of carbamazepine and paracetamol (acetaminophen) may lead to hepatotoxicity), phenazone (antipyrine), tramadol.

Antibiotics: doxycycline, rifabutin.

Anticoagulants: oral anticoagulants (warfarin, phenprocoumon, dicoumarol, acenocoumarol, rivaroxaban, dabigatran, apixaban, edoxaban).

Antidepressants: tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine), bupropion (carbamazepine may lower plasma levels of bupropion and raise those of its metabolite hydroxybupropion, thereby reducing the clinical efficacy and safety of bupropion), citalopram, mianserin, nefazodone, sertraline, trazodone. Tegretol should not be used in combination with MAO inhibitors. Before administering Tegretol, MAO inhibitors should be discontinued for a minimum of 2 weeks, or even longer if the clinical situation permits (see “Contraindications”).

Antiemetics: aprepitant.

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine, it is recommended to adjust the plasma concentration of phenytoin to 13 µg/ml before commencing carbamazepine treatment. There have been rare reports of an increase in plasma mephenytoin levels, which may – in exceptional cases – cause confusional states and even coma.

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

Anthelmintics: praziquantel, albendazole.

Cytostatics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

Antipsychotic agents: clozapine, haloperidol, bromperidol, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone.

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

Anxiolytics: alprazolam, midazolam.

Bronchodilators or antiasthmatics: theophylline.

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

Corticosteroids: e.g. prednisolone, dexamethasone.

Immunosuppressants: ciclosporin, tacrolimus, everolimus, sirolimus.

Thyroid hormones: levothyroxine: Carbamazepine seems to promote the elimination of thyroid hormones and to increase the need for them in patients with hypothyroidism. Thyroid parameters must therefore be determined in patients receiving replacement therapy both at the start and at the end of treatment with Tegretol.
If necessary, the dosage of the thyroid hormone products should be adjusted. Thyroid function may be altered in particular by concomitant use of carbamazepine and other anticonvulsants (e.g. phenobarbital).

Contraceptives: Sudden breakthrough bleeding may occur during use of hormonal contraceptives, in addition to attenuation of the effect of hormonal contraceptives. Therefore, either the contraceptive should contain more than 50 µg oestrogen, or other, non-hormonal methods of contraception should be recommended.

Drugs for the treatment of erectile dysfunction: tadalafil.

Points to consider in connection with combination therapy

There is evidence that concomitant use of carbamazepine and levetiracetam increases the toxicity of carbamazepine.

Concomitant administration of carbamazepine and isoniazid has been reported to increase the hepatotoxicity of isoniazid.

Please note that concomitant use, in particular of lithium or metoclopramide and carbamazepine, may potentiate the neurotoxic effects of both active substances. Therefore, close monitoring of clinical symptoms is necessary. Over 8 weeks should elapse following termination of prior treatment with neuroleptics, and concurrent treatment should also be avoided. Patients should be monitored for the following signs of neurotoxic symptoms: unsteady gait, ataxia, horizontal nystagmus, increased muscle proprioceptive reflexes, muscle twitching (fasciculations).

The literature indicates that the addition of carbamazepine to ongoing neuroleptic therapy may increase the risk of neuroleptic malignant syndrome or Stevens-Johnson syndrome.

Concomitant administration of Tegretol and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium), the dosage of which may therefore need to be raised. Patients should be monitored closely for unexpectedly rapid recovery from neuromuscular blockade.

Like other psychoactive drugs, carbamazepine may reduce alcohol tolerance. Abstention from alcohol is therefore advised.

Concomitant use of carbamazepine with direct-acting oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) may lead to reduced plasma concentrations of direct-acting oral anticoagulants and thus increase the risk of thrombosis. Therefore, if concomitant use is necessary, close monitoring for possible signs and symptoms of thrombosis is recommended.

Considerations for serological testing:

Carbamazepine 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 concentrations in fluorescence polarised immunoassays.

Pregnancy/Breast-feeding

Women of childbearing potential

Women of childbearing potential should use reliable contraception during treatment with carbamazepine and for 2 weeks after the last dose.

Due to enzyme induction, Tegretol may abolish the therapeutic effect of drugs containing oestrogens and/or progesterones, which can lead to failure of contraceptive protection. Women of childbearing potential should therefore use alternative effective and reliable contraceptive methods while on treatment with Tegretol.

Pregnancy

There is clear evidence of risk to the human fetus. Tegretol should therefore not be used during pregnancy unless absolutely necessary.

As with other antiepileptic drugs, ingestion of carbamazepine during pregnancy has been associated with reports of various types of embryonic malformation, including spina bifida and other congenital anomalies such as craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems. It should, however, be borne in mind that developmental disorders, including malformations, are observed 2-3 times more frequently in the offspring of epileptic mothers than in those of healthy controls. The extent to which these effects can be attributed to carbamazepine or to the underlying disease has not been fully elucidated.

Based on data from the North American Pregnancy Registry, the rate of major congenital anomalies, defined as a structural abnormality with surgical, medical or cosmetic importance, diagnosed within 12 weeks of birth, was 3.0% (95% CI 2.1 to 4.2%) among mothers exposed to carbamazepine monotherapy in the first trimester, and 1.1% (95% CI 0.35 to 2.5%) among pregnant women not taking any antiepileptic drug (relative risk 2.7, 95% CI 1.1 to 7.0%).

The nature of, and need for, treatment should always be carefully planned, and reassessed, in epileptic women wishing to conceive. Necessary antiepileptic therapy should not be withdrawn during pregnancy, as deterioration of the condition may have a negative impact on the development of the fetus.

Between days 20 and 40 of pregnancy in particular, the dose administered should be as low as possible. Malformations are probably triggered by peak plasma concentrations, and during this period in particular the total daily amount should therefore be given in several small divided doses spread over the day. Monitoring of plasma levels is recommended. The plasma concentration may be maintained at the lower end of the therapeutic range (4-12 µg/ml), provided that seizure control is maintained. There is evidence to suggest that the risk of malformations with carbamazepine is dose-dependent, i.e. at a dose <400 mg per day, the rates of malformations were lower than with higher doses of carbamazepine.

Throughout pregnancy and postpartum, the patient must be kept under close surveillance (monitoring of serum levels and EEG). Plasma levels should lie at the lower end of the therapeutic range (3-7 µg carbamazepine/ml). The risk of malformations is higher with combination therapy, so combination with other antiepileptics, or other drugs, should be avoided in order to further reduce risks. Monotherapy is recommended. There is evidence to suggest that the risk of malformations with carbamazepine in polytherapy may vary depending on the comedications used, and may be higher in polytherapy combinations that include valproate.

On account of the enzyme-inducing properties of carbamazepine, administration of folic acid is generally recommended before and during pregnancy (prevention of neural tube defects). It is also necessary to administer vitamin K to the mother during the final weeks of pregnancy, and postpartum to the neonate, in order to avoid haemorrhagic complications.

There have been some reports of seizures and/or respiratory depression in neonates whose mothers took Tegretol or another anticonvulsant shortly before or during the birth. Regular intake of carbamazepine by the mother can also produce withdrawal symptoms (vomiting, diarrhoea and/or nutritional disturbances) in the neonate.

Breast-feeding

In postnatal rat studies, adverse effects on the offspring of carbamazepine-treated dams were observed (see “Preclinical data”).

Carbamazepine is excreted in breast milk at concentrations approx. 25-60% of those found in the plasma. The benefits of breast-feeding generally outweigh the risks of possible adverse effects. Breast-feeding should be discontinued if the infant is found to have poor weight gain, excessive drowsiness or an allergic skin reaction. There have been some reports of cholestatic hepatitis in babies exposed to carbamazepine before birth or during breast-feeding. Breastfed infants of mothers treated with carbamazepine should therefore be carefully observed in particular for adverse effects on the hepatobiliary system.

Effects on ability to drive and use machines

The patient’s reactions may be impaired by seizures caused by the medical condition, and by Tegretol-induced adverse effects including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision, especially at the start of treatment or following dose adjustment. Patients should therefore exercise due caution when driving or when using machines.

Adverse effects

Certain types of adverse effects – e.g. central nervous system (CNS) adverse effects (dizziness, headache, ataxia, drowsiness, exhaustion, diplopia), gastrointestinal disturbances (nausea, vomiting) and allergic skin reactions – are uncommon or common, particularly at the start of Tegretol therapy (if the initial dosage is too high) and in elderly patients.

Dose-dependent adverse effects usually abate within a few days, either spontaneously or after transient dose reduction. The occurrence of CNS adverse effects may also be a manifestation of relative overdosage or of significant fluctuation in plasma levels. In such cases, it is advisable to monitor plasma concentrations.

Frequency estimates: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10 000 to <1/1000), very rare (<1/10 000).

Blood and lymphatic system disorders

Very common: Leukopenia (11%), persistent in 2% of cases.

Common: Eosinophilia, thrombocytopenia.

Rare: Lymphadenopathy.

Very rare: Leukocytosis, agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia.

Immune system disorders

Rare: Delayed multi-organ-hypersensitivity syndrome with various combinations of fever, exanthema, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts). Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).

Very rare: Anaphylactic reactions, hypogammaglobulinaemia, angioedema.

Endocrine disorders

Common: Oedema, fluid retention, weight gain; hyponatraemia and reduced plasma osmolality due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication with lethargy, nausea, vomiting, headache, confusion, neurological disturbances, seizures, disorientation, reduced perception, visual disturbances or encephalopathy (“syndrome of inappropriate antidiuretic hormone secretion”, SIADH).

Very rare: Gynaecomastia, galactorrhoea.

Metabolism and nutrition disorders

Rare: Folate deficiency, decreased appetite.

Very rare: Acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda.

Psychiatric disorders

Rare: Hallucinations (visual or acoustic), depression, restlessness, aggressive behaviour, agitation, confusion.

Very rare: Activation of psychosis.

Nervous system disorders

Very common: Dizziness (10-50%), ataxia (children 10.4%, adults 50%), somnolence.

Common: Headache, diplopia.

Uncommon: Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus.

Rare: Dyskinesia, oculomotor disturbances, speech disturbances (e.g. dysarthria, slurred speech), choreoathetoid disturbances, peripheral neuropathy, paraesthesias, paretic symptoms.

Very rare: Dysgeusia, neuroleptic malignant syndrome (NMS), aseptic meningitis with myoclonus and peripheral eosinophilia.

Eye disorders

Common: Accommodation disorders (e.g. blurred vision).

Very rare: Lens opacities, conjunctivitis.

Ear and labyrinth disorders

Very rare: Disturbances of hearing (e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception).

Cardiac disorders

Rare: Disturbances of cardiac conduction.

Very rare: Bradycardia, arrhythmias, AV block with syncope, heart failure, aggravation of coronary heart disease.

Vascular disorders

Rare: Hypertension or hypotension.

Very rare: Circulatory collapse, thrombophlebitis, thromboembolism (e.g. pulmonary embolism), vasculitis.

Respiratory, thoracic and mediastinal disorders

Very rare: Pulmonary hypersensitivity reactions characterised, for example, by fever, dyspnoea, pneumonitis or pneumonia.

Gastrointestinal disorders

Very common: Nausea, vomiting (both 8%).

Common: Dry mouth.

Uncommon: Diarrhoea, constipation.

Rare: Abdominal pain.

Very rare: Glossitis, stomatitis, pancreatitis.

Hepatobiliary disorders

Rare: Jaundice; cholestatic, parenchymal (hepatocellular) or mixed-type hepatitis, vanishing bile duct syndrome.

Very rare: Granulomatous hepatitis, liver failure.

Skin and subcutaneous tissue disorders

Very common: Allergic dermatitis, pruritus, urticaria (which may be severe).

Uncommon: Exfoliative dermatitis.

Rare: Systemic lupus erythematosus.

Very rare: Stevens-Johnson syndrome (reported as rare in some Asian countries; see “Warnings and precautions”), toxic epidermal necrolysis, photosensitivity reactions, erythema multiforme and nodosum, changes in skin pigmentation, purpura, acne, hyperhidrosis, hair loss, hirsutism.

Musculoskeletal and connective tissue disorders

Rare: Muscle weakness.

Very rare: Bone metabolism disorders (decrease in plasma calcium and 25-hydroxycholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia or muscle spasms.

Renal and urinary disorders

Very rare: Tubulointerstitial nephritis, kidney failure, renal dysfunction (e.g. albuminuria, haematuria, oliguria and elevated BUN/azotaemia), urinary frequency, urinary retention.

Reproductive system and breast disorders

Very rare: Sexual dysfunction/erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility).

There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis (see also “Preclinical data”).

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: Elevated alkaline phosphatase.

Uncommon: Elevated transaminases.

Very rare: Elevated intraocular pressure, cholesterol increased (incl. HDL cholesterol and triglycerides), abnormal thyroid function test: decreased L-thyroxine (free thyroxine, thyroxine, tri-iodothyronine) and increased TSH values, usually without clinical manifestations, blood prolactin increased.

List of adverse drug effects from post-marketing spontaneous reports

The following adverse effects have been identified from post-marketing spontaneous reports. Because these reactions are voluntary reports from a population of uncertain size, it is not always possible to reliably state their true frequency.

Infections and infestations

Reactivation of human herpesvirus 6 infection.

Blood and lymphatic system disorders

Bone marrow failure.

Immune system disorders

Drug rash with eosinophilia and systemic symptoms (DRESS).

Nervous system disorders

Sedation, memory impairment.

Gastrointestinal disorders

Colitis.

Skin and subcutaneous tissue disorders

Acute generalised exanthematous pustulosis (AGEP), lichenoid keratosis, onychomadesis.

Musculoskeletal and connective tissue disorders

Fracture.

Investigations

Bone density decreased.

Injury, poisoning and procedural complications

Falls (associated with Tegretol treatment-induced ataxia, dizziness, somnolence, hypotension, confusional states or sedation).

Reporting suspected adverse effects after authorisation of the medicinal product is very important. It allows continued monitoring of the risk-benefit ratio of the medicinal product.

Overdose

Symptoms and signs

The presenting symptoms of overdosage usually involve the central nervous, cardiovascular and respiratory systems, and the adverse drug reactions mentioned under “Adverse effects”.

Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucinations, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia; hyperreflexia followed by hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory tract: Respiratory depression, pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension, occasionally hypertension, conduction disturbances with widening of QRS complex; syncope in association with cardiac arrest.

Gastrointestinal tract: Vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system: Cases of rhabdomyolysis have been reported in association with carbamazepine toxicity.

Renal function: Urinary retention, oliguria or anuria; fluid retention, water intoxication due to an ADH-like effect of carbamazepine.

Laboratory findings: Hyponatraemia, (possible) metabolic acidosis, (possible) hyperglycaemia, elevated levels of muscle creatine phosphokinase.

Management

There is no specific antidote.

Management should initially be determined by the patient’s clinical condition. The patient should be hospitalised. Determination of plasma concentrations to confirm carbamazepine intoxication and ascertain the size of the overdose.

Gastric evacuation, gastric lavage and administration of activated charcoal. Delayed gastric emptying 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 carbamazepine overdose.

Relapse and aggravation of symptoms should be anticipated on the second and third days following overdosage due to delayed absorption.

Properties/Actions

ATC code

N03AF01

Mechanism of action

The mechanism of action of carbamazepine, the active substance of Tegretol, has not yet been fully elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges and reduces synaptic propagation of excitatory impulses.

It is conceivable that inhibition of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action. Whereas reduction of glutamate release and stabilisation of neuronal membranes may account mainly for the antiepileptic activity of carbamazepine, the inhibitory effect on dopamine and noradrenaline turnover might be responsible for its antimanic properties.

Pharmacodynamics

As an *antiepileptic* agent, Tegretol has a spectrum of activity that embraces: partial seizures (simple and complex) with or without secondary generalisation, generalised tonic-clonic seizures, and combinations of these types of seizure.

In some, but not all, clinical studies involving administration of Tegretol as monotherapy to epileptic patients – particularly children and adolescents – the drug was reported to exert a psychotropic action, including a positive effect on attentiveness, cognitive behaviour and symptoms of anxiety and depression, as well as a reduction in irritability and aggressiveness.

As a *neurotropic* agent, Tegretol is clinically effective in a number of neurological disorders, e.g. it reduces paroxysmal attacks of pain in idiopathic and secondary trigeminal neuralgia. In addition, Tegretol has been observed to provide relief of neurogenic pain in a variety of conditions. In alcohol-withdrawal syndrome, Tegretol raises the lowered seizure threshold and has a beneficial effect on withdrawal symptoms (e.g. hyperexcitability, tremor, impaired gait).

As a *psychotropic* agent, Tegretol proved to be clinically effective in affective disorders, e.g. in the treatment of acute mania and in the maintenance treatment of manic-depressive bipolar disorders, when given either as monotherapy or in combination with other neuroleptics, antidepressants or lithium.

Clinical efficacy

No data available.

Pharmacokinetics

Absorption

Carbamazepine is absorbed almost completely from the tablets and relatively slowly depending on the dosage form: following a single dose, t_{max} is attained after 2 (oral suspension), 12 (tablets) or 24 hours (CR Divitabs).

Bioavailability: The bioavailability of carbamazepine is almost 100% following administration of tablets, and approximately 15% lower with CR Divitabs. Food intake has no effect on bioavailability.
At doses of up to 300 mg carbamazepine, approx. 75% of the total amount absorbed reaches the systemic circulation within 6 hours. The maximum recommended daily dose for this dosage form is therefore 250 mg four times daily.

Plasma concentrations: The C_{max} of carbamazepine following a single dose of 400 mg (tablets) is approx. 4.5 µg/ml.

With the CR Divitabs, there was a statistically significant reduction in fluctuation index and C_{max} – but no significant reduction in C_{min} – at steady state. Plasma concentrations in the therapeutic range at steady state are approx. 4-12 µg/ml, equivalent to 17-50 µmol/litre carbamazepine; concentrations of carbamazepine-10,11-epoxide (pharmacologically active metabolite) are approx. 30% of carbamazepine concentrations.

Steady-state plasma concentrations of carbamazepine are reached within 1-2 weeks, depending individually on carbamazepine autoinduction and on heteroinduction by other enzyme-inducing drugs, as well as on pretreatment status, dosage and duration of treatment.

Distribution

Carbamazepine is 70-80% bound to serum proteins. Concentrations of unchanged substance in the CSF and saliva are equivalent to the non-protein-bound portion in the plasma (20-30%). The concentrations found in breast milk are equivalent to 25-60% of those in the plasma. Carbamazepine crosses the placental barrier.

The apparent distribution volume is 0.8-1.9 litres/kg.

Metabolism

Carbamazepine is metabolised in the liver, primarily via the epoxide-diol pathway. The first step involves oxidation to carbamazepine-10,11-epoxide, mainly via the cytochrome P450 3A4 isoenzyme. Human microsomal epoxide hydrolase is considered responsible for the formation of the pharmacologically active carbamazepine-10,11 epoxide, which is almost completely transformed into the 10,11-transdiol derivative and its glucuronides. About 30% of orally administered carbamazepine appears in the urine as the end-product of the epoxide pathway.

9-Hydroxymethyl-10-carbamoyl acridan is a less important metabolite. Other important metabolic pathways lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Carbamazepine induces its own metabolism.

Elimination

Plasma elimination half-life following a single-dose: average of 36 hours; after repeated administration (autoinduction of the hepatic monooxygenase system): average of 16-24 hours; in patients receiving concomitant treatment with other liver-enzyme inducing drugs (e.g. phenytoin, phenobarbital): average of 9-10 hours. Excretion: after a single 400 mg dose, 72% is excreted in the urine (2% unchanged, 1% epoxide, approx. 30% carbamazepine-10,11-transdiol and other inactive metabolites) and 28% in the faeces.

Pharmacokinetics in special patient populations

Note: The pharmacokinetics of carbamazepine are unaltered in the elderly. No data are available on patients with impaired hepatic or renal function.

Preclinical data

Preclinical data reveal no special risks for humans based on conventional studies of single- and repeated-dose toxicity.

Mutagenic and tumorigenic potential

Standard *in vitro* tests and studies in animals provided no evidence that carbamazepine possesses any relevant mutagenic potential. However, some more recent studies using non-standard methods showed an increase in chromosomal aberrations and/or sister chromatid exchange in human lymphocytes. The relevance for humans is unclear.

In a 2-year carcinogenicity study with carbamazepine in rats, there was an increased incidence of hepatocellular tumours in female rats and benign testicular tumours in males. However, there is no evidence that these observations are of any relevance to therapeutic use in humans.

Developmental toxicity

Fertility studies in rats with oral carbamazepine, in some cases in the therapeutic dose range, showed inconsistent effects, ranging from a lack of findings, to impaired sperm quality, through to considerably reduced male fertility, with signs of reversibility.

In various developmental toxicity studies in rats and mice, reduced fetal weights and delayed ossification were found with carbamazepine, in some cases at doses in the therapeutic range. At higher carbamazepine doses (200-600 mg/kg/day), which led to reduced weight gain in the maternal animals, there was an increased incidence of abortions and visceral and skeletal malformations.

In a postnatal toxicity study, nursing offspring whose mothers were given 192 mg/kg/day carbamazepine showed delayed weight gain.

A risk to humans in terms of developmental toxicity cannot be ruled out.

Other information

Shelf life

Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage

Keep out of the reach of children.

Tablets and CR tablets: Protect from moisture and do not store above 30°C.

Oral suspension: Protect from light and do not store above 30°C. After opening, do not use for more than 3 months.

Pack sizes

Tegretol 200 mg CR tablets (scored): Packs containing 50 tablets and 200 tablets

Tegretol 400 mg CR tablets (scored): Packs containing 30 tablets and 200 tablets

Tegretol 250 ml and 100 ml Oral suspension .

Tegretol 200 mg tablets (round): Packs containing 50 tablets.

Tegretol 400 mg tablets (rod-shaped): Packs containing 30 tablets and 200 tablets.

Not all size packs are marketed

Information last revised

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Novartis Pharma AG, Basle, Switzerland

This is a medicament

– A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
– Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
– The doctor and the pharmacist are experts in medicine, its benefits and risks.
– Do not by yourself interrupt the period of treatment prescribed for you.
– Do not repeat the same prescription without consulting your doctor.

Keep medicaments out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists