NOVARTIS

Tegretol®

Composition
Active substance
Carbamazepine

Excipients
Tablets
Tableting excipients

CR tablets
Tableting excipients

2% Syrup
Saccharin sodium; see folding box.

Suppositories
Suppository excipients

Pharmaceutical form and quantity of active substance per unit
Tablets containing 100, 200 or 400 mg carbamazepine.
CR tablets (scored, controlled-release, film-coated tablets) containing 200 or 400 mg carbamazepine.
Syrup containing 100 mg carbamazepine per 5 ml (= 2%). The syrup contains 875 mg/5 ml sorbitol, which is slowly converted to glucose. The syrup is suitable for diabetics.
Suppositories containing 250 mg carbamazepine.

Indications / Potential uses
- Epilepsy
  - Partial seizures (simple or complex, with or without loss of consciousness), with or without secondary generalization.
  - Generalized tonic-clonic seizures.
  - Mixed forms of seizures.
  - Tegretol is suitable for both monotherapy and combination therapy.
  - Tegretol is 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 and 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.

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). In some patients, 1600 mg or even 2000 mg daily may be appropriate.
Suppositories
For continuation of carbamazepine therapy when oral treatment of epilepsy is temporarily not possible (e.g. in unconscious or postoperative patients).
When suppositories are used instead of oral dosage forms, the maximum daily dose is 1000 mg (250 mg four times daily at 6 hour intervals).
A partly absorbed suppository that is excreted prematurely (e.g. due to bowel emptying) should be replaced, unless it is excreted shortly before the time of the next dose, in which case the next dose should be given at the usual time.
Following a residence time of 1, 2, 4 or 6 hours in the rectum, the proportion of absorbed carbamazepine reaching the systemic circulation is 15%, 31%, 57% and 75%, respectively. A reduction in the amount of drug absorbed can therefore be expected if the suppository is excreted before 6 hours have elapsed.

Children
Syrup
10–20 mg carbamazepine per kg bodyweight per day, in divided doses, i.e.
– Up to 1 year of age: 100–200 mg daily (1–2 measuring spoonfuls)
– 1–5 years of age: 200–400 mg daily (= 2 × 1–2 measuring spoonfuls)
– 6–10 years of age: 400–600 mg daily (= 2–3 × 2 measuring spoonfuls)
– 11–15 years of age: 600–1000 mg daily (= 3 × 2–3 measuring spoonfuls)
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.

Suppositories
When suppositories are used instead of oral dosage forms, dosages must be 25% higher than in the dosage schedule above, but must not exceed a maximum daily dose of 1000 mg (250 mg q.i.d. at 6 hour intervals).

Trigeminal neuralgia
A starting dose of 200–400 mg/day should be gradually increased until freedom from pain is achieved (normally with 200 mg t.i.d. or q.i.d.). The dosage should then be gradually reduced to the lowest possible maintenance level. A starting dose of 100 mg b.i.d. is recommended in elderly patients.

Alcohol-withdrawal syndrome
Patients should be given 200 mg t.i.d. or q.i.d 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
The syrup (which should be shaken before use!) and the tablets may be taken – with liquid – during, after or between meals. The CR tablets (either a whole or, if so prescribed, half a tablet) should be swallowed unchewed with liquid.
The syrup (1 measuring spoonful = 5 ml = 100 mg; ½ measuring spoonful = 2.5 ml = 50 mg) is particularly suitable for patients who have difficulty swallowing tablets. The syrup is also suitable for patients who require careful initial dose titration.
CR tablets can normally be administered twice daily owing to the slow, controlled release of active substance from the tablets.
Since a given dose of syrup will produce higher peak plasma concentrations than the same dose in tablet form, it is advisable to start the syrup at a low dosage, which should then be increased slowly, to avoid adverse effects.

Switching dosage forms
– Switching from tablets to syrup: This should be done by giving the same daily dose, but in smaller, more frequent doses (e.g. syrup t.i.d. instead of tablets b.i.d.).
– Switching from standard tablets to CR tablets: Clinical experience shows that the dosage may need to be increased in some patients.
– Switching from oral dosage forms to suppositories: The dosage must be increased by approx. 25%, up to a maximum of 250 mg q.i.d. at 6 hour intervals. Use of suppositories as a replacement for oral forms – when oral treatment of epilepsy is temporarily not possible (e.g. in unconscious or postoperative patients) – has thus far been limited to 7 days.
No clinical data are available on use of the suppositories in indications other than epilepsy.

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% syrup 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 (E 200, E 216, E 218).

Warnings and Precautions
General
Tegretol should only be used under medical supervision.
Tegretol should be used with caution in patients with mixed seizures, which include typical and atypical absences. In all these conditions, Tegretol may exacerbate seizures. If this happens, Tegretol should be discontinued.
An increase in seizure frequency may occur when switching from an oral dosage form to suppositories. Blood levels must be checked on day 3 or 4 after a switch to the suppositories, or in the event of increased seizure frequency.
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: dramatic increase in seizure frequency / verification of patient compliance; during pregnancy; if the patient is a child or adolescent; if an absorption disorder is suspected; if toxicity is suspected in patients using more than one drug (see **Interactions**).

Discontinuation of treatment
Abrupt withdrawal of Tegretol may precipitate seizures. If Tegretol therapy has to be withdrawn abruptly in epileptic patients, the switch to an alternative antiepileptic should be made under cover of a suitable drug (e.g. diazepam i.v. or rectal, or phenytoin i.v.).

Hypersensitivity reactions, intoxication
Tegretol may trigger hypersensitivity reactions, which can affect the skin, liver (including intrahepatic bile ducts), haematopoietic organs and lymphatic system, either individually or together in the context of a systemic reaction (see **Adverse effects**).
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.
Cross-hypersensitivity between carbamazepine and oxcarbazepine (Trileptal®) is possible in approximately 25–30% of patients. Cross-hypersensitivity between carbamazepine and phenytoin is possible.
Tegretol should be withdrawn at once if there are signs or symptoms suggestive of a hypersensitivity reaction.

Serious dermatological reactions
There have been rare reports of severe dermatological reactions, including toxic epidermal necrolysis (TEN, or Lyell's syndrome) and Stevens-Johnson syndrome (SJS) following administration of Tegretol. The patients concerned may require hospitalization, as these conditions may be life-threatening. Most cases of SJS/TEN were reported in the first few months of treatment with Tegretol.
Tegretol must be withdrawn at once, and alternative therapy considered, as soon as signs or symptoms of severe skin reactions are ascertained.
Retrospective studies in patients of Han Chinese ancestry found a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the human leukocyte antigen (HLA)-B*1502 allele. Higher 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 prevalence of the HLA-B*1502 allele. The prevalence of carriers of this allele is over 15% in the Philippines, Thailand, Hong Kong and Malaysia, around 10% in Taiwan, around 4% in North China, around 2 to 4% in South Asia (including India), and less than 1% in Japan and Korea. The prevalence of the HLA-B*1502 allele is negligible in whites, Africans, indigenous peoples of the Americas, and Hispanic populations.
Patients at risk on the basis of their ancestry should be tested prior to 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 is not required in patients from populations in which the prevalence of HLA-B*1502 is low. 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.
Genetic screening cannot substitute for close patient monitoring because many patients who are carriers of the HLA-B*1502 allele do not develop SJS/TEN, while other patients not at genetic risk may develop SJS/TEN anyway. No studies have thus far been made of the extent to which other factors (such as dose, compliance, co-medication and comorbidity) promote the development of SJS/TEN.

Other dermatological 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 such symptoms 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.

Heart, liver or kidney disease
Tegretol should be prescribed only after a critical risk-benefit appraisal – and under close monitoring – in patients with heart, liver or kidney disease, with a history of haematological adverse reactions to other drugs, or with previous interrupted courses of therapy with Tegretol.
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.
Baseline and periodic complete urinalysis and BUN determinations are recommended.
A syndrome of inappropriate antidiuretic hormone secretion (SIADH) may occur during carbamazepine therapy.
Close monitoring is necessary in patients with existing renal disease who require high fluid intake, in patients receiving diuretic therapy and in the event of signs of hyponatraemia (see **Adverse effects**).

Haematology
Agranulocytosis and aplastic anaemia have been associated with Tegretol but the very low incidence 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 spontaneous occurrences in the general population (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 and possibly reticulocytes and serum iron, should be performed 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.

Anticholinergic reactions
Tegretol shows slight anticholinergic activity and patients with increased intraocular pressure should therefore be closely monitored during therapy (see **Adverse effects**).

Central nervous system
The possibility of activation of latent psychosis – and, in elderly patients, the possibility 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 very different indications. Meta-analysis of placebo-controlled studies has shown a slightly increased risk in this connection. The underlying mechanism is not known.
Patients should therefore be monitored for signs of suicidal ideation and suicidal behaviour, and appropriate treatment should be initiated if necessary. Patients / caregivers should be told that they should seek medical advice in such situations.

Reproductive capacity
There have been isolated reports of impaired male fertility and/or abnormal spermatogenesis; a causal relationship has not been established.
Breakthrough bleeding has been reported in women taking oral contraceptives. The efficacy of oral contraceptives may be adversely affected by Tegretol. Women of childbearing potential should therefore be advised to use alternative methods of contraception during Tegretol therapy.
Due to enzyme induction, Tegretol may cause failure of the therapeutic effect of drugs containing oestrogen and/or progesterone (e.g. failure of contraception).

Other
Tegretol syrup contains parahydroxybenzoates, which may cause allergic reactions (possibly delayed). It also contains sorbitol and therefore should not be administered to patients with rare hereditary problems of fructose intolerance.
During treatment with carbamazepine, patients should protect themselves from intense sunlight due to the risk of photosensitization.

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, to 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 co-medications mainly metabolized 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.

Substances 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 substances:

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)

Antifungals
Azole derivatives (e.g. itraconazole, ketoconazole, fluconazole, voriconazole)

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

Other
Grapefruit juice, nicotinamide (in adults, and only at high doses).

Substances that may raise plasma levels of carbamazepine-10,11-epoxide
Elevated plasma levels of carbamazepine-10,11-epoxide may result in 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 substances: loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Substances that may lower plasma levels of carbamazepine
The dose of Tegretol may have to be adjusted if Tegretol is used concomitantly with the following substances:

Antiepileptics
Phenobarbital, primidone, methsuximide, felbamate, oxcarbazepine, phensuximide, phenytoin, 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 substances
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 clinical requirements:

Analgesics, anti-inflammatory agents
Buprenorphine, methadone, fentanyl, paracetamol, phenazone (antipyrine), tramadol

Antibiotics
Doxycycline

Anticoagulants
Oral anticoagulants (warfarin, phenprocoumon, dicoumarol, acenocoumarol)

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**).

Antiepileptics
Clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. Plasma phenytoin levels have been reported both to be raised and lowered by carbamazepine, and 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

Anthelmintics
Praziquantel

Cytostatics
Imatinib

Antipsychotic agents
Clozapine, haloperidol, bromperidol, olanzapine, quetiapine, risperidone, ziprasidone

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

Corticosteroids
E.g. prednisolone, dexamethasone

Immunosuppressants
Ciclosporin, tacrolimus, everolimus

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
Hormonal contraceptives
(In addition to attenuation of the effect of hormonal contraceptives, sudden breakthrough bleeding may occur when the "pill" is taken. Therefore, either the oral contraceptive should contain more than 50 µg oestrogen, or other, non-hormonal methods of contraception should be recommended.)

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 antagonize the effects of non-depolarizing 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.

Pregnancy and Lactation
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 abnormalities such as craniofacial defects, cardiovascular malformations, hypospadias and abnormalities 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.
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.
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.
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 nutrition disorders) in the neonate.

Lactation
Carbamazepine is excreted in the breast milk at concentrations approx. 25–60% of those found in the plasma. The benefits of breastfeeding generally outweigh the risks of possible adverse effects. Breastfeeding should be discontinued if the infant is found to have poor weight gain, excessive drowsiness or an allergic skin reaction.

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

Effects on ability to drive and use machines
Tegretol-induced dizziness or drowsiness may impair the patient's reactions, particularly 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. 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 temporary 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 levels.

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: Leucopenia (11%), persistent in 2% of cases.
Common: Eosinophilia, thrombocytopenia.
Rare: Lymphadenopathy, folic acid deficiency.
Very rare: Leucocytosis, agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia.

Immune system disorders
Rare: Delayed multi-organ-hypersensitivity syndrome with various combinations of fever, exanthema, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leucopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of intrahepatic bile ducts). Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).
Very rare: Anaphylactic reactions, aseptic meningitis with myoclonus and peripheral eosinophilia, 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").
Very rare: Increase in prolactin levels, with or without clinical manifestations (gynaecomastia, galactorrhoea). Abnormal thyroid function tests: decreased L-thyroxin (FT_4,T_4,T_3) and increased TSH values. Disturbances of bone metabolism (decrease in plasma calcium and 25-hydroxycholecalciferol), leading to osteomalacia; increased levels of cholesterol, including HDL cholesterol, and triglycerides.

Psychiatric disorders
Rare: Hallucinations (visual or acoustic), depression, loss of appetite, restlessness, aggressive behaviour, agitation, confusion.
Very rare: Activation of psychosis.

Nervous system disorders
Very common: Dizziness (10–50%), ataxia (children 10.4%, adults 50%), drowsiness (children 8.2%, adults 20–40%), exhaustion.
Common: Headache, diplopia, accommodation disorders (e.g. blurred vision).
Uncommon: Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus.
Rare: Orofacial dyskinesias, oculomotor disturbances, speech disturbances (e.g. dysarthria, slurred speech), choreoathetoid disturbances, peripheral neuropathy, paraesthesias, paretic symptoms.
Very rare: Dysgeusia, neuroleptic malignant syndrome (NMS).

Eye disorders
Very rare: Lens opacities, conjunctivitis, elevated intraocular pressure.

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, circulatory collapse, heart failure, aggravation of coronary heart disease.

Vascular disorders
Rare: Hypertension or hypotension.
Very rare: Thrombophlebitis, thromboembolism (e.g. pulmonary embolism), vasculitis.

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

Gastrointestinal disorders
Very common: Nausea, vomiting (both 8%).
Common: Loss of appetite, dry mouth. Rectal irritation may occur in patients using the suppositories.
Uncommon: Diarrhoea, constipation.
Rare: Abdominal pain.
Very rare: Glossitis, stomatitis, pancreatitis.

Hepatobiliary disorders
Very common: Elevated gamma-GT (9.1%; due to hepatic enzyme induction), normally not clinically relevant.
Common: Elevated alkaline phosphatase.
Uncommon: Elevated transaminases.
Rare: Jaundice; cholestatic, parenchymal (hepatocellular) or mixed-type hepatitis, vanishing bile duct syndrome.
Very rare: Granulomatous hepatitis, hepatic failure.

Skin disorders
Very common: Allergic dermatitis, pruritus, urticaria (which may be severe).
Uncommon: Exfoliative dermatitis and erythroderma.
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 disorders
Rare: Muscle weakness.
Very rare: Arthralgia, muscle pain or spasms.

Renal and urinary disorders
Very rare: Interstitial nephritis, renal 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/impotence, abnormal spermatogenesis (with decreased sperm count and/or motility).

Investigations
Very rare: Hypogammaglobulinaemia.

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

Central nervous system disorders
CNS depression; disorientation, drowsiness, 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 disorders
Tachycardia, hypotension, occasionally hypertension, conduction disturbances with widening of QRS complex; syncope in association with cardiac arrest.

Gastrointestinal disorders
Vomiting, delayed gastric emptying, reduced bowel motility.

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 hospitalized. 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
Hypotension
Give dopamine or dobutamine i.v.

Arrhythmias
Management on a case-by-case basis.

Convulsions
Give a benzodiazepine (e.g. diazepam) or another antiepileptic, such as phenobarbital (with caution because of increased respiratory depression) or paraldehyde.

Hyponatraemia (water intoxication)
Fluid restriction and slow and careful i.v. infusion of 0.9% NaCl to reduce the risk of brain damage.
Activated charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis and peritoneal dialysis have been reported to be ineffective.
Relapse and aggravation of symptoms should be anticipated on the second and third days following overdosage due to delayed absorption.

Properties and 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 stabilizes 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 depolarized neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action. Whereas reduction of glutamate release and stabilization of neuronal membranes may account mainly for the antiepileptic 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 generalization, generalized 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.

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 (syrup), 12 (tablets, suppositories) or 24 hours (CR tablets).

Bioavailability
The bioavailability of carbamazepine is almost 100% following administration of tablets, and approximately 15% lower with CR tablets. Food intake has no effect on bioavailability.
The amount of carbamazepine absorbed from the suppositories is about 25% lower than the amount absorbed from the tablets. 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 q.i.d.

Plasma concentrations
The C_{max} of carbamazepine following a single dose of 400 mg (tablets) is approx. 4.5 µg/ml.
Following use of the suppositories, there was no difference in fluctuation index compared with the tablets, but C_{max} and C_{min} were slightly lower at steady state.
With the CR tablets, 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 placenta.
The apparent distribution volume is 0.8–1.9 litres/kg.

Metabolism
Carbamazepine is metabolized 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-hydroxy-methyl-10-carbamoyl acridan is a less important metabolite. Other important biotransformation pathways for carbamazepine 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 dose of 400 mg carbamazepine, 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
Mutagenic and tumorigenic potential
In vitro tests and studies in animals provided no evidence that carbamazepine possesses any relevant mutagenic potential.
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 male rats. However, there is no evidence that these observations are of any relevance to therapeutic use in humans.

Other information
Shelf-life
See folding box
Do not use after the expiry date (= EXP) printed on the pack.

Special precautions for storage
Keep out of the reach of children.

Tablets
See folding box

CR tablets
See folding box

Syrup
See folding box

Suppositories
See folding box

Manufacturer
See folding box

Pack sizes
Cuntry specific pack sizes

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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