SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carbagen 200 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 200 mg carbamazepine.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.
White to yellowish, round, flat, cloverleaf shaped tablets with bevelled edge, double-sided cross break-mark, 4 notches on the band.

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy

Adults

- either as monotherapy
- or in combination with another antiepileptic treatment
- treatment of generalised epilepsy: generalised tonic-clonic seizures
- treatment of partial seizures with or without secondary generalisation

Children

- either as monotherapy
- or in combination with another antiepileptic treatment
- treatment of generalised epilepsy: generalised tonic-clonic seizures
- treatment of partial seizures with or without secondary generalisation

Pain

- For the treatment of paroxysmal pain of trigeminal and glossopharyngeal neuralgia.
- Treatment of neuralgia in adults.

Psychiatry

- For the prophylaxis of bipolar relapse, especially in patients with relative resistance, or manic or hypomanic phases of manic-depressive psychosis in patients unresponsive or with contraindications to lithium therapy.

4.2 Posology and method of administration

Posology
Dosage must be adjusted to the individual patient based on clinical response and administered in 2 or 3 doses during the day.
Doses should be based on seizure control and the development of clinical intolerance. Plasma levels are indicative whether a patient is within or outside the therapeutic range in order to explain a lack of seizure control or development of intolerance. This may be particularly useful, if combination therapy is used. Therapeutic plasma levels of carbamazepine are typically between 4 and 12 µg/ml corresponding to a dosage of 400 to 1,200 mg per day (17 to 50 micromoles/L) (see section 5.1).

A maximum daily dose of 1,600 to 2,000 mg may be required in adults.

When patients are transferred from an immediate-release carbamazepine product, the same total daily dose will generally be suitable. In a few patients, it may be necessary to increase the total daily dose, particularly when it is used with other antiepileptics.

In patients with severe cardio-vascular disease, liver disease or renal damage and in older people a reduced dose may be sufficient.

Furthermore the dose required by some patients may differ substantially from the recommendation for initial and maintenance dose below, due to increased metabolism caused by auto-induction of hepatic enzymes or drug interactions during combination therapy.

Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 and HLA-A*3101 as these alleles strongly predict the risk of severe carbamazepine-associated Stevens-Johnson syndrome (SJS) (see information on genetic testing and cutaneous reactions in section 4.4).

Dosage recommendations:

Epilepsy
Treatment is started with a low dose set individually according to the type and severity of symptoms. The dose is then slowly increased in intervals of 2 to 5 days to achieve the optimal maintenance dose in about 2 weeks to suit the patient.

Adults
10 to 15 mg/kg/day on average, in 2 or 3 doses.

Paediatric population
For children aged 4 years or less, the initial dose is 20–60 mg/day, increasing the dose by 20–60 mg every second day.

For children aged over 4 years, the initial dose may be 100 mg/day, increasing the dose by 100 mg on a weekly basis.
Maintenance dose: 10 to 20 mg/kg/day on average, divided into several doses throughout the day.
Maximum recommended dose: The maximum recommended dose is 35 mg/kg/day for a child aged under 6 years, 1 000 mg/day for a child aged between 6 and 15 years and 1 200 mg/day for those aged over 16 years.

It is recommended that a carbamazepine monotherapy treatment is used whenever possible. When treatment is changed from another drug to carbamazepine the dose of the other antiepileptic drug should be reduced slowly.

Antiepileptic therapy must be administered daily as a long-term treatment, sometimes indefinitely. The prescription of carbamazepine must be monitored regularly. If a change of therapy to a different antiepileptic drug is required, the change may not be done in one sudden step, but must be done gradually in small increments (see section 4.4).

Carbamazepine therapy is discontinued by slow dose reduction.

Carbamazepine prolonged-release tablets can be broken in half to treat children/adults with divided doses where necessary.

* Carbamazepine prolonged-release tablets are not generally suitable for children under the age of 5 years. A conventional tablet or syrup presentation of carbamazepine may be given.

In general, a dose reduction or withdrawal of antiepileptic medication may be considered, when patients are seizure-free for at least two or three years. Instead of age dependant dose adjustment, children may outgrow the dose per kg body weight.

Pain
Prevention of paroxysmal pain of trigeminal neuralgia
The recommended initial daily dose is 200 to 400 mg/day carbamazepine, in 2 doses. The lower initial dose may be sufficient for older or sensitive patients. The dose is increased until the patient is free of pain, in trigeminal and glossopharyngeal neuralgia, generally with a dose of 600 to 800 mg/day taken in 1 to 2 doses with a maximum dose of 1,600 mg. The dose may be gradually reduced if the patient is pain-free thereafter, and may possibly be stopped after a few weeks of treatment, if there is no recurrence of pain.

Psychiatry
Prophylaxis of bipolar relapse:
400 mg twice daily, i.e. 400 to 800 mg/day on average.

Prophylaxis of manic-depressive psychosis
An initial dose of 100 to 400 mg daily in divided doses, increased gradually until symptoms are controlled, or a maximum of 800 mg, in exceptional cases maximum 1,600 mg, in divided doses is reached. The recommended maintenance dose is 400 to 600 mg daily, given in divided doses.

Prophylaxis of manic-depressive psychosis is a long-term treatment.

In order to prevent a drug interaction, it is necessary to keep the plasma level of carbamazepine below 8 µg/ml and lithium at a low therapeutic dosage (0.3 to 0.8 mval/L), if in exceptional cases carbamazepine is used in combination with lithium for the prophylaxis of

manic depressive psychosis, which cannot be controlled with lithium treatment alone. Neuroleptic treatment must not be done concurrently and must have been discontinued at least 8 weeks beforehand.

The impairment of the ability to react quickly appears in particular with combination therapy with lithium (see section 4.7).

Special populations
Elderly (65 years and above)
Due to possible interactions and differences in the pharmacokinetic properties of various antiepileptics, the dosage of carbamazepine should be chosen with caution in elderly patients.
In elderly patients, an initial dose of 100 mg twice daily is recommended. This initial dose may be increased slowly each day until there is pain relief (usually 200 mg 3–4 times a day). The dose should then be gradually reduced to the lowest possible maintenance dose.

Renal failure/hepatic failure
No data are available on the pharmacokinetics of carbamazepine in patients with renal or hepatic failure.

Method of administration
The tablet can be divided into equal halves and the daily dose is normally taken in two divided doses, during or after a meal with a drink of water. The prolonged-release tablets should be swallowed whole and not chewed or crushed.

Patients who have difficulties in swallowing, may take the prolonged-release tablets in water following their disintegration into their granules. The prolonged-release characteristics of the tablets are maintained for a short period of time after their suspension. Therefore the suspension should be taken immediately.

4.3 Contraindications

Carbamazepine may not be taken with:

- known bone marrow depression.
- atrio ventricular conduction abnormalities.
- hypersensitivity to the active substance or structurally related drugs (for example tricyclic antidepressants) or to any of the excipients listed in section 6.1.
- history of hepatic porphyrias (*e.g.* acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).
- concomitant treatment with monoamine oxidase inhibitors (MAOIs) (see section 4.5)
- concomitant treatment with cobicistat, dasabuvir, delamanid, grazoprevir + elbasvir combination, isavuconazole, ledipasvir, lurasidone, midostaurin, ombitasvir + paritaprevir combination, rilpivirine, sofosbuvir, velpatasvir or voriconazole (see section 4.5).
- herbal preparations containing St. John’s wort (*Hypericum perforatum*) (see section 4.5).

4.4 Special warnings and precautions for use

If reactions such as fever, sore throat, other infections, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage, nausea, yellowing of the skin, and liver enlargement appears, the patient should be advised to consult his physician immediately, and immediate monitoring of complete blood count (see Precautions for use).

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of antiepileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for carbamazepine.

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

Women of childbearing potential
Carbamazepine may cause foetal harm when administered to a pregnant woman. Prenatal exposure to carbamazepine may increase the risks for major congenital malformations and other adverse development outcomes (see Section 4.6).

Carbamazepine should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take carbamazepine during pregnancy.

Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.

Women of childbearing potential should use effective contraception during treatment and for two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see Sections 4.5 and 4.6).

Women of childbearing potential should be counselled regarding the need to consult her physician as soon as she is planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see Section 4.6).

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking carbamazepine.

Serious cutaneous reactions

Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carbamazepine. 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.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions (see section 4.2). The allele frequencies indicated here represent the percentage of chromosomes carrying the allele of interest in the specified population. This means that the percentage of patients carrying a copy of the allele on at least one of their two chromosomes (i.e. the "carrier frequency") is almost twice as high as the allele frequency. Thus, the percentage of patients potentially at risk is almost double the allele frequency.

*HLA-B*1502 allele - in Han Chinese, Thai and other Asian populations*
HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as Stevens-Johnson syndrome (SJS) or TEN when treated with carbamazepine. The prevalence of HLA-B*1502 carrier is between 2% and 12% of Han Chinese and 8% of Thai populations. Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine (see section 4.2). If these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still rarely occur.

There are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations. Because of the prevalence of this allele in other Asian populations (*e.g.* above 15% in the Philippines and Malaysia, and up to 2% and 6% in Korea and India, respectively), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.

The prevalence of the HLA-B*1502 allele is negligible in *e.g.* European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%).

*HLA-A*3101 allele - European descent and Japanese populations*
There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalised exanthematous pustulosis (AGEP) and maculopapular rash (see section 4.8) in people of European descent and the Japanese.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population.

The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0 to 3.8%.

There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment.

If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (*e.g.* progressive skin rash often with blisters or mucosal lesions) are present, carbamazapine treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of carbamazapine, carbamazapine must not be re-started in this patient at any time. The occurrence of febrile, generalised erythema associated with pustules at the beginning of treatment should suggest acute generalised exanthematous pustulosis (see section 4.8); this requires treatment withdrawal and contraindicates further administration of carbamazepine and carbamazepine-containing medicinal products.

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 carbamazepine 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 carbamazepine will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from these severe cutaneous adverse reactions such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Other dermatological reactions
Mild skin reactions *e.g.* isolated macular or macropapular exanthemata, can also occur and are mostly transient and not hazardous, and 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 to 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.

Carbamazepine may only be used after careful risk/benefit evaluation and with special care during the following conditions:

- haematological disturbances
- disturbed sodium metabolism
- severe cardiac, liver and kidney dysfunction

- pregnancy and lactation
- myotonic dystrophy, as cardiac conduction abnormalities are likely in these patients

Haematological events
The occurrence of agranulocytosis and aplastic anaemia has been associated with carbamazepine; however, due to the very low frequency it is difficult to estimate the risk. In the untreated population, the probability of occurrence is 4.7 cases/million/year for agranulocytosis and 2 cases/million/year for aplastic anaemia.

Blood counts, platelet count and serum biochemistry including iron and electrolytes should be checked before commencing treatment with carbamazepine. Blood counts should be performed on a monthly basis for the first five months. Thereafter 2-4 times a year.
Clinical monitoring is of primary importance during the entire treatment period. Carbamazepine must be discontinued, if severe leucopenia or thrombocytopenia appear.

A temporary or lasting lowering of the number of leukocytes or thrombocytes is often seen during carbamazepine treatment, but is usually transient and does not indicate the onset of agranulocytosis or aplastic anaemia. However, carbamazepine must be discontinued if severe leucopenia (mainly neutropenia) or thrombocytopenia accompanied by clinical manifestations *e.g.* fever or sore throat or significant depression of the bone marrow appear.

In patients with severe cardio-vascular disease, liver disease or renal damage and in older people a special observation is necessary. Doses should be adapted to each case.

Epileptic seizures
Carbamazepine is not effective in absences and myoclonic seizures, which may sometimes be aggravated. Carbamazepine should be used with caution in patients with mixed seizures, which include absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate absences. In case of exacerbation of absences, carbamazepine should be discontinued.

As with other antiepileptic drugs some patients may experience an increase in seizure frequency or the onset of new types of seizures, regardless of the fluctuations seen in some epileptic diseases. These phenomena may also be the consequence of: inappropriate choice of medicinal product for the patient's seizures or epilepsy syndrome. toxicity or an overdosage, a decrease in plasma concentrations of concomitant antiepileptic treatment. There may be no explanation other than paradoxical effect.

Hepatic function
Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in older patients. Patients must be instructed to contact the doctor immediately should symptoms of hepatitis occur such as fatigue, loss of appetite, nausea, yellowing of the skin or enlarged liver. Treatment with carbamazepine should be suspended, if signs and symptoms of liver dysfunction develop.

Renal function
Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hypersensitivity reactions

Reactions of type I hypersensitivity (immediate hypersensitivity), including rash, pruritus, urticaria, angioedema and anaphylaxis, have been reported with carbamazepine. Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder, that may be accompanied by fever, rash, vasculitis, polyadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal hepatic function and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts). Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) (see section 4.8). In patients with such reactions, treatment with carbamazepine should be discontinued and alternative therapy should be started.

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

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30% of these patients may experience hypersensitivity reactions to oxcarbazepine. Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).

If signs or symptoms of hypersensitivity reactions occur carbamazepine treatment should be discontinued immediately.

Hyponatraemia
Hyponatraemia can occur when taking carbamazepine. In patients with pre-existing kidney disorders associated with low serum sodium concentrations, or in patients who are being concomitantly treated with medicines that lower serum sodium concentration e.g. diuretics and medicinal products associated with syndrome of inappropriate antidiuretic hormone secretion [SIADH], the serum sodium concentration should be determined before treatment. The serum sodium concentration should be monitored after two weeks and then monthly for three months or according to the clinical necessity. Older patients are particularly susceptible to these risk factors and if hyponatraemia is diagnosed, water restriction is an important countermeasure.

Hypothyroidism
In patients with hypothyroidism, carbamazepine can reduce serum thyroid hormone concentrations through enzyme induction, requiring an increased dose of thyroid hormone replacement therapy (HRT) in patients with hypothyroidism. Monitoring the thyroid function is recommended in order to adjust the thyroid HRT dose.

Due to the possibility of photosensitivity, patients should avoid excessive exposure to sunlight during carbamazepine therapy.

Monitoring plasma levels
The occurrence of CNS-specific adverse reactions may be due to relative overdose or to a significant change in plasma levels (see sections 4.8 and 4.9). 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; during pregnancy; when treating children or adolescents; in suspected absorption disorders; for verification of compliance; in suspected toxicity where more than one drug is being used (see section 4.5).

Dose reduction and withdrawal
Abrupt withdrawal of carbamazepine may precipitate seizures. Patients should be gradually weaned off carbamazepine over a period of a few months. If treatment with carbamazepine has to be withdrawn abruptly, the switch to another antiepileptic drug should if necessary be effected under the cover of a suitable drug e.g. i.v. or rectal benzodiazepines, or i.v. phenytoin.

Interactions (see section 4.5)
Carbamazepine is not recommended to be used in combination with abiraterone, apixaban, apremilast, aprepitant, bedaquiline, bictegravir, bosentan, clozapine, cyclophosphamide, cyproterone, dabigatran, docetaxel, dolutegravir, dronedarone, erythromycin, oestrogen-progestins and progestins (contraceptives), etoposide, fentanyl, idelalisib, 5-alpha reductase inhibitors, metabolised tyrosine kinase inhibitors, irinotecan, isoniazid, itraconazole, ivacaftor, lithium, macitentan, mianserin, St. John's wort, naloxegol, nimodipine, olaparib, oxycodone, paclitaxel, grapefruit (juice and fruit), praziquantel, quetiapine ranolazine, regorafenib, rivaroxaban, rolapitant, sertraline, simvastatin, telithromycin, tenofovir alafenamide, ticagrelor, tramadol, ulipristal, vemurafenib, cytotoxic vinca alkaloids, vismodegib.

Endocrinological effects
Breakthrough bleeding has been reported in women taking carbamazepine while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by carbamazepine and women of childbearing potential should be advised to consider using alternative forms of birth control while taking carbamazepine (see section 4.6).

Precautions
Patients with glaucoma and urinary retention, liver or kidney disease, heart failure and the elderly should be informed about possible hazards associated with carbamazepine's mild anticholinergic activity. The dosage of carbamazepine should be adjusted to each individual. The intra-ocular pressure and kidney function of these patients should be checked regularly.

High doses of carbamazepine could result in activation of latent psychosis and possibly agitation or confusion in older patients.

Carbamazepine should be discontinued in the event of allergic skin reactions, impaired liver function or marked changes in the complete blood count suggesting agranulocytosis or bone marrow failure (rare).

The medicinal product should not be administered at a dose higher than 200 mg daily in children aged under 3 years and, more generally, at a high dose without a prior study of individual tolerance (see section 4.2).

Falls
Carbamazapine treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation 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 carbamazepine treatment.’

Alcohol
Alcohol ingestion is not recommended, carbamazepine may increase its effects.

Carbagen contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 inducers and inhibitors

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

Carbamazepine is a strong inducer of CYP3A4 and other phase I and II enzyme systems in the liver. Concomitant use of carbamazepine may increase the metabolism and thus decrease the plasma concentrations of several drugs that are eliminated by metabolism.

It should be noted especially that rifampicin is known to also be a very strong inducer of CYP 450 and reduces carbamazepine levels.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10, 11-transdiol derivative from carbamazepine-10,11-epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11-epoxide plasma concentrations.

Monoamine oxidase inhibitors

Because it is structurally related to tricyclic antidepressants, it is not recommended to give carbamazepine in combination with monoamine oxidase inhibitors (MAOIs). MAOIs should be discontinued at least 2 weeks before carbamazepine therapy is started if the clinical situation permits (see section 4.3).

Contraindicated combinations (see section 4.3)
Cobicistat: Risk of decreased effectiveness of cobicistat due to increased metabolism by carbamazepine.
Dasabuvir: Risk of decreased plasma concentrations of dasabuvir with carbamazepine.
Delamanid: Decreased plasma concentrations of delamanid due to an increase in its hepatic metabolism by carbamazepine.
Grazoprevir + elbasvir: Risk of decreased concentrations of grazoprevir and elbasvir with carbamazepine, with possible impact on effectiveness.
Isavuconazole: Decreased plasma concentrations of isavuconazole due to an increase in its hepatic metabolism by carbamazepine.
Ledipasvir: Decreased plasma concentrations of ledipasvir due to an increase in its hepatic metabolism by carbamazepine.
Lurasidone: Decreased plasma concentrations of lurasidone due to an increase in its hepatic metabolism by carbamazepine.
Midostaurin: Decreased concentrations of midostaurin with carbamazepine.

Ombitasvir + paritaprevir: Decreased plasma concentrations of dual therapy due to an increase in its hepatic metabolism by carbamazepine.
Rilpivirine: Significant decrease in plasma concentrations of rilpivirine due to an increase in its hepatic metabolism by carbamazepine.
Sofosbuvir: Risk of decreased plasma concentrations of sofosbuvir due to decreased intestinal absorption by carbamazepine.
Velpatasvir: Decrease in velpatasvir plasma concentrations by carbamazepine, with possible impact on effectiveness.
Voriconazole: Risk of decreased effectiveness of voriconazole due to an increase in its hepatic metabolism by carbamazepine.

Combinations not recommended
Abiraterone: Significant decrease in plasma concentrations of abiraterone, with a risk of reduced effectiveness.
Apixaban: Decreased plasma concentrations of apixaban by carbamazpine, with a risk of reduced effectiveness.
Apremilast: Decreased plasma concentrations of apremilast due to a decrease in its metabolism by carbamazepine.
Aprepitant: Risk of very significant decrease in concentrations of aprepitant.
Bedaquiline: Decreased plasma concentrations of bedaquiline due to an increase in its metabolism by carbamazepine.
Bictegravir: Risk of loss of effectiveness due to possibly significant decrease in concentrations of bictegravir.
Bosentan: Risk of decreased plasma concentrations of bosentan.
Clozapine: Decreased plasma concentrations of clozapine with risk of loss of effectiveness.
Risk of increased serious haematological effects.
Cyclophosphamide: Risk of increased plasma concentrations of the active metabolite of cyclophosphamide by carbamazepine and therefore of its toxicity.
Cyproterone: Risk of decreased effectiveness of cyproterone.
Combination not recommended for use as a hormonal contraceptive: preferably use another method of contraception, especially mechanical, for the duration of the combination and for a subsequent cycle.
Dabigatran: Decreased plasma concentrations of dabigatran, with the risk of decreased therapeutic effect.
Docetaxel: Decrease in concentrations of the cytotoxic agent due to increased metabolism by carbamazepine, with risk of reduced effectiveness.
Dolutegravir (+ see Combinations requiring precautions for use): Decreased plasma concentrations of dolutegravir due to an increase in its metabolism by carbamazepine.
Combination not recommended in case of resistance to the integrase inhibitor class.
Dronedarone: Significant decrease in dronedarone concentrations due to increased metabolism, without significant change in the active metabolite.
Erythromycin: Increased plasma concentrations of carbamazepine with signs of overdose by inhibition of its hepatic metabolism.
Estrogestin and progestogen (contraceptives): Decreased contraceptive efficacy, by increasing hepatic metabolism of hormonal contraceptive by carbamazepine.
If the combination is necessary, use an additional method of mechanical contraception (e.g. a condom) for the duration of treatment with carbamazepine, and for one menstrual cycle after stopping carbamazepine.
Etoposide: Decrease in etoposide plasma concentrations with carbamazepine.
If the combination is necessary, clinical monitoring and possible adjustment of etoposide dosage during combination and 1–2 weeks after stopping carbamazepine.
Fentanyl: Decreased plasma concentrations of fentanyl due to an increase in its hepatic metabolism by carbamazepine.
Preferably use another morphine.

Idelalisib: Decreased plasma concentrations of idelalisib due to an increase in its hepatic metabolism by carbamazepine.
5-alpha reductase inhibitors: Decrease in plasma concentrations of 5-alpha reductase inhibitor by carbamazepine.
If the combination cannot be avoided, close clinical monitoring is required.
Metabolised tyrosine kinase inhibitors: Decreased plasma concentrations and effectiveness of tyrosine kinase inhibitor due to increased metabolism by carbamazepine.
Irinotecan: Likely decrease in plasma concentrations of the active metabolite of irinotecan, with possible failure of cytotoxic therapy.
Isoniazid: Increased plasma concentrations of carbamazepine with evidence of overdose by inhibition of its hepatic metabolism.
Itraconazole: Decreased plasma concentrations of itraconazole, with risk of loss of efficacy, by increased hepatic metabolism by carbamazepine.
Ivacaftor: Significant decrease in concentrations of ivacaftor, with risk of loss of effectiveness.
Lithium: Risk of neurotoxicity manifested by cerebellar disorders, confusion, somnolence, ataxia. These disorders are reversible upon discontinuation of lithium therapy.
Macitentan: Decreased plasma concentrations of macitentan due to an increase in its metabolism by carbamazepine.
Mianserin: Risk of ineffectiveness of mianserin.
St. John's Wort: Risk of decreased plasma concentrations and efficacy of carbamazepine.
Naloxegol: Decreased naloxegol concentrations with carbamazepine.
Nimodipine: Decreased plasma concentrations of calcium channel blockers due to an increase in its hepatic metabolism by carbamazepine.
Clinical monitoring and possible adjustment of the dosage of calcium channel blockers during treatment with carbamazepine and after its discontinuation.
Olaparib: Decreased plasma concentrations of olaparib due to an increase in its hepatic metabolism by carbamazepine.
Oxycodone: Decreased plasma concentrations of oxycodone due to an increase in its metabolism by carbamazepine.
Possible adjustment of oxycodone dosage.
Paclitaxel: Decrease in concentrations of the cytotoxic agent due to increased metabolism by carbamazepine, with risk of reduced effectiveness.
Grapefruit (juice and fruit): Increased plasma concentrations of carbamazepine, with risk of overdose, due to inhibition of its metabolism by grapefruit.
Praziquantel: Very significant decrease in plasma concentrations of praziquantel, with risk of treatment failure, due to increased hepatic metabolism by carbamazepine.
Quetiapine: Very significant decrease in plasma concentrations of quetiapine by increased hepatic metabolism by carbamazepine, with risk of inefficacy.
Ranolazine: Risk of significant decrease in ranolazine concentrations.
Regorafenib: Decreased plasma concentrations of regorafenib due to an increase in its metabolism by carbamazepine.
Rivaroxaban: Decreased plasma concentrations of rivaroxaban, with the risk of decreased therapeutic effect.
Rolapitant: Very significant decrease in rolapitant concentrations with risk of loss of effectiveness.
Sertraline: Risk of ineffectiveness of antidepressant treatment.
Simvastatin: Significant decrease in plasma concentrations of simvastatin, due to increase in its hepatic metabolism.
Telithromycin: Decrease in plasma concentrations of telithromycin, with risk of failure of anti-infective treatment, due to an increase in its hepatic metabolism by carbamazepine.

Tenofovir alafenamide: Decreased plasma concentrations of tenofovir alafenamide due to decreased absorption by carbamazepine.
If the combination cannot be avoided, clinical monitoring during the combination and 1–2 weeks after stopping carbamazepine.
Ticagrelor: Significant decrease in plasma concentrations of ticagrelor due to increased hepatic metabolism by carbamazepine, with possible decrease in therapeutic effect.
Tramadol: Risk of decreased plasma concentrations of tramadol.
Ulipristal: Risk of decreased effect of ulipristal due to an increase in its hepatic metabolism by carbamazepine.
An alternative agent with little or no metabolism should be preferred.
Vemurafenib: Risk of decreased vemurafenib concentrations, with reduced effectiveness.
Cytotoxic vinca alkaloids: Decrease in plasma concentrations of vinca alkaloids by carbamazepine, with possible impact on effectiveness.
Vismodegib: Risk of decreased plasma concentrations of vismodegib due to an increase in its hepatic metabolism by carbamazepine.

Combinations requiring precautions for use
Acetazolamide: Increased plasma concentrations of carbamazepine with evidence of overdose.
Clinical monitoring and, if necessary, control of plasma concentrations of carbamazepine and possible reduction of its dosage.
Valproic acid and, by extrapolation, valpromide: Increased plasma concentrations of the active metabolite of carbamazepine with evidence of overdose. In addition, decrease in plasma concentrations of valproic acid by increased hepatic metabolism by carbamazepine.
Clinical monitoring, plasma dosages and dosage adjustment of the two anticonvulsants.
Afatinib: Decreased plasma concentrations of afatinib due to an increase in its metabolism by carbamazepine.
Clinical monitoring during combination and 1–2 weeks after stopping carbamazepine.
Albendazole (Anthelmintics): Significant decrease in plasma concentrations of albendazole and its active metabolite by carbamazepine, with possible decrease in effectiveness.
Clinical monitoring of therapeutic response and possible adjustment of the dosage of albendazole during treatment with carbamazepine and its after discontinuation.
Aminosides (if chronic administration with carbamazepine): Potentiation of curares when the antibiotic is administered parenterally and/or peritoneally before, during or after curare administration.
Monitor degree of neuromuscular blockade at the end of anaesthesia.
Androgens: Risk of decrease in plasma concentrations of androgens and consequently in their effectiveness by increasing their hepatic metabolism by carbamazepine.
Clinical and biological monitoring during combination and 1–2 weeks after stopping carbamazepine.
Calcium channel blockers (see combination not recommended for nimodipine): Decreased plasma concentrations of calcium channel blockers due to an increase in its hepatic metabolism.
Clinical monitoring and possible adjustment of the dosage of calcium channel blockers during treatment with carbamazepine and after its discontinuation.
Class IA antiarrhythmics (disopyramide, hydroquinidine, quinidine): Decreased plasma concentrations and effectiveness of antiarrhythmic due to increased hepatic metabolism by carbamazepine.
Clinical, ECG and plasma concentration monitoring; if necessary, adjustment of antiarrhythmic dosage during and after carbamazepine treatment.

Vitamin K antagonists (VKAs): Decreased effect of vitamin K antagonist by increased hepatic metabolism by carbamazepine.
More frequent monitoring of INR. Possible adjustment of the vitamin K antagonist dose during carbamazepine treatment and 8 days after its discontinuation.
Aripiprazole: Decreased plasma concentrations of aripiprazole.
Clinical monitoring and possible adjustment of aripiprazole dosage during combination and 1–2 weeks after stopping carbamazepine.
Bazedoxifene: Decrease in plasma concentrations of bazedoxifene with carbamazepine.
Monitor for signs of loss of effectiveness (bleeding).
Caspofungin: Decreased plasma concentrations of caspofungin.
If treated with carbamazepine, maintain dosage at 70 mg daily from day 2.
Certain selective serotonin reuptake inhibitor antidepressants (fluoxetine, fluvoxamine, paroxetine) (see combination not recommended for sertraline): Increased plasma concentrations of carbamazepine with signs of overdose.
Clinical monitoring, monitoring of carbamazepine plasma concentrations and possible reduction of the dosage of carbamazepine during treatment with serotonergic antidepressant and after its discontinuation.
Cimetidine ≥ 800 mg/day: At the beginning of treatment, increase in plasma concentrations of carbamazepine due to inhibition of its hepatic metabolism by cimetidine.
Clinical monitoring and possible reduction of carbamazepine dosage, especially during the first days of treatment with cimetidine.
Clarithromycin: Increased plasma concentrations of carbamazepine with evidence of overdose, by inhibition of its hepatic metabolism.
Clinical monitoring and possible reduction of carbamazepine dosage.
Clonazepam: Increased plasma concentrations of the active metabolite of carbamazepine. In addition, decreased plasma concentrations of clonazepam by increased hepatic metabolism by carbamazepine.
Clinical monitoring, plasma dosages and possible adjustment of the dosages of the two anticonvulsants.
Colistin (if chronic administration of carbamazepine): Potentiation of curares when the antibiotic is administered parenterally and/or peritoneally before, during or after curare administration.
Monitor degree of neuromuscular blockade at the end of anaesthesia.
Corticosteroids (e.g. prednisolone, dexamethasone) (gluco-, mineral-) (systemic) (except hydrocortisone in replacement therapy): Decreased plasma concentrations and effectiveness of corticosteroids due to increased hepatic metabolism by carbamazepine: the consequences are particularly significant in hydrocortisone-treated patients with Addison's disease and in cases of transplantation.
Clinical and laboratory monitoring and adjustment of the dosage of corticosteroids during treatment with carbamazepine and after its discontinuation.
Cyproterone (+ see Combinations not recommended): Risk of decreased effectiveness of cyproterone.
For its anti-androgen indications: clinical monitoring and possible adjustment of cyproterone dosage during the combination and after its discontinuation.
Danazol: Increased plasma concentrations of carbamazepine with signs of overdose.
Clinical monitoring and possible reduction of the carbamazepine dosage.
Deferasirox: Risk of decreased plasma concentrations of deferasirox.
Monitor ferritin levels during and after treatment with carbamazepine. If necessary, adjust deferasirox dosage.
Digoxin: Increased plasma concentrations of carbamazepine and decreased digoxin levels.
Caution should be exercised when interpreting plasma concentrations.
Disopyramide: Risk of decrease in disopyramide concentrations by carbamazepine.

Clinical monitoring and possible adjustment of disopyramide dosage during combination and 1–2 weeks after stopping carbamazepine.

Potassium-wasting diuretics (altizide, bendroflumethiazide, bumetanide, chlortalidone, cicletanine, clopamide, furosemide, hydrochlorothiazide, indapamide, methyclothiazide, piretanide)

Risk of symptomatic hyponatraemia.

Clinical and laboratory monitoring. If possible, use another class of diuretics.

Dolutegravir (see Combinations not recommended)

Decreased plasma concentrations of dolutegravir due to an increase in its metabolism by carbamazepine.

In the absence of resistance to the integrase inhibitor class, adjust dosage of dolutegravir to 50 mg twice daily during combination and one week after discontinuation.

Doxycycline: Decreased plasma concentrations of doxycycline due to an increase in its hepatic metabolism by carbamazepine.

Clinical monitoring and possible adjustment of the doxycycline dosage.

Non-contraceptive oestrogens and non-contraceptive progestins, whether or not combined with an oestrogen: Decreased effectiveness of oestrogen or progestin.

Clinical monitoring and possible adjustment of dosage of hormonal therapy during and after carbamazepine administration.

Ethosuximide: Decreased plasma concentrations of ethosuximide.

Clinical monitoring, plasma determination of ethosuximide and possible increase in dosage.

Felbamate: Increased plasma concentrations of the active metabolite of carbamazepine. Also, decreased plasma concentrations of felbamate due to an increase in its hepatic metabolism by carbamazepine.

Clinical monitoring, plasma determinations and possible adjustment of the dosages of both anticonvulsants.

Fluconazole ≥ 200 mg/day: Possible increase in adverse reactions of carbamazepine.

Adjust carbamazepine dosage during and after discontinuation of antifungal treatment.

Haloperidol: Risk of decreased haloperidol plasma concentrations and therapeutic effectiveness due to increased hepatic metabolism by carbamazepine.

Clinical monitoring and, if necessary, dosage adjustment during carbamazepine treatment and after its discontinuation.

Thyroid hormones: Risk of clinical hypothyroidism in hypothyroid patients due to increased metabolism of T3 and T4.

Serum T3 and T4 concentrations should be monitored and thyroid hormone dosage adjusted as necessary during carbamazepine treatment and after its discontinuation.

Hydrocortisone: Risk of decreased effectiveness of hydrocortisone (increased metabolism); serious consequences when hydrocortisone is administered as replacement therapy or in transplantation.

Clinical and laboratory monitoring; adjustment of hydrocortisone dosage during combination and after discontinuation of carbamazepine.

Immunosuppressants (cyclosporine, everolimus, sirolimus, tacrolimus, temsirolimus):

Decreased blood levels and effectiveness of immunosuppressant due to increased hepatic metabolism by carbamazepine.

Increase in dosage of immunosuppressant under monitoring of blood levels. Reduction in dosage after stopping carbamazepine.

Ritonavir-boosted protease inhibitors: Risk of decreased effectiveness of protease inhibitor due to increased hepatic metabolism by carbamazepine.

Regular clinical and laboratory monitoring, especially at the beginning of the combination.

Ivabradine: Risk of decreased effectiveness of ivabradine due to increased metabolism by carbamazepine.

Clinical monitoring and adjustment of ivabradine dosage during the combination and after stopping carbamazepine.
Josamycin: Increased plasma concentrations of carbamazepine with evidence of overdose, by inhibition of its hepatic metabolism.
Clinical monitoring and, if necessary, plasma dosage and possible reduction of carbamazepine dosage.
Lamotrigine: Risk of increased neurological effects (dizziness, ataxia, diplopia) of carbamazepine when lamotrigine is introduced.
Clinical monitoring and possible reduction of the carbamazepine dosage.
Levonorgestrel: With levonorgestrel used for emergency contraception, significant decrease in levonorgestrel plasma concentrations, with risk of ineffectiveness.
If carbamazepine has been taken in the last 4 weeks, the use of non-hormonal emergency contraception (copper IUD) should be considered.
If this is not possible, doubling the dose of levonorgestrel is another option.
Lincosamides (if chronic administration of carbamazepine): Potentiation of curares when the antibiotic is administered parenterally and/or peritoneally before, during or after curare administration.
Monitor degree of neuromuscular blockade at the end of anaesthesia.
Maraviroc: In the absence of co-administration with a potent CYP3A4 inhibitor, maraviroc concentrations are decreased by carbamazepine.
The dose of maraviroc should be increased to 600 mg twice daily in this situation.
Methadone: Decreased plasma concentrations of methadone with a risk of developing a withdrawal syndrome due to increased hepatic metabolism.
Increase the frequency of methadone administration (2 to 3 times daily instead of once daily).
Metronidazole: Decreased plasma concentrations of metronidazole due to an increase in its hepatic metabolism by carbamazepine.
Clinical monitoring and possible adjustment of the dosage of metronidazole during treatment with carbamazepine and after its discontinuation.
Montelukast**:** Risk of decreased effectiveness of montelukast due to increased hepatic metabolism by carbamazepine.
Clinical monitoring and possible adjustment of the dosage of antiasthmatic during treatment with carbamazepine and after its discontinuation.
Nintedanib: Decreased plasma concentrations of nintedanib due to decreased absorption by carbamazepine.
Clinical monitoring during combination.
Olanzapine: Risk of decreased plasma concentrations of olanzapine and its therapeutic efficacy due to increased hepatic metabolism by carbamazepine.
Clinical monitoring, and if necessary, dose adjustment of olanzapine.
Polymyxin B (if chronic administration of carbamazepine): Potentiation of curares when the antibiotic is administered parenterally and/or peritoneally before, during or after curare administration.
Monitor degree of neuromuscular blockade at the end of anaesthesia.
Posaconazole: Decreased plasma concentrations and effectiveness of posaconazole.
Clinical monitoring. If possible, plasma measurements of posaconazole and possible adjustment of its dosage.
Propafenone: Decreased plasma concentrations of propafenone due to an increase in its hepatic metabolism by carbamazepine.
Clinical and ECG monitoring. If necessary, adjust propafenone dosage during combination and after stopping carbamazepine.
Quinine: Risk of loss of effectiveness of quinine due to increased hepatic metabolism by carbamazepine.
Clinical monitoring and adjustment of the dosage of quinine during treatment with carbamazepine and after its discontinuation.

Rifabutin (see Concomitant use to be taken into account): Risk of clinical hypothyroidism in hypothyroid patients due to increased metabolism of T3 and T4.
Serum T3 and T4 concentrations should be monitored and thyroid hormone dosage adjusted as necessary during and after rifabutin treatment.
Rifampicin: Decreased plasma concentrations and efficacy of carbamazepine by increased hepatic metabolism by rifampicin.
Clinical monitoring, control of plasma concentrations and adjustment of carbamazepine dosage during treatment with rifampicin and after discontinuation.
Risperidone: Risk of decreased active fraction of risperidone and its therapeutic efficacy by increased hepatic metabolism by carbamazepine.
Clinical monitoring, and if necessary, dose adjustment of risperidone.
Stiripentol: Increased plasma concentrations of carbamazepine, with risk of overdose, by inhibition of its hepatic metabolism by stiripentol.
Clinical monitoring and plasma dosing, when possible, of carbamazepine combined with stiripentol and possible adjustment of its dosage.
Theophylline (and, by extrapolation, aminophylline): Decreased plasma concentrations and efficacy of theophylline by increased hepatic metabolism by carbamazepine.
Clinical monitoring and, if necessary, theophyllinemia. Possible adjustment of theophylline dosage during and after discontinuation of treatment with carbamazepine.
Tiagabine: Decrease in plasma concentrations of tiagabine by increased hepatic metabolism by carbamazepine.
An increase in the dosage of tiagabine may be necessary in combination with carbamazepine.
Topiramate: Decreased concentrations of topiramate with risk of reduced efficacy, by increasing its hepatic metabolism by carbamazepine.
Clinical monitoring, and if necessary, dose adjustment of topiramate during treatment with carbamazepine and after discontinuation.
Vitamin D: More pronounced decrease in vitamin D concentrations compared to no treatment with carbamazepine.
Vitamin D concentration assay and supplementation if needed.

Concomitant use to be taken into account
Atorvastatin: Risk of decreased plasma concentrations and/or efficacy of these molecules by carbamazepine.
If necessary, adjustment of the dosage of these molecules during treatment with carbamazepine.
Other sodium-lowering medicinal products: Increased risk of hyponatraemia.
Bortezomib: Decrease in concentrations of the cytotoxic agent due to increased metabolism by carbamazepine, with risk of reduced effectiveness.
Cabazitaxel: Decrease in concentrations of the cytotoxic agent due to increased metabolism by carbamazepine, with risk of reduced effectiveness.
Midazolam: Risk of decreased plasma concentrations of midazolam by carbamazepine.
Perampanel: Significant decrease (up to two thirds) in concentrations of perampanel.
Phenobarbital (and by extrapolation, primidone): Gradual decrease in plasma concentrations of carbamazepine with no apparent change in anticomitial efficacy.
Caution in interpreting plasma concentrations.
Phenytoin (and by extrapolation, fosphenytoin): To avoid phenytoin intoxication and subtherapeutic carbamazepine concentrations, it is recommended that the plasma concentration of phenytoin be adjusted to 13 micrograms/mL before the introduction of carbamazepine treatment.
Procarbazine: Increases in hypersensitivity reactions (hyperoesinophilia, rash), by increased metabolism of procarbazine by carbamazepine.

Rifabutin (see combinations subject to precautions for use): Risk of decreased plasma concentrations and/or efficacy of rifabutin by carbamazepine.
If necessary, adjustment of the rifabutin dosage during treatment with carbamazepine.
Tamoxifen: Risk of ineffectiveness of tamoxifen due to increased metabolism by carbamazepine.

Drugs that may decrease carbamazepine plasma levels
The plasma level of carbamazepine may be decreased by other enzyme inducers such as:

Antiepileptics: phenobarbital, phenytoin, primidone, felbamate (~25%), methosuximide, oxcarbazepine, fosphenytoin, progabide, valpromide, valproic acid, phensuximide, and clonazepam
Antimalarials: mefloquine
Bronchodilatators or anti-asthma drugs: theophylline, aminophylline
Antituberculosis: rifampicin,
Antineoplastics: cisplatin or doxorubicin
Cardiovascular drugs: digoxin
Dermatological drugs: isotretinoin

Due to potential interactions during combination therapy of epilepsy, plasma levels should be regularly monitored, and dosage adjusted accordingly as required. Blood assays of their respective plasma levels may vary from one patient to another, and moreover are usually bi-directional.

Serum levels of carbamazepine can be reduced by concomitant use of the herbal preparation St. John's wort (*Hypericum perforatum*). This is due to induction of drug metabolising enzymes, which may persist for at least 2 weeks after cessation of treatment with St. John's wort. For patients taking St. John's wort, serum levels of carbamazepine should be monitored and St. John's wort stopped. Carbamazepine levels may increase on stopping St. John's wort. The dose of carbamazepine may need adjusting.

Drugs that increase the active metabolite carbamazepine-10,11-epoxide plasma levels
Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:
Antiepileptics: progabide, valproic acid, valnoctamide, valpromide, primidone, brivaracetam.

Drugs that may increase carbamazepine plasma levels
Raised plasma levels of carbamazepine may lead to the symptoms listed under section 4.8 *e.g.* vertigo, somnolence, ataxia, dizziness, tiredness, unsteady gait, double vision. The carbamazepine plasma level should be checked and the dosage reduced, if necessary, when used concomitantly with:

Analgesic, anti-inflammatory drugs: dextropropoxyphene, propoxyphene, ibuprofen
Androgens: danazol
Antibiotics: macrolide antibiotics (*e.g.* erythromycin, troleandomycin, josamycin, clarithromycin), ciprofloxacin
Antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine

Antiepileptics: felbamate, lamotrigine, phenobarbital, primidone, stiripentol, vigabatrin
Antifungals: azoles (*e.g.* itraconazole, ketoconazole, voriconazole). Alternative anticonvulsants may be recommended in patients treated with itraconazole or voriconazole
Antihistamines: loratadine, terfenadine
Antipsychotics: olanzapine
Antituberculosis: isoniazid
Antivirals: protease inhibitors for HIV treatment (*e.g.* ritonavir)
Carbonic anhydrase inhibitors: acetazolamide
Cardiovascular drugs: diltiazem, verapamil
Gastrointestinal drugs: omeprazole
Muscle relaxants: oxybutynin, dantrolene
Neuroleptics: loxapine, olanzapine, quetiapine
Platelet aggregation inhibitors: ticlopidine
Other interactions: nicotinamide (in adults, only in high dosage)

Effect of carbamazepine on plasma levels of other drugs taken concomitantly
Carbamazepine may decrease, diminish or even abolish the activity of certain drugs. Concurrent use of carbamazepine with the following drug substances may require dose adjustment to ensure the required clinical response, especially when starting or discontinuing carbamazepine –

Analgesics, anti-inflammatory agents: buprenorphine, paracetamol (long term administration of carbamazepine and paracetamol may be associated with hepatotoxicity), phenazone, tramadol
Antibiotics: rifabutin
Anticoagulants: oral anticoagulants (*e.g.* warfarin, phenprocoumon, dicoumarol, acenocoumarol rivaroxaban, dabigatran, apixaban and edoxaban)
Antidepressants: bupropion, citalopram, mianserin, sertraline, nefazodone, trazodone
Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, clomipramine
Antiemetics: aprepitant
Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, oxcarbazepine, phenytoin, primidone, tiagabine, topiramate, valproic acid, zonisamide.
Antifungals: itraconazole, voriconazole. Alternative anitconvulsants may be recommended in patients treated with itraconazole or voriconazole
Antineoplastics: imatinib, lapatinib, temsirolimus
Antipsychotics: clozapine, bromperidol, olanzapine, quetiapine, risperidone, paliperidone, ziprasidone
Antivirals: protease inhibitors for HIV treatment (*e.g.* indinavir, ritonavir, saquinavir)
Anxiolytics: alprazolam, midazolam, clobazam
Bronchodilatators or antiasthmatic drugs: theophylline
Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered)
Cardiovascular drugs: calcium channel blockers (dihydropyridine group *e.g.* felodipine), isradipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin,
Drugs used in erectile dysfunction: tadalafil
Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus
Thyroid agents: levothyroxine
Other drug interactions: quinidine, hydroquinidine, methylphenidate, propranolol, flunarizine, products containing oestrogens or progesterones (gestrinone, tibolone, toremifene)

Hormonal contraceptives

For products containing oestrogens and/or progestogens, including oral contraceptives and hormone replacement therapy (see section 4.4), reliable alternative contraceptive methods (e.g. condoms) should be used. In patients taking the pill breakthrough bleeding or spotting may appear suddenly due to a decreased activity of the contraceptive. As a result, carbamazepine may cause a failure of the therapeutic effect of drugs containing oestrogens and/or progesterone containing drugs.

Carbamazepine may lower the plasma level of bupropion and may increase the level of its metabolite hydroxybupropion.

Other drug combinations to be taken into consideration
Concurrent use of carbamazepine and other psychotropic drugs, *e.g.* neuroleptics, antidepressants, sedatives, hypnotics, analgesics, sedative antihistaminics, may increase the occurrence of neurological side effects.

Co-administration of carbamazepine and direct-acting oral anticoagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may result in reduced plasma levels of the direct-acting oral anticoagulants. Further details can be found in the following Table:

Direct-acting oral anticoagulants (DOACs)	**Recommendations for concomitant use of DOACs and carbamazepine**
Apixaban	• In the prophylaxis of venous thromboembolism after elective hip or knee replacement surgery, in the prophylaxis of strokes and systemic embolism in patients with non-valvular atrial fibrillation and in the prophylaxis of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), concurrent use should be made with caution. • Concurrent use should be avoided when treating DVT and PE.
Rivaroxaban	Concomitant use should be avoided unless the patient is closely monitored for signs and symptoms of thrombosis.
Dabigatran	Concomitant use should be avoided.
Edoxaban	Concomitant administration should be done with caution.

There is an indication of a higher risk of developing Stevens-Johnson syndrome with concomitant use of neuroleptics.

Co-administration of carbamazepine and paracetamol may reduce the bioavailability of paracetamol (acetaminophen) and long-term co-administration may be associated with hepatotoxicity.

The concomitant use of carbamazepine and lithium or metoclopramide on the one hand and neuroleptics (haloperidol, thioridazine) on the other can favour the occurrence of neurological undesirable effects. In patients treated with neuroleptics, it

must be noted that carbamazepine reduces the plasma levels of these medicinal products and can therefore cause worsening of the disease profile. Dosage adjustment of the neuroleptic may be necessary.

Risk of neurotoxic effects may be increased with concomitant use of carbamazepine (ataxia) and lithium (cerebellar syndrome), despite the lithium plasma concentrations being in the normal range (see section 4.2). The following additional neurotoxic symptoms can be noted: unsteady gait, horizontal nystagmus, increased involuntary muscle reflexes, muscle twitching. These neurological effects are reversible after stopping the lithium.

The hepatic toxicity of isoniazid may be increased by carbamazepine.

The combination of carbamazepine with hypokalaemic diuretics (loop and thiazide diuretics) e.g. hydrochlorothiazide and furosemide, may cause hyponatraemia (see section 4.4).

Concomitant administration of carbamazepine and antiarrhythmics, cyclic antidepressants or erythromycin, increases the risk of cardiac conduction abnormalities.

The activity of muscle relaxants like pancuronium may be reduced by carbamazepine. A rapid recovery from neuromuscular blockade is therefore possible. Patients must be supervised accordingly and the dosage of the relaxant increased, if necessary.

Carbamazepine plasma levels must be checked during concurrent treatment with isotretinoin (acne treatment), as it has been reported to unpredictably alter the bioavailability of carbamazepine and its active metabolite.

Carbamazepine appears to increase the elimination of thyroid hormones and thus increase the hormone requirement of hypothyroid patients. A thyroid test should therefore be performed at the start and discontinuation of carbamazepine therapy in patients receiving thyroid hormone substitution. Dosage adjustment of thyroid hormone may be required.

A toxic serotonin-syndrome may be produced, if carbamazepine is taken together with drugs, which inhibit serotonin re-uptake (*e.g.* fluoxetine).

The severe haematological side effects of clozapine may be increased if used in combination with carbamazepine.

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

An increase in hypersensitivity (*e.g.* rash, hypereosinophilia) may occur when procarbazine is taken concurrently.

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. Therefore patients should abstain from alcohol during treatment.

Interference with serological examinations
Due to its interference with HPLC analysis, carbamazepine can lead to false positives for perphenazine concentrations. Carbamazepine and its 10,11-epoxide metabolite

can lead to false positive concentrations of tricyclic antidepressants in fluorescence polarised immunoassay method.

4.6 Pregnancy and lactation

Women of childbearing age and contraception
Due to the adverse interactions of carbamazepine with oestrogen and/or progesterone containing drugs, an alternative method of contraception should be used during treatment with carbamazepine and for two weeks after the last dose (see section 4.5).

Pregnancy

Risk related to epilepsy and antiepileptic drugs in general:
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.

Sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

It has been shown that in the offspring of epileptic women, the prevalence of malformations is two to three times greater than the rate of about 3% found in the general population. In the treated population an increase in malformed children has been noted with polytherapy, however the extent to which the treatment and/or the illness are respectively responsible has not been elucidated as yet.

The most frequently encountered malformations are labial fusion defects and cardiovascular malformations.

Risk linked to carbamazepine:
Carbagen crosses the placenta in humans. Prenatal exposure to carbamazepine may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, carbamazepine exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 2-3%. Malformations such as neural tube defects (spina bifida), craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias, hypoplasia of the fingers, and other anomalies involving various body systems, have been reported in the offspring of women who used carbamazepine during pregnancy. Specialised antenatal surveillance for these malformations is recommended. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used carbamazepine alone or in combination with other AEDs 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.

Carbamazepine should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking carbamazepine during pregnancy.

Evidence suggest that the risk of malformation with carbamazepine may be dose dependent. If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with carbamazepine is continued, monotherapy and the lowest effective dose of carbamazepine should be used 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.

Some antiepileptic drugs, such as carbamazepine, have been reported to decrease serum folate levels. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy. 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.

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.

Women of childbearing potential

Carbamazepine should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the 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. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with carbamazepine.

Women of childbearing potential should use effective contraception during treatment and for two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives (see section 4.5), therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods. At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

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

In the new-born child:
Enzymatic inducers have provoked:
Uncommon: bleeding disorders occurring in the first 24 hours of the life of a treated mother’s child. Prevention by oral vitamin K1 to the mother, in the month prior to the birth, and an adapted dose to the new-born child at the moment of birth, seem appropriate. Normal outcomes of coagulation tests in the mother do not rule out coagulation defects in the neonate.
Rarely: problems with the calcium and phosphocalcic metabolism and bone mineralisation, which vitamin D supplementation in the mother during the third trimester appears to be able to prevent.

Postnatal follow-up/children: in the event of exposure during pregnancy, close monitoring of the child's neurobehavioural development should be initiated and appropriate treatment started as soon as possible if necessary.

A few cases of convulsions and/or respiratory depression in newborn babies have been reported, as well as some cases of vomiting, diarrhoea and/or reduced nutritional intake have been observed in connection with administration of antiepileptics. These could be signs of withdrawal syndrome in newborn babies.

Breast-feeding
Carbamazepine and its main metabolite, carbamazepine-epoxide, are both present in breast milk in concentrations of about 25 to 60 % of the total plasma concentration. Due to the possible onset of non-dose-dependent adverse effects in the neonate, breast-feeding is not recommended during treatment for safety reasons. Breast-feeding should be stopped if signs of sedation become apparent.

There are some reports of cholestatic hepatitis in newborn babies who were exposed to carbamazepine antenatally or during breast-feeding. As a result, breast-fed children whose mothers are being treated with carbamazepine should be carefully monitored for undesirable hepatobiliary effects.

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

4.7 Effects on ability to drive and use machines

Carbamazapine has major influence on the ability to drive and use machines. Particular attention should be given, especially in drivers and users of machinery, to the risks associated with epileptic seizures. It affects patients' reactions, causing dizziness, light-headedness drowsiness, fatigue, ataxia, disorders of accommodation, double vision, blurred vision, especially in the early stages of treatment. This may be further influenced by higher dose levels or the use of carbamazepine in combination with other centrally acting drugs or in conjunction with alcohol consumption. Patients should be warned of the possible hazards when driving or operating machinery.

4.8 Undesirable effects

The following undesirable effects appear dependent on the dose in particular at the start of therapy, too high initial dose or in older patients. These symptoms may abate spontaneously within a few days or if the dose is transiently reduced:
dizziness, headache, ataxia, drowsiness, fatigue, diplopia, disorders of accommodation, confusion, agitation, 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. Serious adverse reactions involving the blood and lymphatic, hepatic, dermatological and cardiovascular systems (see section 4.9), as well as hypersensitivity reactions, require therapy cessation. 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 the plasma levels and divide the daily dosage into smaller fractional doses.

Adverse reactions compiled from clinical trials are listed by MedDRA system organ class. Within each system organ class, adverse reactions are ranked by frequency, from most to least common. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Side effects listed according to organ system with the frequency estimate 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) and not known (cannot be estimated from the available data):

Infections and infestations
Not known: Reactivation of an infection with human herpes virus 6

Blood and lymphatic system disorders
Very common: Leucopenia
Common: eosinophilia, thrombocytopenia
Rare: Lymphadenopathy, leucocytosis
Very rare: Agranulocytosis, bone marrow failure, aplastic anaemia, pure red cell aplasia, anaemia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia, enlarged spleen, pancytopenia

According to literature sources the most frequent disorder is benign leucopenia, 10% of the cases being of a transient nature, 2% persistent.

Immune system disorders
Uncommon: Delayed multi-organ hypersensitivity disorder (DRESS) with fever, skin rashes, vasculitis, swollen lymph nodes, pseudolymphoma, painful joints (arthralgia), leucopenia, eosinophilia, hypogammaglobulinaemia, enlargement of liver and spleen or altered liver function tests and vanishing bile duct syndrome occurring in various combinations. Other organs such as lung, kidney, pancreas, colon and cardiac muscle may also be affected. The existence of rare cases of cross sensitivity to carbamazepine, phenytoin, phenobarbital and oxcarbazepine calls for caution when substituting carbamazepine with any of these medicinal products.
Rare: Hepatitis, which may be severe
Very rare: Generalised acute allergic reactions, anaphylactic reactions, angioedema
Not known: Drug rash with eosinophilia and systemic symptoms (DRESS)

Endocrine disorders
Common: Weight gain, oedema, hyponatraemia related to syndrome of inappropriate antidiuretic hormone secretion.
Very rare: galactorrhoea, gynaecomastia.

Metabolism and nutrition disorders
Common: Fluid retention
Rare: Folic acid deficiency, reduced appetite
Not known: Hyperammonaemia

Psychiatric disorders
Uncommon: Confusion and agitation in older patients, depressive disorders, aggressive behaviour, thinking difficulties, hallucinations (visual or auditory), activation of latent psychosis
Rare: Restlessness, mania
Very rare: Phobias

Nervous system disorders
Very common: Dizziness, somnolence, sedation, ataxia (atactic and cerebral disturbances)
Common: Headache
Uncommon: Lack of drive, abnormal involuntary movements like asterixis, tremor, dystonia, dyskinetic disorders like orofacial dyskinesia or tics or nystagmus.
Rare: Choreoathetosis, eye movement disturbances, speech disorders, (e.g. dysarthria, slurred speech), paraesthesia, neuropathy peripheral, polyneuropathy, peripheral neuropathy, paresis
Very rare: Taste disturbances, neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia
Not known: Memory impairment

Eye disorders
Common: Accommodation disorders, (e.g. blurred vision), diplopia
Rare: Lenticular opacities, conjunctivitis
Very rare: Retinotoxicity, cataracts

Ear and labyrinth disorders
Uncommon: Tinnitus
Very rare: Change in pitch perception, hearing disorders (hypoacusis or hyperacusis)

Cardiac disorders
Uncommon: Conduction disorders, AV-block, in isolated cases with syncope, bradycardia, cardiac arrhythmias, aggravation of coronary artery disease, congestive heart failure

Vascular disorders
Uncommon: Vasculitis
Rare: Hypertension, hypotension
Very rare: Thrombophlebitis, thrombo-embolism, circulatory collapse

Respiratory, thoracic and mediastinal disorders
Very rare: Pulmonary hypersensitivity reactions with fever, dyspnoea, pneumonitis or pneumonia (alveolitis), lung fibrosis

Gastrointestinal disorders
Very common: Nausea, vomiting
Common: Loss of appetite, dry mouth
Uncommon: Diarrhoea, constipation
Rare: Abdominal pain
Very rare: Stomatitis, gingivitis, glossitis, pancreatitis
Not known: Colitis

Hepatobiliary disorders
Rare: Jaundice, hepatitis (cholestatic, hepatocellular, granulomatous, mixed type), exceptional cases of vanishing bile duct syndrome, liver failure

Skin and subcutaneous tissue disorders
Very common: Allergic skin reactions with or without fever like urticaria (which may be severe)
Uncommon: Pruritus, exfoliative dermatitis, erythroderma, alopecia, hyperhidrosis
Rare: Systemic lupus erythematosus
Very rare: Severe cutaneous adverse reactions (SCARS): Stevens-Johnson syndrome (SJS)* Lyell syndrome* and toxic epidermal necrolysis (TEN) (see section 4.4), alterations in skin pigmentation, acne, hirsutism, photosensitivity, erythema exudativum, multiforme and nodosum, purpura, acute generalised exanthematous pustulosis (AGEP)
Not known: Lichenoid keratosis, onychomadesis

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 (see sections 4.2 and 4.4).

Musculoskeletal and connective tissue disorders
Rare: Muscular weakness
Very rare: Arthralgia, muscle pain, muscle spasms, bone metabolism disorder
Not known: Fracture

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.

Carbamazepine may increase the metabolism of 25-OH-Cholecalciferol leading to a decreased calcium level, which rarely causes osteomalacia, arthralgia, myalgia and muscle cramps.

Renal and urinary disorders
Uncommon: Renal impairment such as proteinuria, elevated creatinine, which may or may not occur as part of hypersensitivity syndrome*, haematuria, oliguria, elevated BUN/azotaemia
Rare: Other micturition disorders like dysuria, pollakiuria, urinary frequency and urinary retention
Very rare: Renal failure, interstitial nephritis

Reproductive system and breast disorders
Rare: Gynaecomastia, galactorrhoea
Very rare: Sexual dysfunction like impotence, decreased libido and impaired male fertility and/or abnormal spermatogenesis (reduces sperm count and/or motility)

Congenital, familial and genetic disorders
Very rare: Porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda)
Not known: Congenital anomalies, other developmental disorders (see sections 4.4 and 4.6).

General disorders and administration site conditions
Very common: Fatigue
Common: Oedema

Investigations
Very common: Elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant
Common: Elevated alkaline phosphatase in the blood, reduced plasma osmolality due to an antidiuretic hormone (ADH)–like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities
Uncommon: Increased transaminases
Very rare: Elevated levels of cholesterol, including HDL cholesterol, and triglycerides, increased intraocular pressure, abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased, increase in serum cortisol

Injury, poisoning and procedural complications

Not known: Fall (associated with carbamazepine treatment-induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 4.4))

Carbamazepine may lower the plasma levels of folic acid and vitamin B12 and may increase the plasma level of homocysteine.

* There is increasing evidence of the association of genetic markers with the development of cutaneous adverse reactions, such as SJS, TEN, DRESS, AGEP and maculopapular rash.
In Japanese and Northern European patients, these reactions have been reported to be associated with 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 in patients of Han Chinese, Thai and Southeast Asian descent (see sections 4.2 and 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Carbamazepine overdose has been reported only with very high doses (4 to 20 g). Plasma levels were always above 20 µg/ml. A plasma level of 38 µg/ml was not lethal for the patient. Lethal cases of carbamazepine overdose have been reported in literature.

Symptoms
The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, gastrointestinal, musculoskeletal, renal or respiratory systems or may consist of the adverse reactions listed in section 4.8.

Central nervous system: CNS depression, disorientation, somnolence, agitation, hallucination, impaired consciousness, which may progress insidiously and lead to deep coma, stupor, vertigo, restlessness, confusion, blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, opisthotonus, involuntary movements, tremor, flushing, seizures, EEG dysrhythmia, hypothermia, mydriasis anticholinergic signs. In severe cases, intoxication may be complicated by respiratory depression.

Respiratory system: Respiratory depression, pulmonary oedema, cyanosis, respiratory arrest.

Cardiovascular system: Tachycardia, changes in blood pressure (hypotension and at times hypertension), cardiac arrhythmias, AV block, cardiac arrest, flushing, conduction disturbance with widening of QRS complex; electrocardiogram changes (atrioventricular and intraventricular conduction disorders, QT prolongation), which may lead to circulatory collapse, heart failure and syncope in association with cardiac arrest.

Gastrointestinal system: Nausea, vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system: Cases of rhabdomyolysis have been reported with carbamazepine intoxication

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

Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatinine phosphokinase, leucocytosis, leucopenia, neutropenia, glycosuria, acetonuria.

Management of symptoms
There is no specific antidote for carbamazepine overdose.
Management of symptoms due to overdosage will vary according to the patient's condition. This includes admission to hospital. Measurement of the plasma levels to confirm carbamazepine poisoning and to ascertain the size of the overdose. Evacuation of the stomach, gastric lavage, and administration of activated charcoal or laxative. Delayed evacuation of the stomach may lead to delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with monitoring of consciousness, cardiovascular parameters (cardiac monitoring) and careful correction of electrolyte imbalance, if required.

Special recommendations:
Hypotension: administer dopamine or dobutamine *i.v.*

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

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

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

Charcoal haemoperfusion has been recommended. Haemodialysis is an effective option in the treatment of carbamazepine overdose. Forced diuresis, and peritoneal dialysis have been reported not to be effective.

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

Pharmacotherapeutic group: Antiepileptic, ATC Code: N03AF01.

Mechanism of action
Carbamazepine acts primarily on voltage-gated sodium channels; other mechanisms of action are not fully understood. In addition, the reduction in glutamate release and stabilisation of neuronal membranes may largely account for the antiepileptic effects. The antimanic properties of carbamazepine seem to stem from the depressant effect on dopamine and noradrenaline turnover.
It is thought to block cyclic-AMP mediated calcium influx associated with transmitter release, and it is known to be an adenosine receptor antagonist: either of these actions might account for its antiepileptic action. Work in animals has shown that it has inhibitory effects on hippocampal discharges and it also inhibits the reticulo-thalamic and thalamocortical projections which are involved in tonic-clonic seizures.

Antiepileptics have membrane-stabilising properties which have been found useful in the relief of neurogenic pain especially where there is a lancinating element, as in trigeminal neuralgia.

5.2 Pharmacokinetic properties

Absorption
Carbamazepine is almost completely absorbed but the rate of absorption is slow and may vary between patients.
Peak plasma concentrations of the unchanged active substance are attained within 24 hours. The bioavailability of carbamazepine has been shown to lie between 85 and 100 % and is unaffected by food.

Evaluation of literature allows the conclusion concerning therapeutic and toxic plasma levels that seizures are controlled at plasma levels between 4 and 12 µg/ml, levels above 20 µg/ml resulted in a deterioration of symptoms. Control of pain of trigeminal neuralgia was effective at plasma levels between 5 and 18 µg/ml. Side effects start appearing at plasma levels above 8 to 9 µg/ml.

Distribution
Carbamazepine is 70 to 80 % bound to plasma. Activity is generally observed at steady-state plasma concentrations (i.e. after one week of treatment) of 4–12 micrograms/mL (17–50 micromoles/L) and toxic reactions occur at concentrations higher that 15 micrograms/mL. The proportion of unbound carbamazepine is constant at a concentration of up to 50 µg/ml. The pharmacologically active metabolite carbamazepine-10,11-epoxide is bound to plasma protein at 48 to 53% (about 0.74 L/kg).

The concentration of carbamazepine in the cerebrospinal fluid is 33% of the current plasma concentration. The concentration of unchanged substance in the saliva represents the unbound portion in plasma, i.e. 20 to 30 % of total plasma concentration. The active substance is also excreted in breast milk where it is two times less concentrated, the concentration is 25 to 60%

of total plasma concentration. Carbamazepine crosses the placental barrier. Apparent volume of distribution: 0.8 to 1.9 L/kg. In addition, during pregnancy, the free fraction is increased. Administration of the prolonged-release form: reduces the peak plasma concentration, maintains plasma concentrations within the usual therapeutic range for carbamazepine, increases the dosing interval.

Biotransformation
Carbamazepine is extensively metabolised in the liver, mainly by oxidative pathways of which only the metabolite carbamazepine-10, 11-epoxide is pharmacologically active. Cytochrome P450 3A4 has been identified as the main enzyme responsible for the formation of this metabolite. Carbamazepine is a potent enzyme inducer and is associated with numerous drug interactions. This may constitute up to 30 % of the circulating active material originality as carbamazepine. The inactive 10,11-diol represents the final stage of carbamazepine biotransformation. In children, the relatively high rate of metabolism of the drug may require higher dose (in mg/kg b.w.) of carbamazepine to maintain therapeutic concentrations.

Elimination
Only about 2 % of the administered dose is excreted in the urine in the unchanged form. A greater part is excreted in the urine almost entirely in the form of its metabolites; some is excreted in faeces.

Plasma clearance in healthy subjects is about 19.8 ± 2.7 ml/h/kg, in patients under monotherapy about 54.6 ± 6.7 ml/h/kg, in patients under combination therapy about 113.3 ± 33.4 ml/h/kg.

The elimination half-life of unchanged drug in the plasma averages approximately 36 hours following a single dose, whereas after repeated administration, it averages only 16 to 24 hours, depending on the duration of the medication. In patients receiving co-medication with other enzyme-inducing drugs such as phenytoin, phenobarbitone, half-life values averaging 9 to 10 hours have been observed.

Special population
Carbamazepine should be used with caution in patients with renal impairment.

In advanced hepatic disease, carbamazepine metabolism may be impaired.

The pharmacokinetics of carbamazepine are unaltered in older people but its metabolism may be affected by hepatic dysfunction. The controlled release formulation of carbamazepine produces a substantial reduction in intra-dose fluctuations in carbamazepine concentrations and tolerability and seizure control in patients with epilepsy may be improved.

The controlled release formulation should be considered in patients receiving high doses who suffer intermittent adverse effects such as diplopia, nausea, dizziness and tiredness and may offer the opportunity to reduce the dosage regimen.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproductive toxicity studies in animals were insufficient to rule out a teratogenic effect of carbamazepine in humans.

Carcinogenicity
In rats treated with carbamazepine for 2 years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence that this observation is of importance for the therapeutic use of carbamazepine in humans.

Reproductive toxicity
In animal studies in mice, rats and rabbits oral administration of carbamazepine during organogenesis led to an increased embryo-foetal mortality and foetal growth retardation at daily doses which were associated with maternal toxicity (above 200 mg/kg/day). Carbamazepine was teratogenic in a number of studies, particularly in mice, however showed no or only minor teratogenic potential at doses relevant to humans. In a reproductive study in rats, nursing offspring exhibited reduced weight gain at a maternal dosage level of 192 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonio methacrylate copolymer (type B) (contains: sorbic acid and sodium hydroxide)
Methacrylic acid - ethyl acrylate copolymer (1:1) (contains: sodium laurilsulfate and polysorbate 80)
Triacetin
Talc
Cellulose, microcrystalline
Crospovidone
Silica, colloidal anhydrous
Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage

6.5 Nature and contents of container

Child-proof containers:
PVC/PVDC Blister with aluminium/pergamyn lidding or
OPA/Alu/PVC Blister with aluminium lidding
Packs containing:
20, 28, 30, 50, 56, 60, 84, 90, 100, 112, 120, 150, 168, 180, 200, 250 or 500 prolonged-release tablets
Sample pack with 30 prolonged-release tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7 MARKETING AUTHORISATION HOLDER

Generics [UK] Ltd t/a Mylan, Station Close, Potters Bar, Hertfordshire, England, EN6 1TL.

8 MARKETING AUTHORISATION NUMBER(S)

PL04569/0444

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

03/08/2025