NOVARTIS

Regulatory Affairs

TEGRETOL®
(carbamazepine)

100 mg, 200 mg and 400 mg tablets 200 mg and 400 mg CR tablets
100 mg chewable tablets
100 mg / 5 mL oral suspension
125 mg and 250 mg suppositories

Prescribing Information

Version# 2.2

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosage regimen, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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1 Tradename(s)

TEGRETOL® 100 mg, 200 mg and 400 mg tablets

TEGRETOL® 200 mg and 400 mg CR tablets (modified-release film-coated tablets)

TEGRETOL® 100 mg chewable tablets

TEGRETOL® 100 mg / 5 mL oral suspension

TEGRETOL® 125 and 250 mg suppositories

2 Description and composition

Pharmaceutical forms

Tablets: 100 mg, 200 mg and 400 mg carbamazepine.

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

Chewable tablets (scored): 100 mg carbamazepine.

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

Suppositories: 125 mg and 250 mg carbamazepine.

Information might differ in some countries.

Active substance Carbamazepine.

Excipients

Tablets: Silica, colloidal anhydrous, cellulose, microcrystalline, magnesium stearate, carmellose sodium, low substituted.

CR tablets: Silica, colloidal anhydrous, ethylcellulose aqueous dispersion, cellulose, microcrystalline, polyacrylate dispersion, magnesium stearate, croscarmellose sodium, talc. Coating: hypromellose, macrogolglycerol hydroxystearate, iron oxide red, iron oxide yellow, talc, titanium dioxide.

Chewable tablets: Silica, colloidal anhydrous, aroma cherry mint, erythrosin, gelatine, glycerin pure, magnesium stearate, maize starch, sodium carboxymethyl starch, stearic acid, sucrose (directly compressible).

Oral suspension: Cellulose, microcrystalline + sodium CMC, caramel aroma 52929 A, methylparaben, hydroxyethylcellulose, propylene glycol, polyethylene glycol 400 stearate, propylparaben, saccharin sodium, sorbic acid, sorbitol solution, water purified.

Suppositories: Hypromellose, Suppository mass 15 (hard fat).

Information might differ in some countries.

3 Indications

- Epilepsy [22,24,35,47b,49,56-58,63,149,172]
  - Complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalization [287].
  - Generalized tonic-clonic seizures. Mixed forms of seizures.

    Tegretol® is suitable for both monotherapy and combination therapy [24,35,47b,5658,172].

Tegretol is usually not effective in absences (petit mal) and myoclonic seizures (see section 6 Warnings and precautions) [35,47b,149,172,208].

- Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence [51,59-61,64,82,156,157].
- Alcohol withdrawal syndrome [47b,98,150].
- Idiopathic trigeminal neuralgia and trigeminal neuralgia due to multiple sclerosis (either typical or atypical). Idiopathic glossopharyngeal neuralgia [21,22,33,179].
- Painful diabetic neuropathy [47b,48].
- Diabetes insipidus centralis [33,47b,48,155]. Polyuria and polydipsia of neurohormonal origin.

4 Dosage regimen and administration

Epilepsy

When possible, Tegretol should be prescribed as monotherapy.

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

The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre) [311] (see section 6 Warnings and precautions).

When Tegretol is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see sections 8 Interactions and 11 Clinical pharmacology - Pharmacokinetics).

General target population / Adults

Dosage in Epilepsy

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 [22,33,44,172].

Suppositories

When suppositories are used instead of oral forms the maximum daily dose is limited to 1000 mg (250 mg q.i.d. at 6-hour interval).

No clinical data are available on the use of suppositories in indications other than epilepsy.

Dosage in 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 [50,72,156,157].

Dosage in Alcohol-withdrawal syndrome

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

Dosage in Trigeminal neuralgia

The initial dosage of 200 to 400 mg should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs [311].

Dosage in Painful diabetic neuropathy Average

dosage: 200 mg 2 to 4 times daily.

Dosage in Diabetes insipidus centralis

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

Special populations Renal impairment / Hepatic impairment

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

Pediatrics / Children and adolescents

Dosage in Epilepsy

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 [75,161].

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

- Up to 1 year of age: 100 to 200 mg daily (= 5 to 10 mL = 1-2 measures of oral suspension)
- 1 to 5 years of age: 200 to 400 mg daily (= 10 to 20 mL = 2 1-2 measures of oral suspension)
- 6 to 10 years of age: 400 to 600 mg daily (= 20 to 30 mL= 2-3 2 measures of oral suspension)

- 11 to 15 years of age: 600 to 1000 mg daily (= 30 to 50 mL = 3 2-3 measures of oral suspension (plus an extra measure of 5 mL in case of administration of 1000 mg)) >15 years of age: 800 to 1200 mg daily (same as adult dose) [311].

Maximum recommended 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 [311].

Suppositories

When suppositories are used instead of oral forms, the maximum daily dose is limited to 1000 mg (250 mg q.i.d. at 6-hour intervals).

No clinical data are available on the use of suppositories in indications other than epilepsy.

Dosage in Diabetes insipidus centralis

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

Geriatric patients (65 years or above)

Dosage in Trigeminal neuralgia

Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of Tegretol should be selected with caution in elderly patients [292].

In elderly patients, an initial dose of 100 mg twice daily is recommended. The initial dosage of 100 mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs [311].

Method of administration

The tablets and the oral suspension (to be shaken before use) may be taken during, after, or between meals. Tablets should be taken with a little liquid [8,9,47b], and possible remnants of the chewable tablets should be washed down with a little liquid.

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

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

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

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

Switching patients from conventional tablets to CR tablets: clinical experience shows that in some patients the dosage in the form of CR tablets may need to be increased [163,165,171,175].

Switching patients from oral formulations to suppositories: the dosage in the form of suppositories needs to be increased by about 25% and given in divided doses, up to a maximum of 250 mg four times a day (q.i.d.) at 6-hour intervals [203-205]. Experience in administration of suppositories is limited to 7 days as replacement therapy in patients in whom oral treatment of epilepsy is temporarily not possible, for example in postoperative or unconscious subjects.

5 Contraindications

- Known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) [49,72] or any other component of the formulation
- Patients with atrioventricular block [72]
- Patients with a history of bone-marrow depression [68]
- Patients with a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda) [67,70,71,79,90,295]
- The use of Tegretol is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs) [33,50,69,83,295] (see section 8 Interactions).

6 Warnings and precautions

Tegretol should be given only under medical supervision [49,65,72]. Tegretol should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse hematological reactions to other drugs, or interrupted courses of therapy with Tegretol [22,33,67,87].

Hematological effects

Agranulocytosis and aplastic anemia have been associated with Tegretol; however, due to the very low incidence of these conditions, meaningful risk estimates for Tegretol are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anemia [206].

Transient or persistent decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Tegretol. However, in the majority of cases these effects prove transient and are unlikely to signal the onset of either aplastic anemia or agranulocytosis [23,24,47b,50,90]. Nonetheless, complete pretreatment blood counts,

including platelets (and possibly reticulocytes and serum iron), should be obtained at baseline, and periodically thereafter [23,47b,50,65,66,72,73,75,76,90,118,159,160].

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 [72,23,68,89,90].

Patients should be made aware of early toxic signs and symptoms of a potential hematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage appear, the patient should be advised to consult the physician immediately [49,90].

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. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, Tegretol should be withdrawn at once and alternative therapy should be considered [24,25,49,65,300,312].

Pharmacogenomics

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

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigene (HLA)-B*1502 allele. The frequency of HLAB*1502 allele ranges from 2 to 12% in Han Chinese populations and is about 8% in Thai populations. Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the population (e.g. above 15% in the Philippines and some Malaysian populations). Allele frequencies up to about 2% and 6% have been reported in Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%) [300,312].

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e. the "carrier frequency") is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency [312].

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 below Information for the healthcare professionals). The use of Tegretol should be avoided in tested patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other antiepileptic 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 [300].

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 [309].

Association with HLA-A*3101

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

The frequency of the HLA-A*3101 allele varies widely between ethnic populations and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population [312]. The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations, with some exceptions within 5-12%. Prevalence above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10%-15% in other native ethnicities in these same regions.

The allele frequencies listed here represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a copy of the allele on at least one of their two chromosomes (i.e. the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency [312].

Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with Tegretol (see below Information for the healthcare professionals). The use of Tegretol should be avoided in patients who are found to be positive for HLA-A*3101, unless the benefits clearly outweigh the risks. Screening is generally not recommended for any current Tegretol users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status [309].

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 HLAA*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 [300,309].

Information for the healthcare professionals

If testing for the presence of the HLA-B*1502 allele is 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 [300]. Similarly if testing for the presence of the HLA-A*3101 allele is 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 [309].

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 [25,50,65,138,300].

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 [300,309].

Hypersensitivity

Tegretol may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), [307] that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon). See section 7 Adverse drug reactions [295,312].

The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopapular rash [309].

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®) [293].

Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital) [293, 315].

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Tegretol should be withdrawn immediately [295].

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 [24,81,87,88,178].

An increase in seizure frequency may occur during the switch from an oral formulation to suppositories.

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 [47b,49,91].

Renal function

Baseline and periodic complete urinalysis and BUN determinations are recommended [49].

Hyponatremia

Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodiumlowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after

approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatremia is observed, water restriction is an important counter-measurement if clinically indicated [312].

Hypothyroidism

Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction requiring an increase in dose of thyroid replacement therapy in patients with hypothyroidism. Hence thyroid function monitoring is suggested to adjust the dosage of thyroid replacement therapy [312].

Anticholinergic effects

Tegretol has shown mild anticholinergic activity. Patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy (see section 7 Adverse drug reactions) [33,80,312].

Psychiatric effects

The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind [35,49,65].

Suicidal ideation and behaviour

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

Therefore patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge [305].

Pregnancy and females of reproductive potential

Carbamazepine may be associated with fetal harm when administered to a pregnant woman (see section 9 Pregnancy, lactation, females and males of reproductive potential). Tegretol should be used during pregnancy only if the potential benefit justifies the potential risks.

Adequate counselling should be made available to all pregnant women and women of childbearing potential, regarding the risks associated with pregnancy due to potential teratogenic risk to the fetus (see section 9 Pregnancy, lactation, females and males of reproductive potential).

Women of childbearing potential should use effective contraception during treatment with carbamazepine and for 2 weeks after the last dose (see below sub-sections “Endocrinological effects” and “Interactions”) (see section 9 Pregnancy, lactation, females and males of reproductive potential) [317].

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 [33,49,69,72] and women of child-bearing potential should be advised to consider using alternative forms of birth control while taking Tegretol.

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 section 8 Interactions) [1,21,44,49,50,77].

Dose reduction and withdrawal effects

Abrupt withdrawal of Tegretol may precipitate seizures, therefore carbamazepine should be withdrawn gradually over a 6-month period. If treatment with Tegretol has to be withdrawn abruptly in a patient with epilepsy, the switch to the new antiepileptic compound should be made under cover of a suitable drug [312].

Interactions

Co-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can induce adverse reactions (increase of carbamazepine or carbamazepine10,11 epoxide plasma concentrations, respectively). The dosage of Tegretol should be adjusted accordingly and/or the plasma levels monitored.

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

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 co-medications mainly metabolized by CYP3A4 by induction of their metabolism. See section 8 Interactions.

Female patients of child-bearing potential should be warned that the concurrent use of Tegretol with hormonal contraceptives may render this type of contraceptive ineffective (see sections 8 Interactions and 9 Pregnancy, lactation, females and males of reproductive potential). Alternative non-hormonal forms of contraception are recommended when using Tegretol [312].

Driving and using machines

The patient's ability to react may be impaired by the medical condition, resulting in seizures, and adverse reactions including dizziness, drowsiness ataxia, diplopia, impaired accommodation and blurred vision have been reported with Tegretol, especially at the start of

treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery [68,312].

Falls

Tegretol treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 7 Adverse drug reactions) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term Tegretol treatment [315].

Special excipients

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

7 Adverse drug reactions

Summary of the safety profile

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 [33,48,49,50,65,72,149,178].

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 [50,72].

Tabulated summary of adverse drug reactions compiled from clinical trials and from spontaneous reports

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 7-1 Adverse drug reactions

Blood and lymphatic system disorders	Very common: leukopenia.

Common:	thrombocytopenia, eosinophilia.
Rare:	leukocytosis, lymphadenopathy [23-25,50,65,90,178].
	Very rare: agranulocytosis, aplastic anaemia, pancytopenia [295], aplasia pure red cell, anaemia [295,312], anaemia megaloblastic, reticulocytosis, haemolytic anaemia [23,24,50,65,67,80,90,162,312].

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 vanishing bile duct syndrome (destruction and disappearance of the

intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) [22,49,67,80,86,135,164,178,222,223,307,312].

Very rare: anaphylactic reaction [80], angioedema [224,312], hypogammaglobulinaemia [298,312].

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 [22,23,49,50,67,178].

Very rare: galactorrhoea, gynaecomastia [80,312].

Metabolism and nutrition disorders

Rare: folate deficiency, decreased appetite [312].

Very rare: porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda) [295,312].

Psychiatric disorders

Rare: hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state.

Very rare: activation of psychosis [48-50].

Nervous system disorders

Very common: ataxia, dizziness, somnolence [312].

Common: diplopia, headache, [48,50,65,72].

Uncommon: abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics) [80,178], nystagmus [48,50,67].

Rare: dyskinesia [312], eye movement disorder [312], speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, paresis [49,50,67,80].

Very rare: neuroleptic malignant syndrome [218-220,295], aseptic meningitis with myoclonus and peripheral eosinophilia [184,185,312], dysgeusia [25,65,312].

Eye disorders

Common accommodation disorders (e.g. blurred vision) [312] Very rare: lenticular opacities [80], conjunctivitis [80].

Ear and labyrinth disorders

Very rare: hearing disorders, e.g. tinnitus [49,80,181], hyperacusis [80], hypoacusis [225], change in pitch perception [226,227]. **Cardiac disorders**

Rare: cardiac conduction disorders [49,50,67,80].

Very rare: arrhythmia, atrioventricular block with syncope, bradycardia, cardiac failure congestive, coronary artery disease aggravated, [22,33,35,49,50,67,68,80,84,295,312].

Vascular disorders

Rare: hypertension or hypotension [312]

	Very Rare: circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis [22,33,35,49,50,67,68,80,84,295,312].

Respiratory, thoracic and mediastinal disorders

Very rare: pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia [48,67,80,85].

Gastrointestinal disorders

Very common: vomiting, nausea [48-50,72].

Common: dry mouth [33,49,68]; with suppositories, rectal irritation may occur [203,205].

Uncommon: diarrhoea, constipation [33,48,49,72].

Rare: abdominal pain.

Very rare: pancreatitis [135,221], glossitis, stomatitis [33,48,49,68].

Hepatobiliary disorders

Rare: hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome [307], jaundice.

Very rare: hepatic failure [293], granulomatous liver disease [33,49,65,67,312].

Skin and subcutaneous tissue disorders

Very common: urticaria which may be severe, dermatitis allergic [24,33,48-50,65].

Uncommon: dermatitis exfoliative [312].

Rare: systemic lupus erythematosus [25,48,50,80,90], pruritus.

Very rare: Stevens-Johnson syndrome* [288-291], toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder [312], purpura, acne, hyperhydrosis, alopecia [25,33,48-50,67,80,90,312], hirsutism [190,191,302].

Musculoskeletal, connective tissue and bone disorders

Rare muscular weakness

Very rare: bone metabolism disorders (decrease in plasma calcium and blood 25hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis [50,67,80,149,295,312], arthralgia, myalgia, muscle spasms [49,80,312].

Renal and urinary disorders

Very rare: tubulointerstitial nephritis [312], renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and blood urea increased/azotemia), urinary retention, urinary frequency.

Reproductive system

Very rare: sexual dysfunction/erectile dysfunction, spermatogenesis abnormal (with decreased sperm count and/or motility) [23,33,48,49,80,295,312].

General disorders and administration site conditions

Very common fatigue [312].

Investigations

Very common: gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant [24,72,312].

Common: blood alkaline phosphatase increased [312].

Uncommon: transaminases increased [23,33,50,65,72,81,90,312].

Very rare: intraocular pressure increased [295,312], blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased [80,9294,312]. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations [23,50,65,80,312], blood prolactin increased [80,312],

* In some Asian countries also reported as rare. See also section 6 Warnings and precautions.

Additional adverse drug reactions from spontaneous reports (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.

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Infections and infestations Reactivation of Human herpes virus 6 infection [312].
Blood and lymphatic system disorders Bone marrow failure [312].
Injury, poisoning and procedural complications Fall (associated with Tegretol treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) [315] (see section 6 Warning and precautions).
Nervous system disorders Sedation, memory impairment [312].
Gastrointestinal disorders Colitis [312].
Immune system disorders Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) [308].
Skin and subcutaneous tissue disorders Acute Generalized Exanthematous Pustulosis (AGEP) [308], lichenoid keratosis, onychomadesis [312].
Musculoskeletal and connective tissue disorders Fracture [312].
Investigations Bone density decreased [312].

8 Interactions

Cytochrome P450 3A4 (CYP3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine-10,11-epoxide. Co-administration of inhibitors of CYP3A4 may result in increased carbamazepine plasma concentrations which could induce adverse reactions [294]. Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and therapeutic effect [214,294]. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels [293].

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 co-medications mainly metabolized by CYP3A4 by induction of their metabolism [294].

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 [301]. Coadministration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations [301].

Interactions resulting in a contraindication

The use of Tegretol is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering Tegretol MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see section 5 Contraindications) [33,50,69,83,295].

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 [295].

Androgens: danazol [125,126].

Antibiotics: macrolide antibiotics (e.g. erythromycin, troleandomycin [119,120], josamycin [121], clarithromycin [246-248]), ciprofloxacine [310].

Antidepressants: possibly desipramine [128], fluoxetine [186,187], fluvoxamine [234-241], nefazodone [242-245], paroxetine [297], trazodone [294,295], viloxazine [303,304].

Antiepileptics: stiripentol [294,295], vigabatrin [294,295].

Antifungals: azoles [214,249,250] (e.g. itraconazole, ketoconazole, fluconazole, voriconazole [294,295]). Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole [313].

Antihistamines: loratadine, terfenadine [251].

Antipsychotics: olanzapine [295].

Antituberculosis: isoniazid.

Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir) [293].

Carbonic anhydrase inhibitors: acetazolamide [26,27,123,124].

Cardiovascular drugs: diltiazem, verapamil.

Gastrointestinal drugs: possibly cimetidine, omeprazole [294,295].

Muscle relaxants: oxybutynin [294,295], dantrolene [294,295].

Platelet aggregation inhibitors: ticlopidine [294,295].

Other interactions: grapefruit juice, nicotinamide (only in high dosage) [129,130,313].

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 [294,301], quetiapine [294,301], primidone, progabide [69,146,301], valproic acid, valnoctamide and valpromide [69,101,102,301].

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 [258-262], methsuximide [252,253], oxcarbazepine, phenobarbital [69,137,138], phensuximide [254], phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms/mL before adding carbamazepine to the treatment [313]) and fosphenytoin [100,136,137,294], primidone [137,69,82], and, although the data are partly contradictory, possibly also clonazepam [99,69,139].

Antineoplastics: cisplatin or doxorubicin [256,257].

Antituberculosis: rifampicin [255].

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline [69,112,294].

Dermatological drugs: isotretinoin [100,144].

Other interactions: herbal preparations containing St John's wort (*Hypericum perforatum*) [293].

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 [1,69,123,134]. The dosage of the following drugs may have to be adjusted to clinical requirements:

Analgesics, anti-inflammatory agents: buprenorphine [306], methadone [69,110], paracetamol (long-term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity) [283-286,313], phenazone (antipyrine) [294], tramadol.

Antibiotics: doxycycline [106], rifabutin [313].

Anticoagulants: oral anticoagulants (e.g. warfarin, phenprocoumon, dicoumarol [69,82,114,115,134], acenocoumarol [294,295], rivaroxaban, dabigatran, apixaban, edoxaban [316]).

Antidepressants: bupropion [294,295], citalopram [294,295], mianserin [306], nefazodone [301], sertraline [306], trazodone [294], tricyclic antidepressants (e.g. imipramine [127], amitriptyline, nortriptyline, clomipramine) [273-279].

Antiemetics: aprepitant [310]

Antiepileptics: clobazam [97,98,149], clonazepam [99,149], ethosuximide [103,104,149], felbamate [256-262], lamotrigine [263,264], eslicarbazepine [315], oxcarbazepine, primidone, tiagabine [269,270], topiramate [271,272], valproic acid [100,69,101], zonisamide [265-268]. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment [313]. There have been rare reports of an increase in plasma mephenytoin levels [118].

Antifungals: itraconazole, voriconazole. Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole [313].

Antihelmintics: praziquantel, albendazole [310].

Antineoplastics: imatinib [294,295], cyclophosphamide [308], lapatinib [308], temsirolimus [310].

Antipsychotics: clozapine [280-282], haloperidol [107-109] and bromperidol [294], olanzapine [293], quetiapine [294,295], risperidone, ziprasidone [293], aripiprazole [308], paliperidone [310].

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

Anxiolytics: alprazolam [145], midazolam.

Bronchodilatators or anti-asthma drugs: theophylline [69,113].

Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered) [69,72,111].

Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g. felodipine [122], digoxin [105], simvastatin, atorvastatin, lovastatin, cerivastatin [312,313], ivabradine [313].

Corticosteroids: corticosteroids (e.g. prednisolone, dexamethasone) [134,141,142].

Drugs used in erectile dysfunction: tadalafil [310].

Immunosuppressants: ciclosporin [95,96], everolimus [294,295], tacrolimus [308], sirolimus [310].

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 [297].

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazidinduced hepatotoxicity [69,147,148].

Combined use of carbamazepine and lithium [132,133,149] or metoclopramide [131] on the one hand, and carbamazepine and neuroleptics (haloperidol, thioridazine) [107,108] 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 hyponatremia [140].

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 [100,143].

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol [69].

Concomitant use of carbamazepine with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban, and edoxaban) may lead to reduced plasma concentrations of direct acting oral anti-coagulants, which carries the risk of thrombosis. Therefore, if a concomitant use is necessary, close monitoring of signs and symptoms of thrombosis is recommended [316].

Interference with 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 concentration in fluorescence polarized immunoassay method [313].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. Although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking, developmental disorders and malformations, including spina bifida [24,30,31,35-38,41,180-183,193,194] and also other congenital anomalies, e.g. craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with the use of Tegretol [293,295]. Based on data in a North American pregnancy registry, the rate of major congenital malformations, 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) [312].

Clinical considerations

Taking these data into consideration:

- Pregnant women with epilepsy should be treated with special care [30,31,37,112,195,196].
- If women receiving Tegretol become pregnant or plan to become pregnant, or if the need of initiating treatment with Tegretol arises during pregnancy, the drug's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of child-bearing potential Tegretol should, wherever possible, be prescribed as monotherapy [30,31], 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 [30-32,36]. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific drugs used and may be higher in polytherapy combinations that include valproate [312].
- Minimum effective doses should be given and monitoring of plasma levels is recommended [30,31,33]. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained. There is evidence to suggest that the risk of malformation with carbamazepine may be dosedependent, i.e. at a dose < 400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine [312].
- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening [207].

- During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus [296].

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 [31,34,188,189,192,194].

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 [24,30,31,159].

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, diarrhea and/or decreased feeding have also been reported in association with maternal Tegretol use. These reactions may represent a neonatal withdrawal syndrome [228].

Animal data

The cumulative evidence from various animal studies in mice, rats and rabbits indicates that carbamazepine has no or only minor teratogenic potential at doses relevant to man. However, the animal studies were insufficient to rule out a teratogenic effect of carbamazepine. In a reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day [314].

9.2 Lactation

Risk summary

Carbamazepine passes into the breast milk (about 25 to 60% of plasma concentrations) [42-44]. 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) [35,45,46,80]. There have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during antenatal and or during breast feeding. Therefore breast-fed infants of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects [312].

9.3 Females and males of reproductive potential

Contraception

Women of childbearing potential should use effective contraception during treatment with Tegretol and for 2 weeks after the last dose [317]. Due to enzyme induction, Tegretol may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen

and/or progesterone. Therefore, women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with Tegretol [312].

Infertility

There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis [295].

10 Overdosage

Signs and symptoms [50,151-154]

The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under section 7 Adverse drug reaction [312].

Central nervous system

CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis [229,312].

Respiratory system

Respiratory depression, pulmonary edema.

Cardiovascular system

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

Gastrointestinal system

Vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system

There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity [312].

Renal function

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

Laboratory findings

Hyponatremia, possibly metabolic acidosis, possibly hyperglycemia, increased muscle creatine phosphokinase.

Management [50,151-154,158]

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 [230-233]. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations

Charcoal hemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose [312].

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

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

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

Dibenzazepine derivative.

Mechanism of action (MOA)

The mechanism of action of carbamazepine, the active substance of Tegretol, has only been partially elucidated [54]. Carbamazepine stabilizes hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses [54]. 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 [215-217].

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 [173,174].

Pharmacodynamics (PD)

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 [24,35,47,48,56-58].

In clinical studies Tegretol given as monotherapy to patients with epilepsy - in particular children and adolescents - has been reported to exert a psychotropic action [24,47,52,63,97,166,172,177,223], including a positive effect on symptoms of anxiety and depression [52,78,168,169,176] as well as a decrease in irritability and aggressiveness [47b,52,169,176,177]. As regards cognitive and psychomotor performance, in some studies equivocal or negative effects, depending also upon dosages administered, were reported [18,74,166,167,170,197,198]. In other studies, a beneficial effect on attentiveness, cognitive performance/memory was observed [52,53,169,170,172,176,177,198,199].

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 [22,33,210]; 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 [209]; in alcohol withdrawal syndrome it raises the lowered convulsion threshold and improves withdrawal symptoms (e.g. hyperexcitability, tremor, impaired gait) [47b,98,150]; in diabetes insipidus centralis, Tegretol reduces the urinary volume and relieves the feeling of thirst [48,155].

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 [50,51,59,60,61,64,82,156,157], in excited schizo-affective disorder and excited mania in combination with other neuroleptics, and in rapid cycling episodes [211213].

Pharmacokinetics (PK) Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets [1,14]. 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 [2,3]. With the oral suspension, mean peak plasma concentrations are attained within 2 hours [1,4], and with the suppositories within a mean of 12 hours [200-202]. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms [8,9]. 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 [2,3].

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 [2,5-7,62,171].

When suppositories are administered, the amount of carbamazepine absorbed is about 25% lower than with tablets [200]. No change of fluctuation index, but slight decrease of C_{max} and C_{min} compared to tablets was found at steady state [203-205]. For doses up to 300 mg carbamazepine about 75% of the total amount absorbed reaches the general blood circulation within 6 hours after application [201,202]. The result has led to the recommendation that the maximal daily dose be limited to 250 mg q.i.d.

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 [55].

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 [1,7,10,11,16,21,22,33,44].

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Tegretol [8,9].

Distribution

Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg [1,10-13,33,44].

Carbamazepine crosses the placental barrier [33].

Carbamazepine is bound to serum proteins to the extent of 70 to 80% [1,10-13]. 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/metabolism

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 [301]. 9Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway [16]. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway [14]. Other important biotransformation pathways for carbamazepine lead

to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7 [14,16,294].

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 (autoinduction 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 [14,16,44].

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 [15].

After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the feces [14,16]. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10,11-epoxide metabolite [14,16].

Special populations

Pediatric patients

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults [1,17-19].

Geriatric patients (65 years or above)

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults [20].

Patients with hepatic or renal impairment

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

12 Clinical studies

No recent clinical trials have been conducted with Tegretol.

13 Non-clinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, genotoxicity and carcinogenic potential. However, the animal studies were insufficient to rule out a teratogenic effect of carbamazepine [314].

Rectal local toxicity

The local tolerability of carbamazepine suppositories administered by the rectal route to rabbits once daily for 2 weeks was not different to control animals receiving vehicle only.

Carcinogenicity

In rats treated with carbamazepine for 2 years, there was an increased incidence of hepatocellular tumors in females and benign testicular tumors in males. However, there is no evidence that these observations are of any relevance to the therapeutic use of carbamazepine in humans. **Genotoxicity**

Carbamazepine was not found to be genotoxic in various standard bacterial and mammalian mutagenicity studies. **Reproductive toxicity**

For reproductive toxicity, see section 9 Pregnancy, lactation, females and males of reproductive potential.

14 Pharmaceutical information

Incompatibilities None

known.

Special precautions for storage

Tablets: do not store above 25°C, protect from moisture.

CR tablets: do not store above 25°C protect from moisture.

Chewable tablets: protect from heat (do not store above 30°C) and protect from moisture.

Oral suspension: protect from heat (do not store above 30°C) and protect from light.

Suppositories: protect from heat (do not store above 30°C).

Information might differ in some countries.

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

Instructions for use and handling

There is no specific instruction for use/handling.

15 References

Including references (26-47) Pregnancy and Lactation and Reproduction Toxicity (BDI 05 July 89)

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314 2.4 Nonclinical Overview - Rationale for changes to Core Data Sheet (CDS)/Product Information – Non-clinical safety data. Novartis. 26-Feb-2013.

Newly added references - CDS update and Amendment (bundling) 30-Jun-2017

315 2.5 Clinical Overview - Rationale for changes to Core Data Sheet (CDS)/Product Information – Safety sections- Adverse drug reactions, Warning and precautions and Interactions (Fall, cross-hypersensitivity to aromatic antiepileptic drugs, drug-drug interaction with eslicarbazepine). Novartis. 30-May-2017

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Newly added references - CDS Amendment 01-Dec-2017

317 2.5 Clinical Overview - Rationale for changes to Core Data Sheet (CDS)/Product Information – Section Warnings& precautions- Pregnancy and females of reproductive potential. Novartis. 10-Oct-2017

16 CDS history table

Version	Effective date	GLC/PSB approval date	SLC Tracking No.	Section keyword	Refs.	Author(s) GLM/GPRD/GPRM
1.0	21-Mar-2013	26-Feb-2013	2013-PSB/GLC-0609-s	Changes made to following sections: • Dosage and administration • Warnings and precautions • Adverse drug reactions • Women of child-bearing potential, pregnancy, breast-feeding and fertility • Interactions • Overdosage • Non-clinical safety data	311 312 313 314	Eric Randolph
2.0	11-Jul-2017 (Bundled both changes)	30-May-2017	2017-PSB/GLC-0883-s (to facilitate the CDS dispatch, tracking	**Section 6 Warnings and precautions** **□ Hypersensitivity** Cross-hypersensitivity with other aromatic antiepileptics (primidone and phenobarbital)	315	Raghuram Akinapelli
Version	**Effective date**	**GLC/PSB approval date**	**SLC Tracking**	**Section keyword No.**	**Refs.**	**Author(s) GLM/GPRD/GPRM**

			number assigned 2017-PSB/GLC0888-s for DDIs with oralanticoagulants was pruned)	□ Addition of warning for "Fall" **Section 7 Adverse drug reactions** Addition of new PT Fall **Section 8 Interactions** Addition of DDI with eslicarbazepine to existing AEDs		
2.1		08-Jun-2017		**Section Interactions** Addition of DDIs with new oral anti-coagulants (rivaroxaban, dabigatran, apixaban, edoxaban)	316	Raghuram Akinapelli
2.2	01-Dec-2017	10-Oct-2017	2017-PSB/GLC-0902-s	Addition of new warning "Pregnancy and females of reproductive potential"	317	Raghuram Akinapelli