1. PRODUCT NAME

TEGRETOL® 200 mg Tablets
TEGRETOL® 200 mg CR Tablets
TEGRETOL® 400 mg CR Tablets
TEGRETOL® Syrup 2%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Tablets

- 200 mg: Each tablet contains 200 mg carbamazepine

CR tablets

- 200 mg: Each slow-release film-coated, divisible tablet contains 200 mg carbamazepine
- 400 mg: Each slow-release film-coated, divisible tablet contains 400 mg carbamazepine

Syrup

5 mL: Each 1 mL of syrup contains 20 mg carbamazepine. Each 5 ml in a measuring spoon contains 100 mg carbamazepine.

For a full list of excipients, see section 6.1.

The syrup contains propyl hydroxybenzoate, methyl hydroxybenzoate, propylene glycol and Sorbitol (refer to section 4.4, Special warnings and precautions for use, subsection *Excipients of known effect*).

3. PHARMACEUTICAL FORM

- Tablet containing 200mg carbamazepine. Round, white, flat tablet, 9mm in diameter, with bevelled edges. Imprinted CG on one side, and G/K on the scored side. The tablet can be divided into equal doses, but should not be chewed.
- Controlled Release Tablet containing 200mg carbamazepine. Beige-orange, ovaloid-shaped, film-coated divisible tablet with slightly convex faces. Approximate length is 12.2mm, and approximate width is 5.6mm. Both sides are scored; one side is imprinted C/G, and the other side H/C. The tablet can be divided into equal doses, but should not be crushed or chewed.
- Controlled Release Tablet containing 400mg carbamazepine. Brown-orange, ovaloid-shaped, film-coated divisible tablet, with slightly convex faces. Approximately 16.7mm in length, and approximately 6.7mm in width. Imprinted CG/CG on one side, and ENE/ENE on the other side; both sides are scored. The tablet can be divided into equal doses, but should not be crushed or chewed.

- Syrup containing 20mg/1mL carbamazepine. A viscous white suspension with a caramel odour and taste. It contains sorbitol (875mg/5mL), which is converted slowly into glucose, making the syrup suitable for diabetics.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy, Trigeminal neuralgia, Diabetes insipidus, Mania, prophylactic in manic-depressive illness.

4.2 Posology and method of administration

Dosage

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) (see Section 4.4 Special warnings and precautions for use, & Section 5.2 Pharmacokinetic properties: absorption).

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 Interactions).

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

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.

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.

Diabetes insipidus centralis
Average dosage for adults: 200 mg 2 to 3 times daily.

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.

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 10mL = 1-2 measures of syrup)
- 1 to 5 years of age: 200 to 400 mg daily (= 10 to 20 mL = 2× 1-2 measures of syrup)
- 6 to 10 years of age: 400 to 600 mg daily (= 20 to 30 mL = 2-3× 2 measures of syrup)
- 11 to 15 years of age: 600 to 1000 mg daily (= 30 to 50 mL = 3× 2-3 measures of syrup (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)

Note: one 5 mL measure of syrup is equivalent to 100 mg carbamazepine.

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

Diabetes insipidus centralis

In children the dosage should be reduced proportionally to the child's age and body weight.

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.

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.

Method of Administration

The tablets and the syrup (to be shaken before use) may be taken during, after, or between meals. Tablets should be taken with a little liquid.

The CR tablets (either whole or, if so prescribed, only half a tablet) should be swallowed unchewed with a little liquid. The syrup (one measure = 5 mL = 100 mg; half a measure = 2.5 mL = 50 mg) is 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 Syrup will produce higher peak levels than the same dose in tablet form, it is advisable to start with low doses and increase slowly so as to avoid adverse reactions.

Switching patients from Tegretol tablets to syrup

This should be done by giving the same number of mg per day in smaller, more frequent doses (e.g. Syrup three times a day (t.i.d.) instead of tablets twice a day (b.i.d)).

Switching patients from conventional tablets to CR tablets

Clinical experience shows that in some patients the dosage in the form of CR tablets may need to be increased.

4.3 Contraindications

- hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any of the excipients listed in section 6.1.
- Patients with atrioventricular block
- Patients with a history of bone-marrow depression

- Patients with a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda)
- The use of Tegretol is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Tegretol should be given only under medical supervision. Tegretol should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with Tegretol.

Haematological effects

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

Transient or persistent decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Tegretol. However, in the majority of cases these effects prove transient and are unlikely to signal the onset of either aplastic anaemia or agranulocytosis. Nonetheless, complete pretreatment blood counts, including platelets (and possibly reticulocytes and serum iron), should be obtained at baseline, and periodically thereafter.

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

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

Serious dermatologic reactions

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN; also known as Lyell's syndrome) and Stevens-Johnson syndrome (SJS), have been reported 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, but the risk in some Asian countries is estimated to be about 10 times higher. 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.

Pharmacogenomics

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

Association with HLA-A*3101

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of hypersensitivity syndrome and cutaneous adverse drug reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash (see section 4.4 Special warnings and precautions for use: Hypersensitivity). 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. 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.

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 Information for Healthcare professionals in this section). The use of Tegretol should be avoided in patients who are found to be positive for HLA-A*3101, unless the benefits clearly outweigh the risks. Screening is generally not recommended for any current Tegretol users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of therapy, regardless of HLA-A*3101 status.

Association with HLA-B*1502

Retrospective studies in patients of Han Chinese 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 HLA-B*1502 allele ranges from 2 to 12% in Han Chinese populations and is about 8% in Thai populations. Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the population e.g. above 15% in the Philippines and some Malaysian populations. Allele frequencies up to about 2% and 6% have been reported in

Korea and India, respectively. The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%).

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

Testing for the presence of HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with Tegretol (see Information for Healthcare professionals in this section). The use of Tegretol should be avoided in tested patients who are found to be positive for HLA-B*1502 unless the benefits clearly outweigh the risks. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low. Screening is generally not recommended for any current Tegretol users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Limitation of genetic screening

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with Tegretol will not develop SJS/TEN and patients negative for HLA-B*1502 of any ethnicity can still develop SJS/TEN. Similarly many patients positive for HLA-A*3101 and treated with Tegretol will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from these severe cutaneous adverse reactions, such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for 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. 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.

Other dermatologic reactions

Mild skin reactions, e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.
The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine and may predict the risk of these reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However, The HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions.

Hypersensitivity

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been reported with Tegretol. If a patient develops these reactions after treatment with Tegretol, the drug must be discontinued, and an alternative treatment started.Tegretol may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a delayed multi-organ hypersensitivitydisorder with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium and colon).(See section 4.8 Undesirable effects).
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 (Trileptin®).

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

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

Seizures

Tegretol should be used with caution in patients with mixed seizures, which includes absences, either typical or atypical. In all these conditions, Tegretol may exacerbate seizures. In the event of exacerbation of seizures, Tegretol should be discontinued.

Hepatic function

Baseline and periodic evaluations of hepatic function must be performed during treatment with Tegretol, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.

Renal function

Baseline and periodic complete urinalysis and BUN determinations are recommended.

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 sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatraemia is observed, water restriction is an important counter-measurement if clinically indicated.

Hypothyroidism

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.

Anticholinergic effects

Tegretol has shown mild anticholinergic activity. Patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy (see section 4.8 Undesirable effects).

Psychiatric effects

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

Suicidal ideation and behaviour

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

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

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

Pregnancy and females of reproductive potential

Carbamazepine may be associated with fetal harm when administered to a pregnant woman (see section 4.6 Fertility, pregnancy and lactation). Tegretol should be used during pregnancy only if the potential benefit justifies the potential risks, following careful consideration of alternative suitable treatment options.
The woman should be fully informed of and understand the risk of potential harm to the foetus if carbamazepine is taken during pregnancy and therefore the importance of planning any pregnancy. Adequate counselling should be made available to all pregnant women and women of childbearing potential, regarding the risks associated with pregnancy due to potential teratogenic risk to the foetus (see section 4.6 Fertility, pregnancy and lactation).
Women of childbearing potential should use effective contraception during treatment with carbamazepine and for 2 weeks after the last dose (see below sub-section "Endocrinological effects" and section 4.5 Interaction with other medicinal products and other forms of interaction and section 4.6 Fertility, pregnancy and lactation). Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.
If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking carbamazepine, she should be referred to a specialist to reassess carbamazepine treatment and consider alternative treatment options.

Endocrinological effects

Breakthrough bleeding has been reported in women taking Tegretol while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by Tegretol and women of 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 4.5 Interaction with other medicinal products and other forms of interaction).

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.

Excipients with known effect

Tegretol Syrup
5 ml syrup contains 2 mg saccharin sodium, 875 mg liquid sorbitol and preservatives: Methylparaben 6 mg, Propylparaben 1.5mg, Sorbic acid 5 mg.

Sorbitol: This medicine contains 175mg sorbitol in each milliliter, which is equivalent to 175mg/ ml. Patients with hereditary fructose intolerance (HFI) should not take / be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Propylene glycol: This medicine contains 125mg propylene glycol in each 5ml which is equivalent to 25mg per ml. The excipient propylene glycol (PG), is generally considered safe. However, Co-administration with any substrate for alcohol dehydrogenase such as ethanol may induce serious adverse effects in neonates. In the neonate, if high doses or prolonged administration are warranted, PG toxicity can occur. Effects such as lactic acidosis, central nervous system depression/toxicity, hyperosmolarity, haemolysis, cardiac arrhythmia and seizures have been observed.

Para hydroxybenzoates: This medicine contains methyl hydroxybenzoate and propyl hydroxybenzoate which may cause allergic reactions (possibly delayed).

Tegretol Syrup contains less than 1mmol sodium (23mg) per ml, that is to say essentially 'sodium free'.

Tegretol tablets and CR tablets
Tegretol tablets and Tegretol CR tablets contain less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium free'.

Falls

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

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.

Genotoxicity

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

Carcinogenicity

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

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 3A4 (CYP3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine-10,11-epoxide. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide.

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

Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels. The dose 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.

Female patients of childbearing potential should be warned that the concurrent use of Tegretol with hormonal contraceptives may render this type of contraceptive ineffective (see section 4.4 Special warnings and precautions for use; Endocrinological effects). Alternative non-hormonal forms of contraception are recommended when using Tegretol (see section 4.6 Fertility, pregnancy and lactation).

<u>Interactions resulting in a contraindication</u>

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 Effect of Tegretol on plasma levels of concomitant agents in this section).

<u>Agents that may raise carbamazepine plasma levels</u>

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

Analgesics, anti-inflammatory drugs:	dextropropoxyphene, ibuprofen
Androgens	danazol
Antibiotics	macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin), ciprofloxacin

Antidepressants	possibly desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine.
Antiepileptics	stiripentol, vigabatrin
Antifungals	azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole
Antihistamines	terfenadine
Antipsychotics	olanzapine
Antituberculosis	isoniazid
Antivirals	protease inhibitors for HIV treatment (e.g. ritonavir)
Carbonic anhydrase inhibitors	acetazolamide
Cardiovascular drugs:	diltiazem, verapamil
Gastrointestinal drugs:	possibly cimetidine, omeprazole
Muscle relaxants	oxybutynin, dantrolene
Platelet aggregation inhibitors	ticlopidine
Other interactions:	grapefruit juice, nicotinamide (only in high dosage)

<u>Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels</u>

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:

Antipsychotics	Loxapine, quetiapine
Antiepileptics	Primidone, progabide, valproic acid, valpromide, brivaracetam
Hypnotics and sedatives	valnoctamide

<u>Agents that may decrease carbamazepine plasma levels</u>

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

Antiepileptics	felbamate, methsuximide, oxcarbazepine, phenobarbital, phensuximide, 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) and fosphenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam.
Antineoplastics	cisplatin or doxorubicin
Antituberculosis	rifampicin
Bronchodilatators or anti-asthma drugs	theophylline, aminophylline
Antimalarials:	mefloquine may antagonise the anticonvulsant effect of carbamazepine.
Dermatological drugs:	isotretinoin

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

Effect of Tegretol on plasma levels of concomitant agents

Carbamazepine may lower the plasma level, or diminish - or even abolish - the activity of certain drugs. Dose adjustments may be required for several medicines. Examples of such medicines are listed below. Note that the list does not include all affected medicines. For more information regarding how individual medicines are affected by induction, see also the product information of the co-administered medicine:

Analgesics, anti-inflammatory agents	buprenorphine, methadone, paracetamol (long-term administration of carbamazepine and paracetamol may be associated with hepatotoxicity), phenazone (antipyrine), tramadol
Antibiotics	doxycycline, rifabutin.
Anticoagulants:	oral anticoagulants (e.g. warfarin, phenprocoumon, dicoumarol, acenocoumarol , rivaroxaban, dabigatran, apixaban, edoxaban)
Antidepressants:	bupropion, citalopram, mianserin, nefazodone, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine).
Antiemetics:	Aprepitant
Antiepileptics:	clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment. There have been rare reports of an increase in plasma mephenytoin levels
Antifungals	itraconazole, voriconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole
Antihelmintics	praziquantel, albendazole
Antineoplastics	imatinib, cyclophosphamide, lapatinib, temsirolimus
Antiplatelet	ticagrelor
Antipsychotics	clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone
Antivirals	protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir)
Anxiolytics	alprazolam, midazolam
Bronchodilatators or anti-asthma drugs	theophylline
Contraceptives:	hormonal contraceptives (alternative contraceptive methods should be considered)
Cardiovascular drugs	calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine
Corticosteroids	corticosteroids (e.g. prednisolone, dexamethasone)
Drugs used in erectile dysfunction	tadalafil
Immunosuppressants	cyclosporin, everolimus, tacrolimus, sirolimus
Thyroid agents	levothyroxine

Other drug interactions	products containing oestrogens and/or progesterones

Combinations that require specific consideration

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

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

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

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

Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g. pancuronium). Their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

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

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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animals (mice, rats, rabbits) oral administration of carbamazepine during organogenesis led to increased embryonic mortality at daily doses which caused maternal toxicity (above 200 mg/kg body weight daily, i.e. 10 to 20 times the usual human dosage). In the rat there was also some evidence of abortion at 300 mg/kg body weight daily. Near-term rat foetuses showed growth retardation, again at maternally toxic doses. There was no evidence of teratogenic

potential in the three animal species tested, but, in one study using mice, carbamazepine (40 to 240 mg/kg body weight daily, orally) caused defects (mainly dilatation of cerebral ventricles) in 4.7% of exposed foetuses as compared with 1.3% in controls.

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 and also other congenital anomalies, e.g. craniofacial defects, cardiovascular malformations, hypospadias, microcephaly and anomalies involving various body systems, have been reported in association with the use of Tegretol.

Based on data in a North American pregnancy registry and EURAP registry (European and International Registry of Antiepileptic Drugs and Pregnancy), the prevalence of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth following maternal exposure to carbamazepine monotherapy in the first trimester was 3.0% (95% CI 2.1-4.2%) and assessed after 1 year of birth was 5.4% (95% CI 4.5 to 6.4) respectively. The prevalence of congenital malformations in patients not exposed to any antiepileptic was 1.1% (95% CI 0.35 to 2.5%). The relative risk (RR) of congenital abnormalities in pregnant women on carbamazepine compared with pregnant women not exposed to any antiepileptic drug was 2.7 (95% CI 1.0-7.0). There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent.

Data from an epidemiological study suggests an increased risk for infants of being born small for gestational age (potentially associated with fetal growth restriction) in pregnant women receiving antiepileptic drugs (including carbamazepine) during pregnancy compared to unexposed pregnant women with epilepsy. Neurodevelopmental disorders (such as developmental delay, Autism spectrum disorder, Intellectual disability, ADHD, etc.) have been reported among children born to women with epilepsy treated with carbamazepine alone or in combination with other antiepileptic drugs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are contradictory and a risk cannot be excluded.

Specialist medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.

Clinical considerations
Taking these data into consideration:

- Pregnant women with epilepsy should be treated with special care.

- If women receiving Tegretol become pregnant or plan to become pregnant, or if the 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, 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. 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.

- Minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained (See section 4.2 Posology and method of administration). There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent, i.e. at a dose < 400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine.

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

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

Monitoring and prevention
Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate folic acid deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy. Folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception.

In the neonate
In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Tegretol and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal Tegretol use. These reactions may represent a neonatal withdrawal syndrome.

Lactation

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

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. Due to enzyme induction, Tegretol may result in a failure of the therapeutic effect of hormonal contraceptive drugs containing oestrogen and/or progesterone. Women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with Tegretol.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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.

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.

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

Adverse drug reactions from clinical trials (Table 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 1

Blood and lymphatic system disorders	
Very common:	leukopenia
Common:	thrombocytopenia, eosinophilia
Rare:	leukocytosis, lymphadenopathy
Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia
Immune system disorders	
Rare:	a delayed multiorgan hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon)
Very rare:	anaphylactic reaction, angioedema, hypogammaglobulinaemia
Endocrine disorders	
Common:	oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders
Very rare:	galactorrhoea, gynecomastia
Metabolism and nutrition disorders	
Rare:	folate deficiency, decreased appetite, anorexia
Very rare:	porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda)
Psychiatric disorders	
Rare:	hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state
Very rare:	activation of psychosis
Nervous system disorders	
Very common:	ataxia, dizziness, somnolence
Common:	diplopia, headache
Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics); nystagmus
Rare:	orofacial dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria, slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, paresis
Very rare:	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia
Eye disorders	
Common:	accommodation disorders (e.g. blurred vision)
Very rare:	lenticular opacities, conjunctivitis

Ear and labyrinth disorders

Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception

Cardiac disorders

Rare:	cardiac conduction disorders
Very rare:	arrhythmia, atrioventricular block with syncope, bradycardia, , cardiac failure congestive, coronary artery disease aggravated

Vascular disorders

Rare:	hypertension or hypotension
Very rare:	circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis

Respiratory, thoracic and mediastinal disorders

Very rare:	pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia

Gastrointestinal disorders

Very common:	vomiting, nausea
Common:	dry mouth
Uncommon:	diarrhoea, constipation
Rare:	abdominal pain
Very rare:	pancreatitis, glossitis, stomatitis

Hepatobiliary disorders

Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice
Very rare:	hepatic failure, granulomatous liver disease

Skin and subcutaneous tissue disorders

Very common:	urticaria which may be severe, dermatitis allergic
Uncommon:	dermatitis exfoliative and erythroderma
Rare:	systemic lupus erythematosus, pruritus
Very rare:	Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythemanodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism

Musculoskeletal, connective tissue and bone disorders

Rare	muscular weakness
Very rare:	bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms

Renal and urinary disorders

Very rare:	tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and 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)

General disorders and administration site conditions

Very common:	fatigue
Investigations	
Very common:	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant
Common:	blood alkaline phosphatase increased
Uncommon:	transaminases increased
Very rare:	intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased

*In some Asian countries also reported as rare. See also section 4.4 Special Warnings and precautions for use.

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

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 2

Infections and infestations:	Reactivation of Human herpesvirus 6 (HHV-6) infection
Blood and lymphatic system disorders:	Bone marrow failure
Injury, poisoning and procedural complications	Fall (associated with Tegretol treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4 Special warning and precautions for use).
Nervous system disorders:	Sedation, memory impairment
Gastrointestinal disorders:	Colitis
Immune system disorders:	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Skin and subcutaneous tissue disorders:	Acute Generalized Exanthematous Pustulosis (AGEP) lichenoid keratosis, onychomadesis, fixed drug eruption, generalised bullous fixed drug eruption.
Musculoskeletal and connective tissue disorders:	Fracture
Investigations:	Bone density decreased

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il and to Novartis using the following email address: safetydesk.israel@novartis.com.

4.9 Overdose

Signs and symptoms
The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, respiratory systems and reactions mentioned under Adverse drug reactions.

Central nervous system	CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.
Respiratory system	Respiratory depression, pulmonary oedema.
Cardiovascular system	Tachycardia, hypotension, at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.
Gastrointestinal system	Vomiting, delayed gastric emptying, reduced bowel motility.
Musculoskeletal system	There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.
Renal function	Retention of urine, oliguria or anuria; fluid retention, water intoxication due to an ADH-like effect of carbamazepine.

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

Management
There is no specific antidote.

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

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

Special recommendations
Charcoal hemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.
Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

Dibenzazepine derivative.

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.

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

As a neurotropic agent Tegretol is clinically effective in a number of neurological disorders, e.g. it prevents paroxysmal attacks of pain in idiopathic and secondary trigeminal neuralgia; in addition, it is used for the relief of neurogenic pain in a variety of conditions, including tabes dorsalis, post-traumatic paresthesia, and post-herpetic neuralgia; in diabetes insipidus centralis, Tegretol reduces the urinary volume and relieves the feeling of thirst.

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

Clinical efficacy and safety

No recent clinical trials have been conducted with Tegretol.

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours, following single oral doses. With the Syrup, mean peak plasma concentrations are attained within 2 hours. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400 mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5 micrograms/mL.

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

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

of carbamazepine-10,11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

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

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

Carbamazepine crosses the placental barrier.

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

Biotransformation/ 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. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway. Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination
The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16 to 24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other liver-enzyme inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9 to 10 hours have been found.

The mean elimination half-life of the 10,11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.
After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10,11-epoxide metabolite.
Characteristics in patients

Special populations

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets: microcrystalline cellulose), carmellose sodium (low substitued), magnesium stearate, colloidal silica (anhydrous).

CR tablets: cellulose microcrystalline, croscarmellose sodium, polyacrylate dispersion 30%, ethylcellulose aqueos dispertion, talc, silica colloidal anhydrous, magnesium stearate.
Coating: hypromellose, talc, titanium dioxide, castor oil - polyoxyl 40 hydrogenated, iron oxide red, iron oxide yellow.

Syrup: sorbitol liquid (sorbitol 70% non crystallising), propylene glycol, dispersible cellulose (microcrystalline cellulose and sodium carboxymethylcellulose), hydroxyethylcellulose methyl parahydroxybenzoate, polyethylene glycol 400 stearate (macrogol stearate), sorbic acid, saccharin sodium, propyl parahydroxybenzoate, caramel aroma 52929 A, purified water.
For further information, see section 4.4

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Tablets: Store below 25°C and protect from moisture.
CR tablets: Store below 25°C and protect from moisture.
Syrup: Store below 30°C and protect from light.
After first opening of the bottle, store below 25ºC and use within 3 months and no later than the expiry date of the preparation.

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

6.5 Nature and contents of container

Tegretol 200 mg tablets: PVC/PE/PVDC blisters containing 50 and 500 tablets
Tegretol CR 200 mg tablets: PVC/PE/PVDC blisters containing 50 slow release tablets

Tegretol CR 400 mg tablets: PVC/PE/PVDC blisters containing 30 slow release tablets
Tegretol syrup 2%: glass type III bottle 250mL. The package contains a measuring spoon
Pack sizes: Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

There are no specific instructions for use/handling.

7. Registration Holder and Importer:

Novartis Israel Ltd., P.O.B 9240, Tel Aviv- Yafo, 6109102.

8. Registration numbers:

TEGRETOL 200 mg tablets:	015-41-24602
TEGRETOL 200 mg CR tablets:	041-24-25416
TEGRETOL 400 mg CR tablets:	041-23-25417
TEGRETOL syrup 2%:	022-90-24971

Revised in May 2026.