SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Curatil 400 mg Prolonged-Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 400 mg carbamazepine.
Excipient with known effect
Each prolonged-release tablet contains 60mg lactose (as lactose monohydrate)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release tablet
White to off-white, round, biconvex tablets, approximately 12 mm diameter, debossed with “298” on one side and “HP” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy – generalised tonic-clonic and partial seizures. Curatil is indicated in newly diagnosed patients with epilepsy and in those patients who are uncontrolled or unable to tolerate their current anti-convulsant therapy.

Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures.

The paroxysmal pain of trigeminal neuralgia.

For the prophylaxis of manic-depressive psychoses in patients unresponsive to lithium therapy.

4.2 Posology and method of administration

Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for the HLA-B*1502 gene variant as this allele strongly predicts the risk of severe carbamazepine-associated Stevens-Johnson syndrome (See information on genetic testing and cutaneous reactions in section 4.4).

Posology

Dosage

Treatment with Carbamazepine is gradually started, with a low initial dose, depending on the type and severity of the clinical picture, on an individual basis, after which the dose is slowly increased to the most effective maintenance dose.

The daily dose is usually administered in 1 to 2 single doses.

The general daily dosage range is between 400 and 1,200 mg of carbamazepine. A total daily dose of 1,600 mg of carbamazepine should generally not be exceeded because higher doses increase the number of side effects.

The therapeutic dose should be determined, especially in combination therapy, by determining plasma levels and depending on efficacy. Experience has shown that the therapeutic carbamazepine level is between 4 and 12 micrograms/ml.

In individual cases, the required dose can deviate considerably from the specified starting and maintenance dose (e.g. due to accelerated metabolism through enzyme induction or due to drug interactions in the event of combined medication).

Carbamazepine should preferably be used alone (monotherapy) to treat epilepsy. Treatment should be supervised by a specialist doctor experienced in the treatment of epilepsy.

When switching to treatment with carbamazepine, the dose of the antiepileptic to be discontinued should be reduced gradually.

The following general dosing regimen is recommended for the treatment of epileptic seizure disorders:

	Initial daily dose in mg (or number of prolonged-release tablets)	**Maintenance dose daily in mg (or number of prolonged-release tablets)**
Adults:	200 mg in the evening (1 prolonged-release tablet)	200 to 600 mg in the morning (1 to 3 prolonged-release tablets) 400 to 600 mg in the evening (2 to 3 prolonged-release tablets)
Children:* 6 to 10 years old	200 mg in the evening (1 prolonged-release tablet)	200 mg in the morning (1 prolonged-release tablet) 200 to 400 mg in the evening (1 to 2 prolonged-release tablets)
11 to 15 years	200 mg in the evening (1 prolonged-release tablet)	200 to 400 mg in the morning (1 to 2 prolonged-release tablets) 400 to 600 mg in the evening (2 to 3 prolonged-release tablets)
> 15 years	According to the adult dose	

* Note:
For children under 6 years of age, non-delayed dosage forms (suspension or tablets) are available for initial and maintenance dosing. The administration of prolonged-release tablets cannot be recommended due to insufficient knowledge.

Maximum recommended dose:

6 to 15 years of age: 1,000 mg/day
>15 years of age: 1,200 mg/day

Children under 6 years of age
Carbamazepine is unsuitable for children under the age of 6 because of the high active ingredient content and lack of experience with retard tablets.

The following dosage recommendations apply:

Epilepsy:
In general, in adults the initial dose of 1 to 2 prolonged-release tablets of carbamazepine (equivalent to 200 to 400 mg carbamazepine/day) is slowly increased to the maintenance dose of 4 to 6 prolonged-release tablets of carbamazepine (equivalent to 800 to 1,200 mg carbamazepine).

In general, the maintenance dose for children is an average of 10 to 20 mg carbamazepine/kg bodyweight/day.

For recommended dosing schedule, see above.

Trigeminal neuralgia*:*
The initial dose of 200 to 400mg is slowly increased until freedom from pain is achieved (normally at 200mg 3-4 times daily). In the majority of patients, a dosage of 200mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600mg carbamazepine daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the lowest possible maintenance level. The maximum recommended dose is 1200mg/day. Once pain relief has been achieved, attempt should be made to gradually discontinue therapy until another pain episode occurs.

Elderly and sensitive patients
In elderly and sensitive patients, an initial dose of 1 prolonged-release tablet (equivalent to 200 mg carbamazepine) in the morning or evening is sufficient.

Prophylaxis of manic depressive psychoses in patients unresponsive to lithium therapy:
The initial dose, which is usually also sufficient as a maintenance dose, is 1 to 2 prolonged-release tablets of carbamazepine 200mg (equivalent to 200 to 400mg carbamazepine) daily. If necessary, the dose can be increased to 2 prolonged-release tablets of carbamazepine 200mg (equivalent to 800mg carbamazepine) twice a day.

Elderly and patients with severe cardiovascular disease, liver and kidney disease
A lower dosage is indicated in patients with severe cardiovascular disease, liver and kidney disease and in the elderly.

Method of administration
The prolonged-release tablets should be swallowed whole and not chewed or crushed.

The prolonged-release tablets are taken with sufficient liquid (e.g. 1 glass of water) during or after meals.

In some cases, dividing the daily dose into 4 to 5 individual doses has proven to be particularly effective. In these cases, immediate release formulations of carbamazepine are preferable to prolonged release formulations.

The duration of use depends on the respective indication and the individual reaction of the patient. In any case, this medicine must not be discontinued by the patient on their own initiative.

The duration of use varies individually and is determined by the attending physician.

Antiepileptic therapy is basically a long-term therapy.

The adjustment duration of treatment and discontinuation of carbamazepine should be decided on a case-by-case basis by a specialist experienced in the treatment of epilepsy. In general, dose reduction and discontinuation of the medication should be considered after two to three years of seizure freedom at the earliest.

Discontinuation must be done in gradual dose reduction over one to two years; children may outgrow the dose per kg body weight, instead of age-appropriate dose adjustment, and EEG findings should not worsen.

In the treatment of neuralgia, it has proven useful to carry out the therapy over a period of a few weeks with a maintenance dose that is just about sufficient for freedom from pain. Careful dose reduction should be used to determine whether spontaneous remission has occurred in the meantime.

If pain attacks recur, the original maintenance dose should be continued.

The prophylaxis of manic-depressive phases is a long-term treatment.

Children
Carbamazepine is unsuitable for children under the age of 6 because of the high active ingredient content and lack of experience with retard tablets.

4.3 Contraindications

- Hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any of the other ingredients listed in section 6.1;
- Atrioventricular block;
- Presence of bone marrow damage, history of bone marrow depression;
- Hepatic porphyria, including also history (e.g. acute intermittent porphyria, variegata porphyria, porphyria cutanea tarda);
- Concomitant treatment with a monoamine oxidase inhibitor.

4.4 Special warnings and precautions for use

Carbamazepine may only be used under medical supervision and after a strict benefit-risk assessment and under corresponding close-meshed monitoring can be applied to:

- Previous or existing haematological diseases, history of haematological reactions to other medicines;
- Disturbed sodium metabolism;

- Cardiac, hepatic or renal impairment, including history (see sections 4.2 and 4.8);
- Patients who have previously discontinued treatment with carbamazepine;
- Patients with myotonic dystrophy, since cardiac conduction disorders are common in this patient group.

Haematological events

Agranulocytosis and aplastic anaemia have been associated with carbamazepine; however, an assessment of the risk is difficult due to the very low frequency. In the untreated population, the probability of occurrence is 4.7 cases per million per year for agranulocytosis and 2.0 cases per million per year for aplastic anaemia.

A temporary or permanent reduction in the number of blood platelets or the number of white blood cells is uncommon to common with carbamazepine. In the majority of cases this is transient and does not predict the onset of agranulocytosis or aplastic anaemia. However, blood counts (including platelets and reticulocytes and serum iron) should be checked prior to treatment with carbamzepine, then at weekly intervals during the first month of treatment, and then at monthly intervals. After 6 months of treatment, checks 2 to 4 times a year are sometimes sufficient.

Patients should be alerted to early signs of potential haematologic problems and likewise to symptoms of dermatologic and hepatic reactions. If reactions such as fever, sore throat, allergic skin reactions such as rash with lymph node swelling and/or flu-like illness symptoms, ulcers in the mouth, haematoma tendency, petechial or purpuric haemorrhages occur during treatment with carbamazepine, the patient should immediately consult the physician and the blood count should be determined. Discontinuation of carbamzepine may be required if certain blood count abnormalities (especially leukocytopenia and thrombocytopenia) occur; this is always the case if symptoms such as allergic symptoms, fever, sore throat or skin bleeding occur at the same time. The following listings provide some clues:

Short-term checks (within 1 week) required for:
- Fever, infection;
- Skin rash;
- General feeling of weakness;
- Sore throat, mouth ulcers;
- Rapid formation of bruises;
- Increase in transaminases;
- Decrease in leukocytes below 3,000/mm3 or of granulocytes below 1,500/mm3;
- Decrease in platelets below 125,000/mm3;
- Decrease in reticulocytes below 0.3% = 20,000/mm3;
- Increase in serum iron over 150 micrograms%.

Discontinuation of carbamazepine required for:
- Petechial or purpuric bleeding;
- Decrease in erythrocytes below 4 million/mm3;
- Decrease in hematocrit below 32%;
- Decrease in hemoglobin below 11 g%;
- Decrease in leukocytes below 2,000/mm3 or granulocytes below 1,000/mm3 or thrombocytes below 80,000/mm3;
- Symptomatic blood disorders.

Severe skin reactions

Cases of life-threatening skin reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) have been reported in association with the use of

carbamazepine. Patients should be informed of the signs and symptoms of these serious adverse reactions and monitored closely for the occurrence of skin reactions. The risk for the occurrence of SJS or TEN is highest during the first few weeks of treatment. If signs or symptoms of SJS or TEN occur (e.g., a progressive rash, often with blistering or accompanying mucosal lesions), therapy with carbamazepine must be discontinued. The course of SJS and TEN is largely determined by early diagnosis and immediate discontinuation of all suspected drugs, i.e. early discontinuation improves the prognosis. After the occurrence of SJS or TEN associated with the use of carbamazepine, the patient must never be treated with carbamazepine again.

Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens- Johnson Syndrome (SJS), are estimated to occur in 1 to 6 in 10,000 new users in predominantly Caucasian countries, but in some Asian countries the risk 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).

Allele HLA-A*3101 - Individuals of European and Japanese descent
There are data indicating that the HLA-A*3101 allele is associated with an increased risk of carbamazepine-induced skin adverse drug reactions in individuals of European descent and Japanese, e.g. SJS, TEN, drug rash with eosinophilia and systemic symptoms (DRESS syndrome) or less severe acute generalised exanthematous pustulosis (AGEP) and maculopapular drug rash (see section 4.8). The frequency of the HLA-A*3101 allele shows strong variation between different population groups. The HLA-A*3101 allele has a prevalence of 2% to 5% in the European population and about 10% in the Japanese population.

The presence of the HLA-A*3101 allele may increase the risk of carbamazepine-induced skin reactions (in most cases mild in severity) from 5.0% in the general population to 26.0% in patients of Caucasian descent, while the absence of this allele can reduce the risk from 5.0% to 3.8%. There are insufficient data to recommend testing for the presence of the HLA-A*3101 allele prior to initiating carbamazepine treatment. If patients of European or Japanese origin are known to carry the HLA-A*3101 allele, the use of carbamazepine may be considered if the expected benefit outweighs the risk.

Allele HLA-B*1502 in Han Chinese, Thai and other Asians
Population groups
It has been demonstrated that the presence of the HLA-B*1502 allele in individuals of Han Chinese or Thai descent is strongly associated with the risk of developing severe skin reactions, namely Stevens-Johnson Syndrome. The prevalence of carriers of the HLA-B*1502 allele is approximately 10% in Han Chinese and Thais. If at all possible, these individuals should be genetically tested for this allele prior to initiating therapy with carbamazepine (see section 4.2). If the test is positive, treatment with carbamazepine should not be started unless, no alternative treatment is available. Tested individuals who do not have HLA-B*1502 have a low risk of developing Stevens-Johnson syndrome; however, these reactions can occur rarely.

Some data suggest an increased risk of severe carbamazepine-associated TEN/SJS cases in other Asian populations. Due to the prevalence of this allele in other Asian populations (e.g. over 15% in the Philippines and Malaysia), testing for the presence of the HLA-B*1502 allele in patients from genetically vulnerable populations may be considered.

The prevalence of the HLA-B*1502 allele is negligible in individuals of European descent, African and Latin American population groups as well as Japanese and Koreans (< 1%).

The identification of individuals who are HLA-B*1502 allele positive and therefore not treated with carbamazepine, reduced the incidence of carbamazepine-induced SJS/TEN.

Limitation of genetic testing
Genetic testing can never replace careful medical care. Many Asian patients who are HLA-B*1502 positive and treated with carbamazepine do not develop SJS/TEN and patients who are HLA-B*1502 negative can still develop SJS/TEN. Likewise, many HLA-A*3101 positive patients will not develop SJS, TEN, DRESS, AGEP, or maculopapular rash despite treatment with carbamazepine, and patients from any ethnic group who have tested negative for HLA-A*3101, can still develop these severe skin reactions. The role of possible other factors in the development and morbidity of this severe skin reaction such as AED dosage, compliance, concomitant use of other medicinal products and the level of dermatological monitoring have not been evaluated.

Other skin reactions
Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are
usually transient and not dangerous. They usually resolve within a few days or weeks, either with continued therapy or after dose reduction. However, because it can be difficult to distinguish the early signs of severe skin reactions from those of mild and transient skin reactions, the patient should be kept under close observation and immediate discontinuation should be considered should skin reactions worsen with continued use.

It has been observed that the HLA-A*A3101 allele is associated with less severe skin reactions caused by carbamazepine and may predict the risk of carbamazepine side effects such as anticonvulsant drug hypersensitivity syndrome or non-serious rash (maculopapular rash). The HLA-B*1502 allele is not predictive for the occurrence of the skin reactions listed above.

Hypersensitivity reactions
Carbamazepine can trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a delayed multi-organ hypersensitivity reaction with fever, rash, vasculitis, lymph node swelling, arthralgia, leukopenia, eosinophilia, enlargement of the liver and spleen, abnormal liver function tests and vanishing bile duct syndrome (destruction and loss of the intrahepatic bile ducts), which can occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, heart muscle, colon) (see section 4.8 Undesirable Effects).

It has been observed that the HLA-A*3101 allele is associated with the occurrence of hypersensitivity syndrome, including maculopapular rash.

Patients who have demonstrated hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of these patients may experience hypersensitivity reactions to oxcarbazepine.

A cross-reaction can occur with carbamazepine and aromatic antiepileptic drugs (e.g., phenytoin, primidone, phenobarbital).

If signs or symptoms of a hypersensitivity reaction occur, carbamazepine should be discontinued immediately.

Seizures
Since carbamazepine can cause absences or intensify existing ones, carbamazepine should not be used in patients who suffer from absences or mixed forms of epilepsy that include them. In these constellations, carbamazepine could lead to seizure exacerbation.

If seizures exacerbate, carbamazepine should be discontinued.

Liver function
Liver values must be checked before and during treatment with carbamazepine; assessment is recommended before starting treatment, then at weekly intervals during the first month of treatment, then at monthly intervals thereafter. This is especially true for patients with a history of liver disease or for elderly patients. After 6 months of treatment, checks 2 to 4 times a year are sometimes sufficient.

Patients must be instructed to seek medical attention immediately if symptoms of hepatitis such as fatigue, loss of appetite, nausea, yellowing of the skin, enlargement of the liver occur. If hepatic dysfunction worsens or florid liver disease occurs, carbamazepine should be discontinued immediately.

Kidney function
It is recommended that urinary status and urea nitrogen be measured before and regularly during treatment with carbamazepine.

Hyponatremia
Hyponatremia is known to occur with the use of carbamazepine. In patients with pre-existing renal disease associated with low serum sodium levels or in patients taking concomitant sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), the serum sodium concentration should be determined prior to treatment. Thereafter, serum sodium levels should be measured initially after approximately two weeks and then at monthly intervals for the first three months of treatment or as clinically necessary. The risk factors mentioned above occur particularly in elderly patients. If hyponatremia is detected, fluid restriction is an important countermeasure when clinically indicated.

Hypothyroidism
Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction, necessitating an increase in the dose of thyroid hormone replacement therapy in patients with hypothyroidism. Therefore, monitoring of thyroid function is recommended to adjust the dosage of thyroid hormone replacement therapy.

Anticholinergic effects
Carbamazepine has weak anticholinergic activity. Patients with glaucoma (glaucoma) and urinary retention should therefore be carefully monitored during treatment (see section 4.8 Undesirable effects).

Psychiatric Reactions
The possibility of activation of latent psychoses and, especially in elderly patients, the occurrence of states of confusion or agitation should always be taken into account.

Suicidal thoughts and suicidal behavior
Suicidal ideation and behavior have been reported in patients treated with antiepileptic medicinal products for various indications. A meta-analysis of randomized placebo-controlled trials of antiepileptic drugs also showed a slightly increased risk for the occurrence of suicidal ideation and behavior. The mechanism for triggering this side effect is not known and the available data do not exclude the possibility of an increased risk when taking carbamazepine.

Therefore, patients should be monitored for signs of suicidal ideation and behavior and appropriate treatment should be considered. Patients (and their caregivers) should be advised to seek medical help if signs of suicidal thoughts or behavior occur.

Women of childbearing potential
Carbamazepine may cause foetal harm when administered to a pregnant woman. Prenatal exposure to carbamazepine may increase the risk of major congenital malformations and other adverse developmental effects (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 women 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 (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.

Hormonal contraceptives
Breakthrough bleeding has been reported in patients treated with carbamazepine and using hormonal contraceptives (the "pill") at the same time. The reliability of hormonal contraception with estrogen and/or progesterone derivatives can be negatively influenced or even eliminated due to the enzyme-inducing properties of carbamazepine. Therefore, alternative, non-hormonal methods of contraception should be recommended to women of childbearing potential (see section 4.6).

Sexual dysfunction
There have been isolated cases of sexual dysfunction, such as impotence or decreased libido (see section 4.6).

Plasma level monitoring

Although the correlation between carbamazepine dose and plasma level on the one hand and between plasma level and clinical efficacy or tolerability on the other hand is very doubtful, plasma level monitoring can be useful in the following cases: noticeable increase in the frequency of seizures, checking patient compliance, during pregnancy, when treating children or adolescents, when resorption disorders are suspected, when toxic effects are suspected, when several drugs are given concomitantly (see section 4.5 Interaction with other medicinal products and other forms of interaction).

Carbamazepine is a potent inducer of drug metabolising enzymes and transporters, which may decrease plasma concentration and clinical effect of concomitantly administered substances. Monitoring of effect or plasma concentration of concomitantly used substances is recommended during the first weeks when starting carbamazepine, and also when discontinuing carbamazepine (see section 4.5).

Administration along with lithium
If carbamazepine is to be given together with lithium in exceptional cases for the prophylaxis of manic-depressive phases when lithium alone is insufficiently effective, to avoid undesirable interactions (see Section 4.5), care must be taken to ensure that a certain plasma concentration of carbamazepine is not exceeded (8 micrograms/ml), to maintain the lithium level in a low therapeutic range (0.3 to 0.8 mval/L) and to avoid treatment with neuroleptics longer than 8 weeks ago or taken at the same time.

Photosensitisation
Due to the possibility of photosensitization, patients should protect themselves from strong sunlight exposure during treatment with carbamazepine.

Dose reduction and withdrawal effects
Abrupt discontinuation of carbamazepine can lead to seizures. Therefore, carbamazepine should be discontinued gradually over a period of 6 months. If it is necessary to change the treatment of patients with epilepsy who are being treated with carbamazepine, the change must not be made suddenly, but the changeover to treatment with a different antiepileptic drug must be done gradually. If an abrupt switch from carbamazepine to another antiepileptic drug is necessary in epilepsy patients, this should be done under protection with appropriate medication.

Laboratory controls
Due to the above-mentioned possible side effects and hypersensitivity reactions, blood counts, kidney and liver function and carbamazepine levels as well as the plasma concentrations of the other antiepileptic drugs in combination therapy, should be checked regularly, especially in long-term therapy, and the daily doses should be reduced if necessary.

Falls
Carbamazepine treatment may be associated with ataxia, dizziness, somnolence, hypotension, confusional state and sedation (see section 4.8 Undesirable effects). This can lead to falls, resulting in fractures or other injuries. A comprehensive fall risk assessment should be considered in patients with diseases, conditions, or medications that could increase these effects. This should be done repeatedly in patients on long-term treatment with carbamazepine.

<u>Lactose</u>
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The use of carbamazepine in combination with monoamine-oxidase inhibitors (**MAO inhibitors**) is not recommended. therefore, treatment with **MAO** inhibitors must be stopped at least 2 weeks before starting treatment with carbamazepine.

Influence of carbamazepine on the plasma concentration of other drugs:
Carbamazepine induces the cytochrome P450 system (predominantly the isoenzyme CYP3A4) and other phase I and phase II enzyme systems in the liver, so that the plasma concentrations of substances that are primarily metabolized by CYP3A4 are reduced and these may become ineffective under certain circumstances. Your dose may need to be adjusted according to clinical needs.

This applies, for example, to:

Analgesics, anti-inflammatory substances: buprenorphine, fentanyl, methadone, paracetamol (long term use of carbamazepine and paracetamol (acetaminophen) may result in hepatotoxicity), phenazone, tramadol.

Antihelmintics: praziquantel, albendazole.

Anticoagulants: warfarin, phenprocoumon, dicoumarol, acenocoumarol, rivaroxaban, dabigatran, apixaban and edoxaban.

Antidepressants: bupropion, citalopram, mianserin, nefazodone, sertraline, trazodone (however, it appears that the antidepressant effect of trazodone is increased).
Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, clomipramine.

Antiemetics: aprepitant.

Other Anticonvulsantss: clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. In order to avoid phenytoin intoxication and sub-therapeutic concentrations of carbamazepine, it is recommended to adjust the plasma concentration of phenytoin to 13 microgram/ml before starting the additional treatment with carbamazepine.

Antifungals: caspofungin, azole-type antifungals: e.g. itraconazole, voriconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.

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

Anxiolytics: alprazolam, midazolam, clobazam.

Bronchodilators or Anti-asthmatics: theophylline.

Immunosuppressants: ciclosporin, tacrolimus, sirolimus, everolimus.

Cardiovascular Drugs: calcium antagonists (dihydropyridine group e.g. felodipine), digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.

Hormonal contraceptives (alternative contraceptive methods should be considered).

Corticosteroids: e.g. prednisolone, dexamethasone.

Typical Neuroleptics: haloperidol and bromperidol,
Atypical Neuroleptics: clozapine, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone.

Thyroid Hormones: levothyroxine.

Tetracyclines: e.g. doxycycline.

Cytostatics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

Other: quinidine, oestrogens, methylphenidate, progesterone derivatives, propranolol, flunarizine, rifabutin.

Drugs used to treat erectile dysfunction: tadalafil.

When taking the "tablet", sudden bleeding between periods can occur, in addition to the reduced effectiveness of the hormonal contraceptives. Therefore, other, non-hormonal contraceptive methods should be recommended.

The plasma concentration of phenytoin can be both increased and decreased by carbamazepine, which in exceptional cases can lead to confusional states and even coma.

Carbamazepine may decrease plasma levels of bupropion and increase that of the metabolite hydroxybupropion, thereby reducing the clinical efficacy and safety of bupropion.

Carbamazepine may decrease plasma levels of trazodone, but appears to increase the antidepressant effect of trazodone.

Carbamazepine may accelerate the metabolism of zotepine.

Decreased plasma concentration of carbamazepine
Carbamazepine is metabolised by the cytochrome P450 system (mainly by the isoenzyme CYP3A4). Inducers of CYP3A4 could therefore increase carbamazepine metabolism and thereby possibly lead to a decrease in carbamazepine plasma concentrations and therapeutic effect. Conversely, after stopping a CYP3A4 inducer, there could be a reduced metabolism of carbamazepine and consequently an increase in carbamazepine plasma concentrations. A reduction in the carbamazepine plasma concentration is possible, e.g. with the following substances (arranged according to substance class):

Other Anticonvulsants: felbamate, methosuximide, oxcarbazepine, phenobarbital, phensuximide, phenytoin (to avoid phenytoin intoxication and sub-therapeutic concentrations of carbamazepine, it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms/ml before starting the additional treatment with carbamazepine), fosphenytoin, primidone, progabide and possibly (here the data are partially contradictory) clonazepam, valproic acid, valpromide.

Tuberculosis drug: rifampicin.

Bronchodilators or Anti-Asthmatics: theophylline, aminophylline.

Dermatics: isotretinoin.

Cytostatics: cisplatin, doxorubicin.

Other: St John's wort (Hypericum perforatum).

On the other hand, the plasma levels of the pharmacologically active metabolite carbamazepine-10, 11-epoxide can be increased by valproic acid and primidone.

Administration of felbamate can reduce the plasma level of carbamazepine and increase that of carbamazepine-10, 11-epoxide, while at the same time the felbamate level can be reduced.

Due to the mutual influence, especially when several antiepileptic drugs are administered at the same time, it is recommended to monitor the plasma levels and, if required, to adjust the dosage of carbamazepine.

Increased plasma concentration of carbamazepine and/or carbamazepine-10, 11-epoxide
Carbamazepine is primarily metabolized by cytochrome P-450 3A4 (CYP3A4) to the active metabolite, carbamazepine-10, 11-epoxide. The concomitant use of inhibitors of CYP3A4 can therefore lead to an increase in carbamazepine plasma concentrations, which can result in side effects.

Elevated plasma levels of carbamazepine can lead to the symptoms mentioned in section 4.8 (e.g. dizziness, drowsiness, unsteady gait, double vision). Therefore, if such symptoms occur, the carbamazepine plasma concentration should be monitored and the dose should be reduced if required.

The plasma concentration of carbamazepine can be increased, e.g. by the following substances (arranged according to substance class):

Analgesics, anti-inflammatory substances: dextropropoxyphene/propoxyphene, ibuprofen.

Androgens: danazol.

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

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

Other anticonvulsants: stiripentol, vigabatrin.

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.

Antihistamines: loratadine, terfenadine.

Tuberculosis medicine: isoniazid.

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

Carbonic anhydrase inhibitors (diuretics): acetazolamide.

Calcium antagonists: diltiazem, verapamil.

Muscle relaxants: oxybutynin, dantrolene.

Neuroleptics: loxapine, olanzapine, quetiapine.

Platelet aggregation inhibitor: ticlopidine.

Ulcer therapeutics: omeprazole, possibly cimetidine.

Other: grapefruit juice, nicotinamide (in high doses).

Increased plasma concentration of the active metabolite carbamazepine-10,11-epoxide:
Human microsomal epoxide hydrolase has been identified as the enzyme involved in the formation of the 10, 11-trans diol from carbamazepine-10, 11-epoxide. Concomitant administration of human microsomal epoxide hydrolase inhibitors may therefore lead to increased plasma concentrations of carbamazepine-10, 11-epoxide.

Increased plasma levels of carbamazepine-10, 11-epoxide can lead to the symptoms mentioned in section 4.8 (e.g. dizziness, drowsiness, unsteady gait, double vision). Therefore, if such symptoms occur, the plasma concentration should be monitored and the dose should be adjusted if necessary when the following substances are co-administered:

Loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide, valpromide and brivaracetam.

Other interactions that require special attention:
Concomitant use of carbamazepine and levetiracetam may increase carbamazepine-induced toxicity.

The liver toxicity of isoniazid can be increased by carbamazepine.

The simultaneous use of carbamazepine and lithium or metoclopramide on the one hand and neuroleptics (Haloperidol, Thioridazine) on the other hand can promote the occurrence of neurological side effects. In patients treated with neuroleptics, it should be noted that carbamazepine can reduce the plasma level of these drugs and thereby cause a worsening of the clinical picture. A dose adjustment of the respective neuroleptic may be required.

It should be noted that the simultaneous use of lithium and carbamazepine in particular can increase the neurotoxic effects of both active substances, even in the presence of therapeutic lithium levels. Therefore, careful monitoring of blood levels of both is required. A previous treatment with neuroleptics should be more than 8 weeks ago and not take place at the same time. The following signs of neurotoxic symptoms should be observed: Unsteady gait, ataxia, horizontal nystagmus, increased muscle reflexes, muscle twitching (muscle fasciculations).

The combined administration of carbamazepine and some diuretics (hydrochlorothiazide, furosemide) can lead to symptomatic hyponatraemia.

The effectiveness of non-depolarising muscle relaxants such as pancuronium can be impaired by carbamazepine. As a result, the neuromuscular blockade can be removed more quickly. Patients treated with muscle relaxants should be monitored for this and the dose of these drugs should be increased if required.

Like other psychoactive substances, carbamazepine can reduce the pateint's alcohol tolerance. Therefore, patients should not drink alcohol during treatment.

Concomitant administration of carbamazepine and direct-acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma levels of the direct-acting oral anti-coagulants. Please refer to the following table for more details:

Direct-acting oral anticoagulants (DOAC)	**Recommendations for concomitant use of DOAC and carbamazepine**
Apixaban	In the prophylaxis of venous thromboembolism (VTE) after elective hip or knee replacement surgery, in the prophylaxis of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) as well as in the prophylaxis of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE), concomitant use should only be done with caution. Concomitant 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 only be done with caution.

There are indications in the literature that the additional intake of carbamazepine in the case of pre-existing neuroleptic therapy increases the risk of the occurrence of a neuroleptic malignant syndrome or Stevens-Johnson syndrome.

If isotretinoin (active ingredient for acne treatment) and carbamazepine are administered at the same time, the carbamazepine plasma level should be monitored.

Concomitant administration of carbamazepine with paracetamol can reduce the bioavailability of paracetamol.

Carbamazepine appears to increase the elimination of thyroid hormones and increase the need for them in patients with hypothyroidism. For this reason, the thyroid parameters should be determined at the start and end of treatment with carbamazepine in patients who are receiving substitution therapy. If necessary, a dose adjustment of the thyroid hormone preparations should be made. In particular, concomitant treatment with carbamazepine and other anticonvulsants (e.g. phenobarbital) may change thyroid function.

The concomitant administration of antidepressants of the serotonin reuptake inhibitor type (e.g. fluoxetine) can lead to toxic serotonin syndrome.

It is recommended not to use carbamazepine in combination with nefazodone (an antidepressant), as carbamazepine can lead to a significant reduction in the nefazodone plasma level up to a loss of efficacy. In addition, when nefazodone and carbamazepine are taken at the same time, the carbamazepine plasma level increases and that of its active degradation product, carbamazepine-10, 11-epoxide, decreases.

Concomitant use of carbamazepine and anti-arrhythmics, cyclic antidepressants, or erythromycin increases the risk of cardiac conduction disorders.

Impairment of serological examinations
By interfering with the HPLC analysis, carbamazepine can lead to false positive perphenazine concentrations.

Carbamazepine and its 10, 11-epoxide metabolite can cause false positive concentrations of tricyclic antidepressants in fluorescence polarisation immunoassays.

4.6 Fertility, Pregnancy and lactation

Women of childbearing potential
Carbamazepine should not be used in women of childbearing potential unless the potential benefits outweigh the risks after careful consideration of alternative appropriate treatment options. The woman should be fully informed of the risks of possible harm to the foetus when taking carbamazepine during pregnancy and understand the importance of planning a pregnancy. A pregnancy test should be considered before starting treatment with carbamazepine in women of childbearing potential.

Women of childbearing potential must use effective contraception during treatment and for two weeks after stopping treatment. Due to enzyme induction, carbamazepine can lead to failure of the therapeutic effect of hormonal contraceptives (see section 4.5). Therefore, women of childbearing potential should be counseled about the use of other reliable methods of contraception. At least one reliable method of contraception (such as an intrauterine device) or two complementary methods of contraception, including a barrier method, should be used. When choosing the contraceptive method, the individual circumstances should be evaluated in each case and the patient should be included in the discussion.

Pregnancy
Risk related to antiepileptic medicinal products 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.

Risks related to carbamazepine

Carbamazepine 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 suggests 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 re-assess 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 first three months of pregnancy, which are particularly prone to malformations, and especially between days 20 and 40 post-fertilisation, the lowest effective dose should be used because malformations are likely to be caused by high plasma concentrations. Monitoring of plasma levels is recommended. It should be in the lower part of the therapeutic range (3 to 7 micrograms/ml). At a dose of < 400 mg carbamazepine per day, malformation rates are lower than at higher doses. A few cases of convulsions and/or respiratory depression in newborns have been reported with the use of carbamazepine and other antiepileptic drugs, as well as some cases of vomiting, diarrhoea and/or reduced feeding. These could be signs of withdrawal syndrome in the newborn.

Breast-feeding
Carbamazepine and its active metabolite are excreted in breast milk **(**milk/plasma concentration ratios of 0.24 to 0.69). However, the benefits of breast-feeding should be weighed against the small risk of side effects in the infant. Carbamazepine may be taken during breast-feeding, provided the breast-fed infant is observed for possible adverse effects (decreased weight gain, sedation, allergic skin reactions). If such effects occur, breastfeeding should be discontinued. There have been a few reports of cholestatic hepatitis in neonates exposed to carbamazepine prenatally or during breastfeeding. Therefore, breast-fed infants whose mothers are being treated with carbamazepine should be carefully monitored for adverse hepatobiliary side effects.

Fertility
There have been isolated cases of sexual dysfunction, such as impotence or decreased libido.

There have been very rare reports of decreased male fertility and/or abnormal spermatogenesis. Effects on ability to drive and use machines.

4.7 Effects on ability to drive and use machines

Due to the occurrence of central nervous side effects such as dizziness, drowsiness, fatigue, ataxia, double vision, accommodation disorders and blurred vision, at the beginning of treatment or in higher doses and/or when taking other medicines that also affect the central nervous system, carbamazepine can, even when used as intended, alter the ability to react - irrespective of the effect of the underlying condition being treated - to such an extent that, for example, the ability to participate actively in road traffic or operate machinery or work without a safe footing is reduced. This applies even more in combination with alcohol.

4.8 Undesirable effects

The observed side effects occurred less frequently with the administration of carbamazepine alone (monotherapy) than with concomitant administration of other antiepileptic drugs (combination therapy).

Some of the side effects occur very commonly or frequently, depending on the dose, especially at the beginning of treatment, with too high initial dose or in elderly patients, such as central nervous disorders (dizziness, headache, ataxia, drowsiness, sedation, double vision); gastrointestinal disorders (nausea, vomiting) and allergic skin reactions.

Dose-related side effects usually resolve on their own within a few days or after a temporary dose reduction. Therefore, carbamazepine should be dosed gradually if possible. Central nervous adverse reactions may be a manifestation of relative overdose or significant fluctuations in plasma levels; therefore, it is recommended that plasma levels be determined in these cases.

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

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Not known (cannot be estimated from the available data)

System organ class	**Adverse drug reactions**
Infections and infestations	
*Not known***	Reactivation of human herpes virus 6 infection.
Blood and the lymphatic system disorders	
Very common	Leukopenia. According to literature, benign leukopenia occurs most commonly, in about 10% cases it is transient and in 2% persistent. Benign leukopenia occurs mainly within the first four month of therapy.
Common	Thrombocytopenia, eosinophilia.
Rare	Leucocytosis, lymphadenopathy.
Very rare	Agranulocytosis, aplastic anaemia, pancytopenia, erythrocyte aplasia, anaemia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia, spleen enlargement.
Not known	Bone marrow depression
Immune system disorders	
Uncommon	A delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (progressive cholestatic hepatopathy with destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon).
Very rare	Acute allergic general reactions, anaphylactic reactions, angioedema, hypogammaglobulinaemia.
*Not known***	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).
Endocrine disorders	
Common	Oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases

	to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders.
Very rare	Galactorrhoea, gynaecomastia,
Metabolism and nutrition disorders	
Rare	Folic acid deficiency, decreased appetite.
Very rare	Porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).
*Not Known***	Hyperammonemia
Psychiatric disorders	
Uncommon	In elderly patients, states of confusion and restlessness (agitation).
Rare	Hallucinations (visual or auditory), depression, depressed or manic moods, restlessness, aggressive behaviour.
Very rare	Activation of latent psychoses, mood changes such as phobic disorders, difficulty thinking, impaired drive.
Nervous system disorders	
Very common	Ataxia (atactic and cerebellar disorder), dizziness, somnolence, sedation drowsiness
Common	Headache, double vision
Uncommon	Involuntary movements (e.g. tremor, asterixis, dystonia, tics), oculomotor disorders associated with nystagmus.
Rare	Dyskinesia, disorders such as orofacial dyskinesia, choreoathetosis (involuntary movements in the mouth and face area such as grimacing, screwed movements), speech disorders (e.g. dysarthria or slurred speech), polyneuropathy, peripheral neuritis, neuropathy peripheral, paraesthesia, and paresis.
Very rare	Neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
*Not known***	Memory impairment.
There is evidence that carbamazepine can lead to worsening of symptoms of multiple sclerosis. As with use of other medications for seizure disorder, carbamazepine can lead to seizure frequency: in particular, absences can be intensified or newly occurring.	
Eye disorders	
Common	Accommodation disorders (e.g. blurred vision)
Very rare	Lens opacification, conjunctivitis. Retinotoxicity associated with long term carbamazepine therapy was reported in two patients, which resolved after carbamazepine discontinuation.
Ear and labyrinth disorders	
Very rare	Hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac disorders	
Uncommon	Conduction disorders, AV block in isolated cases with syncope.
Uncommon to rare	Bradycardia, cardiac arrhythmia, heart failure, worsening of pre- existing coronary artery disease.
Vascular disorders	
Rare	Hypertension or hypotension.
Very rare	Circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis.
Respiratory, thoracic and mediastinal disorders	

Very rare	Hypersensitivity reactions of the lungs with fever, dyspnea and pneumonitis or pneumonia (alveolitis), isolated cases of pulmonary fibrosis have been described in literature.
Gastrointestinal disorders	
Very common	Vomiting, nausea.
Common	Loss of appetite, dry mouth,
Uncommon	Diarrhoea, constipation.
Rare	Abdominal pain.
Very rare	Inflammation of the mucous membranes in the mouth and throat area (glossitis, stomatitis, gingivitis), pancreatitis.
*Not known***	Colitis
Hepatobiliary disorders	
Rare	Various forms of Hepatitis (cholestatic, hepatocellular or mixed type), vanishing bile duct syndrome, jaundice, life – threatening acute hepatitis, especially within the first month of therapy, liver failure.
Very rare	Granulomatous liver disease.
Skin and subcutaneous tissue disorders	
Very common	Allergic skin reactions with and without fever, such as urticaria (also very severe).
Uncommon:	Dermatitis exfoliative, erythroderma.
Rare	Disseminated lupus erythematosus, pruritus.
Very rare	Stevens-Johnson syndrome*, Lyell's syndrome (toxic epidermal necrolysis), photosensitivity reaction, exudative erythema multiforme and nodosum, pigmentation disorder, purpura, acne, increased sweating, alopecia, hirsutism and vasculitis have been reported very rarely, but the causal relationship is unclear,
*Not known***	Acute Generalised Exanthematous Pustulosis (AGEP)**, lichenoid keratosis, onychomadesis.
There is increasing evidence for an association between gene markers and the occurrence of adverse drug reactions of the skin such as SJS, TEN, DRESS, AGEP, and maculopapular rash. In Japanese and European patients, an association has been reported between these reactions and the use of carbamazepine in the presence of the HLA-A*3101 allele. Another marker, the allele HLA-B*1502, has been shown to have a strong association with the occurrence of SJS and TEN in Han Chinese, Thai, and some other Asian populations (see Sections 4.2 and 4.4 for further information).	
Musculoskeletal, connective tissue and bone disorders	
Rare	Muscular weakness.
Very rare:	Disturbance in bone metabolism (decreased serum calcium and decreased 25-OH-cholecalciferol), which occasionally led to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms/cramps.
*Not known***	Fractures.
There are case reports of decrease in bone density accompanied by osteoporosis to pathological fractures in patients who have used carbamazepine for a long time. The mechanism by which carbamazepine affects bone metabolism is not known.	
Renal and urinary tract disorders	
Uncommon	Renal dysfunction (e.g. albuminuria, hematuria, oliguria, increased blood urea nitrogen/azotaemia).

Very rare	Tubulointerstitial nephritis, renal failure, other urinary disorders (e.g. frequent urination, dysuria, pollakiuria, urinary retention).
Reproductive system	
Very rare	Sexual dysfunction, decreased libido, erectile dysfunction, decreased male fertility, and /or abnormal spermiogenesis (decreased sperm count and/or motility).
General disorders and administration site conditions	
Very Common	Fatigue.
Investigations	
Very common	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant.
Common	Increase in blood alkaline phosphatase.
Uncommon	Increase in transaminases.
Very rare	Intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased TSH in the blood, usually without clinical symptoms, increased free cortisol in the serum, increased prolactin level in the blood.
There is evidence of decreased vitamin B12 levels and increased serum homocysteine levels.	
Injury, poisoning and procedural complications	
*Not known***	Fall (associated with carbamazepine treatment-induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4 warning and precautions)

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

** Spontaneous reports and cases in the literature of adverse reactions (frequency cannot be estimated from the available data).

Additional adverse drug reactions from spontaneous reports (frequency not known)
In post-marketing experience with carbamazepine, side effects have been identified through spontaneous reporting and literature. Since the reports were voluntary and from an unknown population size, the frequency cannot be estimated from the available data.

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 at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Any assessment of intoxication must also consider the possibility of multiple intoxications due to possible ingestion of several drugs, for example with suicidal intent.

Carbamazepine intoxications usually occur at very high doses (4 to 20 g), with plasma levels always above 20 micrograms/ml. Accidental or suicidal ingestions with plasma concentrations of 38 micrograms/ml have been survived.

Intoxications (following ingestion of carbamazepine with suicidal intent or accidental ingestion) have been reported in the literature, some with lethal outcomes.

Symptoms of an overdose
In the event of an overdose with Carbamazepine, the symptoms mentioned in section 4.8 may become more pronounced. Normally, the central nervous system, the cardiovascular system and the respiratory system are affected in the event of overdoses.

Central nervous system:
CNS depression, disturbances in consciousness (drowsiness, somnolence, stupor, coma), dizziness, disorientation, restlessness, agitation, confusion, hallucinations, blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, reflex abnormalities (first increased then decreased reflexes), tonic-clonic convulsions, seizures, psychomotor disturbances, myoclonus, opisthotonus, involuntary movements, tremor, hypothermia, flushing, mydriasis, EEG dysrhythmias.

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

Cardiovascular system:
Usually hypotonic blood pressure values (possibly also hypertension), conduction disturbances, ECG changes (arrhythmias, with prolongation of the QRS complex), tachycardia, syncope, AV block, cardiac arrest, flushing.

Gastro-intestinal system:
Nausea, vomiting, delayed gastric emptying, reduced intestinal motility.

Musculoskeletal system:
There have been a few cases where rhabdomyolysis has been reported in association with carbamazepine toxicity.

Renal system:
Urinary retention, oliguria or anuria, fluid retention, water intoxication due to ADH-like effect.

Laboratory findings:
Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle creatine phosphokinase, leukocytosis, leukopenia, neutropenia, glycosuria, acetonuria.

Therapeutic measures in case of overdose
A specific antidote for intoxication with carbamazepine does not yet exist.

Therefore, treatment is symptomatic: hospitalization, determination of carbamazepine levels to confirm carbamazepine intoxication and to determine the extent of the overdose.

Removal of the noxious agent as quickly as possible (gastric emptying, gastric lavage) and reduction of resorption (administration of e.g. activated charcoal or a laxative). Delayed gastric emptying may result in delayed absorption. This may result in the patient's condition deteriorating again during recovery from intoxication.

Vital signs must be assured under clinical conditions; plasma concentrations and cardiac function must be checked, and careful correction of electrolyte balance may be necessary.

Haemoperfusion with activated charcoal was recommended. Haemodialysis is an effective way of treating carbamazepine overdose.

A possible deterioration of symptoms on days 2 and 3 day due to delayed absorption, should be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; Dibenzazepine derivative.

ATC Code: N03AF01.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

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

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

5.2 Pharmacokinetic properties

Absorption
Carbamazepine is (depending on the dosage form) relatively slowly and almost completely absorbed after oral administration.

The absorption half-life is 8.5 hours on average and shows large intra-individual differences (approx. 1.72 to 12 hours).

After a single dose (depending on the dosage form), the maximum plasma concentrations are reached in adults after 4 to 16 hours (very rarely up to 35 hours) and in children about 4 to 6 hours. The plasma levels are not linearly dependent on the dose and show a flat curve in the higher dose range.

The plasma levels are lower after administration of prolonged-release tablets.

Steady state is reached after 2 to 8 days. There is no close correlation between the dose of carbamazepine and the plasma concentration at steady state.

At steady-state, fluctuations in plasma levels of carbamazepine and its metabolite carbamazepine-10,11-epoxide are small at the 8-hour and 12-hour dosing intervals, respectively.

With regard to therapeutic and toxic plasma concentrations, literature reports indicate that relief from seizure can be achieved at plasma levels of 4 to 12 micrograms/ml. Exceeding the plasma level of 20 micrograms/ml led to a worsening of the clinical picture. Pain relief in trigeminal neuralgia is achieved at plasma concentrations of 5 to 18 micrograms/ml.

The threshold concentration for the occurrence of side effects is approximately 8 to 9 micrograms/ml.

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

Distribution
The volume of distribution in humans is given as values between 0.8 and 1.9 l/kg.
Plasma protein binding of carbamazepine ranges from 70% to 80%. The percentage of unbound carbamazepine is constant at concentrations up to 50 micrograms/ml. The pharmacologically active metabolite carbamazepine-10,11-epoxide is bound to plasma protein at 48 to 53% (approximately 0.74 l/kg).

Pharmacokinetic interactions are expected, see section 4.5.

The carbamazepine concentration in the CSF is 33% of the respective plasma concentration.

The carbamazepine concentration in the saliva corresponds to the concentration of the free parent substance and correlates well with the plasma level (about 20 to 30%). With the multiplier 4, it can be used to estimate the plasma level as part of therapy.

Carbamazepine crosses the placenta and is excreted in breast milk (concentration approximately 58% of that in plasma). In the breastfed infant, this can lead to plasma concentrations similar to those in breast milk.

Biotransformation
Carbamazepine is oxidized, deaminated, hydroxylated, and subsequently esterified with glucuronic acid in the liver.

To date, 7 metabolites of carbamazepine have been identified in human urine. Of these, the pharmacologically inactive metabolite trans-10,11-dihydroxy-10,11-dihydrocarbamazepine accounts for the largest proportion. The metabolite carbamazepine-10,11-epoxide is found at about 0.1 to 2%; it has anticonvulsant effects. Human microsomal epoxide hydrolase has been identified as the enzyme

responsible for the formation of the 10,11-trans diol from carbamazepine-10,11-epoxide.

Elimination
After single doses, carbamazepine is eliminated from plasma with a half-life of approximately 36 hours (range: 18 to 65 h).

With long-term therapy, the half-life decreases by about 50% (10 to 20 hours) as a result of enzyme induction. Half-lives are shorter (on average 6 to 10 hours) in combination therapy with other antiepileptic drugs than in monotherapy (11 to 13 hours); shorter in children than in adults, longer in newborns than in infants.

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

After administration of a single oral dose of 400mg carbamazepine, 72% is excreted in the urine and 28% in the faeces, partially in unchanged form. In the urine, about 2 to 3 % of the dose is recovered as unchanged drug.

Special populations
Paediatric populations
Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

Elderly population (65 years or above)
There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

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

5.3 Preclinical safety data

Preclinical data show no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential.
However, animal studies were insufficient to rule out the teratogenic effects of carbamazepine.

Carcinogenicity
In a 2-year carcinogenicity study in rats with carbamazepine, increased incidences of hepatocellular tumors in females and benign testicular tumors in males were observed. However, there is no evidence that these observations are relevant to therapeutic use in humans.

Genotoxicity
Various standard mutagenicity studies in bacteria and mammals revealed no evidence of carbamazepine genotoxicity.

Reproductive toxicity

The cumulative evidence from various animal studies in mice, rats and rabbits demonstrated that carbamazepine at doses 10 to 20 times higher than the recommended human dose during organ development resulted in increased embryonic lethality and growth retardation. Embryonic damage (mainly to the cerebral ventricles) was observed in mice. In reproduction studies in rats, the breastfed offspring demonstrated reduced weight gain at a maternal dosage level of 192mg/kg/day in the dam.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Ammonio methacrylate copolymer
Lactose monohydrate
Maize starch
Sodium starch glycolate type A
Magnesium stearate
Talc
Triethyl citrate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (Alu-PVC/PE/PVDC) packs of 30, 50, 56, 100 and 200 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Ltd
220 Butterfield Great Marlings
Luton LU2 8DL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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