SUMMARY PRODUCT CHARACTERISTIC (SmPC)

Carbamazepine
200 mg tablets

1. NAME OF THE MEDICINAL PRODUCT – Carbamazepine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 mg of Carbamazepine
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Tablet
White or off white, round biconvex, scored on one side tablets, odorless.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Epilepsy - generalised tonic-clonic and partial seizures.
Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences. The paroxysmal pain of trigeminal neuralgia.
For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

4.2 Posology and method of application
Carbamazepine is given orally, usually in two or three divided doses. Carbamazepine may be taken during, after or between meals, with a little liquid e.g., a glass of water. Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 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).

Epilepsy:
The dose of Carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of Carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre) (see warnings and precautions).
Adults: It is advised that with all formulations of Carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. Carbamazepine should be taken in a number of divided doses although initially 100- 200 mg once or twice daily is recommended. This may be followed by a slow increase until the best response is obtained, often 800-1200 mg daily. In some instances, 1600 mg or even 2000 mg daily may be necessary. Elderly: Due to the potential for drug interactions, the dosage of Carbamazepine should be selected with caution in elderly patients.

Children and adolescents: It is advised that with all formulations of Carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. Usual dosage 10-20 mg/kg bodyweight daily taken in several divided doses. Carbamazepine tablets are not recommended for very young children.

5-10 years: 400 to 600 mg daily (2-3 x 200 mg tablets per day, to be taken in divided doses).
10-15 years: 600 to 1000 mg daily (3-5 x 200 mg tablets per day, to be taken in several divided doses).
>15 years of age 800 to 1200mg daily (same as adult dose).

Maximum recommended dose
Up to 6 years of age: 35mg/kg/day
6-15 years of age: 1000mg/day
>15 years of age: 1200mg/day.
Wherever possible, anti-epileptic agents should be prescribed as the sole anti-epileptic agent but if used in

polytherapy the same incremental dosage pattern is advised. When Carbamazepine is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see 4.5 interaction with other medicaments and other forms of interaction).

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

Elderly:
Dosage in Trigeminal neuralgia
Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of Carbamazepine should be selected with caution in elderly patients.

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

For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy:
Initial starting dose of 400 mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600 mg given in divided doses is reached. The usual dosage range is 400-600 mg daily, given in divided doses.

Special populations
Renal impairment / Hepatic impairment

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

4.3 Contraindications

Known hypersensitivity to Carbamazepine or structurally related drugs (e.g., tricyclic antidepressants) or any other component of the formulation. Patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias (e.g., acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).
The use of Carbamzepine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs) (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Carbamazepine may only be done under medical supervision and, after a rigorous risk-benefit balance and the corresponding closely meshed monitoring can be applied in the case of:

– Previous or existing hematologic disorders, hematological reactions to other drugs in the history;
– Disturbed sodium metabolism;
– Heart, liver or kidney dysfunction, also in prehistory (see sections 4.2 and 4.8);
– Patients who had treatment with Carbamazepine aborted have;
– Patients with myotonic dystrophy, as in this patient group often cardiac conduction abnormalities occur.

<u>Hematological events</u>

The occurrence of agranulocytosis and aplastic anemia have been with Carbamazepine in connection; an assessment of the risk, however, is due to the very low frequency difficult. In the untreated population is the probability of the occurrence of 4.7 cases/million/year for agranulocytosis and 2.0 cases/million/year for aplastic anemia.
A temporary or permanent reduction in the platelet count or the number of white blood cells occurs under Carbamazepine occasionally to frequently. In the majority of cases this is temporary and forecast, not the start of agranulocytosis or aplastic anemia. Nevertheless, the complete blood count (including platelets, and reticulocytes and serum iron) first of all, prior to treatment with Carbamazepine , then at weekly intervals for the first month of treatment, then monthly intervals to be controlled. After 6 months of treatment in part, the 2 - to 4- times the controls in the year.

Patients should be on the early signs and symptoms of a potential hematological problem, and also on symptoms, dermatologic, and hepatic reactions made aware of it. Reactions occur, such as fever, sore throat, allergic skin reactions such as skin rash with swelling of the lymph nodes and/or flu-like illness, discomfort, ulcers in the mouth, hematoma inclination, petechial or purpura, blood in the treatment with Carbamazepine, the patient should immediately consult the doctor and the blood image can be determined. Upon the occurrence of certain blood disorders (in particular, leukocytopenia and thrombocytopenia) may be the discontinuation of Carbamazepine may be required; this is always the case, if symptoms such as allergic symptoms, fever, neck pain, or bleeding of the skin occur. Evidence of the following statements:

Short-term controls (within 1 week) required in case of:
- Fever, Infection;
- Skin rash;
- General feeling of weakness;
- Sore Throat, Mouth Ulcers;
- Rapid training blue spots;
- Increase in transaminases;
- Fall in leukocytes under 3,000/mm^3 and of granulocytes less than 1,500/mm^3;
- Fall in of platelets under 125.000/mm^3;
- Fall in of reticulocytes less than 0.3 % = 20.000/mm^3;
- Increase in serum iron about 150 micrograms %.

Discontinuation of Carbamazepine required in case of:
- Petechiae or Purpura-bleeding;
- Waste of erythrocytes under 4 million/mm^3;
- Drop in the hematocrit 32 %;
- Waste of hemoglobin below 11 g%;
- Waste of leukocytes under 2,000/mm^3 and of granulocytes less than 1,000/mm or the platelets under 80,000/mm^3;
- Symptomatic blood disorders.

Severe skin reactions
Cases of life-threatening skin reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been associated with the use of Carbamazepine have been reported. The patients should be about the signs and symptoms of these severe side effects informed and followed up for the occurrence of skin reactions to be monitored. The risk for occurrence of SJS or TEN is within the first weeks of treatment at the highest.
If signs or symptoms for a SJS or TEN occur (e.g., progressive skin rash often with blisters or accompanying mucosal lesions), the therapy with Carbamazepine will be terminated. The history of SJS and TEN is crucial for the early diagnosis and immediate discontinuation of the suspect drug is determined, i.e., early weaning improved the prognosis. After the occurrence of SJS or TEN in connection with the application of Carbamazepine the patient never again with Carbamazepine to be treated.
Severe and, in some cases, fatal skin reactions such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), occur in an estimated 1 to 6 of 10,000 new users in countries with mainly Caucasian population but the risk in some Asian countries is estimated to be about 10 times higher. There

are frequent references to the fact that different HLA alleles in predisposing patients to immune-mediated adverse reactions have a role to play (see section 4.2).

*Allele HLA-A*3101 – People of European and Japanese descent*

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 generalized 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. HLAA*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 Northern 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 or Japanese origin are known to the allele HLAA* 3101 wear, the application of Carbamazepine be considered, if the expected benefit is greater than the risk.

Allele HLA-B*1502 in Han Chinese, Thai and other Asian populations.

It has been demonstrated that the presence of the allele HLA-B*1502 in individuals of Han Chinese or Thai countries descended, with the risk of occurrence of serious skin reactions, and of the Stevens-Johnson syndrome, is connected. The prevalence of carriers of the HLA-B*1502 allele is Han Chinese and Thai people, approximately 10 %. These individuals should be before the start of therapy with Carbamazepine genetically on this allele examined, if this is somehow possible (see section 4.2). If the Test is positive, treatment with Carbamazepine will not be started unless there is no alternative treatment available. Tested persons in whom no HLA-B*1502 was found to have a low risk for the occurrence of Stevens-Johnson syndrome; however, these reactions occur rarely. Some of the data in other Asian population groups at increased risk of serious Carbamazepine-associated TEN/SJS cases. Due to the prevalence of this allele in other Asian populations (e.g., above 15 % in the Philippines and Malaysia) can be considered to be patients from genetically vulnerable groups of the population to the presence of the allele HLAB* 1502 testing. The prevalence of the allele HLA-B*1502 is negligible in people from European descent, in tested, African and Latin American demographic groups, and in Japanese and Koreans (< 1 %).

The identification of the Individual, the HLA-B*1502 allele-positive and, therefore, not with Carbamazepine therapy were, reduced the incidence of Carbamazepine induced SJS/TEN.

Limitation of genetic testing

Genetic testing can never replace a careful medical supervision. Many Asian patients, the HLA-B*1502 positive and with Carbamazepine to be treated, will not develop SJS/TEN and patients for HLA-B*1502-negative are; however, SJS/TEN develop. Likewise, many of the HLA-A*3101-positive patients despite treatment with Carbamazepine no SJS, TEN, DRESS, AGEP or maculopapular rash develop, and patients from each ethnic group, the HLA-A*3101- negative tested are, nevertheless, these severe skin reactions develop. The role of other possible factors in the development and morbidity of these severe skin reactions, such as AED dose, compliance, concomitant use of other drugs and the level of dermatologic monitoring have not been studied.

Other skin reactions

Mild skin reactions, e.g., isolated macular or were maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either in the unaltered continuation of the therapy or after dose reduction. However, since it can be difficult, the early signs of serious skin reactions, which is easier and transient skin reactions to distinguish, the patient should be under close observation stay, and immediate discontinuation is considered, and the skin reactions in the case of continued application to deteriorate.

It has been observed that the HLA-A*3101 allele with less severe due to Carbamazepine-induced skin reactions is associated, and possibly the risk for Carbamazepine side effects such as anticonvulsant Hypersensitivity syndrome or non-serious rash (maculopapular rash) predictable power.

The HLA B*1502 allele is not predictive for the occurrence of the above-listed skin reactions.

Hypersensitivity reactions

Under Carbamazepine was about hypersensitivity reactions of the class I (immediate) reactions, including skin rash, itching, urticaria, angioedema and reports of anaphylaxis have been reported. If a patient has these reactions after treatment with Carbamazepine developed, must Carbamazepine be discontinued and an alternative treatment started.
Carbamazepine can cause allergic reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), and a delayed, several institutions concerned hypersensitivity reaction with fever, rash, vasculitis, lymphadenopathy, joint pain, leukopenia, eosinophilia, enlargement of the liver and spleen, changes in liver function tests and vanishing bile duct syndrome (destruction and loss of the intrahepatic bile ducts), in various combinations can occur. Other organs can also be affected (e.g., lung, kidney, pancreas, heart, muscle, colon) (see section 4.8 undesirable effects).
It has been observed that the HLA-A*3101 allele with the occurrence of hyper sensitivity syndrome.
Patients on Carbamazepine hypersensitivity reactions have shown, should be informed that approximately 25 to 30 % of these patients, hypersensitivity reactions to oxcarbazepine (trileptal) show.
A cross-reaction with Carbamazepine and aromatic antiepileptic drugs (e.g., phenytoin, primidone, phenobarbital) may occur.
If signs or symptoms of a hypersensitivity reaction occur, should Carbamazepine immediately be disposed of.

Seizures
As Carbamazepine can cause absences or worsen existing ones, carbamazepin should not be used in patients suffering from absences or mixed forms of epilepsy that include such. In these constellations, carbamazepin could lead to a worsening of seizures.
If seizures exacerbate, Carbamazepine should be discontinued.

Liver function
Before and during treatment with Carbamazepine, liver values must be checked; it is recommended that they be checked before starting treatment, then at weekly intervals in the first month of treatment, and then at monthly intervals. This applies in particular to patients with a history of liver disease or to elderly patients. After 6 months of treatment, 2 to 4 checks per year are sometimes sufficient.
Patients must be advised to consult a doctor immediately if symptoms of hepatitis such as fatigue, loss of appetite, nausea, yellowing of the skin, enlarged liver occur.
If liver dysfunction worsens or active liver disease occurs, Carbamazepine should be discontinued immediately.

Renal function
It is recommended to determine urinary status and urea nitrogen before and regularly during treatment with Carbamazepine.

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

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

Anticholinergic effects
Carbamazepine has shown mild anticholinergic activity; patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy (see section 4.8).

Psychiatric reactions

The possibility of activation of latent psychosis and, especially in older patients, the occurrence of mess or agitation should be borne in mind.

Suicidal ideation and behaviour
Suicidal thoughts and behaviour have been reported in patients treated with antiepileptics for various indications. A
meta-analysis of randomised, placebo-controlled trials of antiepileptics also showed a slightly increased risk of suicidal thoughts and behaviour. The mechanism of this side effect is not known and the available data do not exclude the possibility of an increased risk when taking Carbamazepin.
Therefore, patients should be monitored for signs of suicidal thoughts and behaviour and appropriate treatment should be considered. Patients (and their carers) should be advised to seek medical help if signs of suicidal thoughts or behaviour occur.

Pregnancy and women of childbearing potential
Carbamazepine can cause fetal harm when used during pregnancy. 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 benefits outweigh the risks after careful evaluation of alternative appropriate treatment options.

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

Before initiating treatment with Carbamazepine in women of childbearing potential, a pregnancy test should be considered.

Women of childbearing potential must use an effective method of contraception during treatment and for two weeks after treatment has been stopped. Due to enzyme induction, Carbamazepine may cause failure of the therapeutic effect of hormonal contraceptives; therefore, women of childbearing potential should be advised to use other reliable methods of contraception (see below under the heading “Hormonal contraceptives” and sections 4.5 and 4.6).

Women of childbearing potential should be advised to consult their doctor as soon as they plan to become pregnant in order to discuss switching to alternative treatment before conception and before stopping contraception (see section 4.6).

Women of childbearing potential should be advised to contact their doctor immediately if they become pregnant or think they may be pregnant and are taking Carbamazepine.

Hormonal contraceptives
Breakthrough bleeding has been reported in patients treated with Carbamazepin who were also using hormonal contraceptives (the “pill”). 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 Carbamazepin. Therefore, other, non-hormonal methods of contraception should be recommended to women of childbearing age (see section 4.6).

Plasma level monitoring
Although the correlation between the dose of Carbamazepine and plasma levels on the one hand and between plasma levels 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, if absorption disorders are suspected, if toxic effects are suspected when several
medicines are administered at the same time (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Alcohol withdrawal syndrome

In the application area of seizure prevention in alcohol withdrawal syndrome, Carbamazepine may only be used under inpatient conditions.
It should be noted that the side effects of Carbamazepine that occur in the treatment of alcohol withdrawal syndrome are similar to withdrawal symptoms or can be confused with them.

Administration with lithium
If Carbamazepin is to be given together with lithium in exceptional cases for the prophylaxis of manic-depressive phases when lithium alone is insufficient, care must be taken to avoid undesirable interactions (see section 4.5) that a certain plasma concentration of Carbamazepine is not exceeded (8 micrograms/ml), the lithium level is kept in a low therapeutic range (0.3 to 0.8 mval/l) and that treatment with neuroleptics was more than 8 weeks ago and is not carried out at the same time.

Photosensitization
Due to the possibility of photosensitization, patients should protect themselves from strong sunlight during treatment with Carbamazepine.

Dosage 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 a change in therapy is necessary in patients with epilepsy who are being treated with Carbamazepin, the change must not be made suddenly, but rather a gradual transition to treatment with another antiepileptic drug. If an abrupt change from Carbamazepine to another antiepileptic drug is necessary in epilepsy patients, this should be done under cover of suitable medication.

Laboratory tests
Due to the possible side effects mentioned above and hypersensitivity reactions, blood counts, kidney and liver function and Carbamazepine levels should be checked regularly, especially in long-term treatment, and the plasma concentrations of other antiepileptic drugs in combination therapy should be checked; if necessary, the daily doses should be reduced.
Falls Carbamazepin treatment can be associated with ataxia, dizziness, somnolence, hypotension, confusion and sedation (see section 4.8 Side effects). This can lead to falls and thus to fractures or other injuries. In patients with diseases, conditions or medications that could exacerbate these effects, a comprehensive assessment of the risk of falls should be considered. In patients on long-term treatment with Carbamazepine, this should be done repeatedly.

Excipients
Carbamazepine contains less than 1 mmol (23 mg) sodium per tablet, i.e. it is essentially “sodium-free”

4.5 Interactions 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, a treatment with MAO-inhibitors, at least two weeks prior to the start of treatment with Carbamazepine finishes have been.
Influence on the plasma concentrations of other drugs by Carbamazepine induces the cytochrome P-450 system (most of the isoenzyme CYP3A4) and other phase I and phase II enzyme systems in the liver, so that the plasma concentrations of substances, mainly by CYP3A4 reduced to be reduced, and this may become invalid can. Your dose if appropriate to the clinical needs.

This applies for example to:
- Analgesics, anti-inflammatory substances: Buprenorphine, Fentanyl, Methadone, Paracetamol (long-term use of Carbamazepine and Paracetamol (Acetaminophen) may lead to hepatotoxicity lead), Phenazone, Tramadol
- Anthelmintics: Praziquantel, Albendazole
- Anticoagulants: Warfarin, Phenprocoumon, Dicumarol, Acenocumarol, Rivaroxaban, Dabigatran, Apixaban, Edoxaban
- Antidepressants: Bupropion, Citalopram, Mianserin, Nefazodone, Sertraline, Trazodone (apparently, however, the gain of the anti-depressive effect of Trazodone)
- Tricyclic Antidepressants: Imipramine, Amitriptyline, Nortryptilin, Clomipramine
- Anti-Mimetics: Aprepitant

- Other Antiepileptic Drugs: Clonazepam, Ethosuximide, Felbamate, Lamotrigine, Eslicarbazepin, Oxcarbazepine, Primidone, Tiagabine, Topiramate, Valproic Acid, Zonisamide. A Phenytoin intoxication, and result in subtherapeutic concentrations of Carbamazepine to avoid, it is recommended that the plasma concentration of Phenytoin to 13 micrograms/ml, before the additional treatment with Carbamazepine is added.
- Antifungals: Caspofungin, Azole antifungals: e.g., Itraconazole, Voriconazole. For patients with voriconazole or itraconazole to be treated, alternative anticonvulsants are recommended.
- Antiviral agents: Protease inhibitors for the treatment of HIV, such as Indinavir, Ritonavir, Saquinavir
- Anxiolytics: Alprazolam, Midazolam, Clobazam
- Bronchodilators, Anti-Asthmatics: Theophylline
- Immunosuppressants: Cyclosporine, Tacrolimus, Sirolimus, Everolimus
- Cardiovascular drugs: calcium channel blockers (the dihydropyridine type, e.g., Felodipine), Digoxin, Simvastatin, Atorvastatin, Lovastatin, Cerivastatin, Ivabradine.
- Hormonal Contraceptives
- Corticosteroids: e.g., Prednisolone, Dexamethasone
- Typical Neuroleptics: Haloperidol, Bromperidol
- Atypical Antipsychotic Drugs: Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasonid,
- Aripiprazole, Paliperidone
- Thyroid Hormones: Thyroxine
- Tetracyclines: for example, Doxycycline
- Cytostatic Drugs: Imatinib, Cyclophosphamide, Lapatinib, Temsirolimus
- Other: Quinidine, Estrogens, Methylphenidate, Progesterone Derivatives, Propranolol, Flunarizine, Rifabutin
- Medicines for the treatment of erectile dysfunction: Tadalafil.

When taking the pill, in addition to the reduced effect of hormonal contraceptives, sudden intermenstrual bleeding can occur. Therefore, other, non-hormonal methods of contraception should be recommended.

The plasma concentration of phenytoin can be increased or decreased by Carbamazepine, which in exceptional cases can lead to states of confusion and even coma.

Carbamazepine can reduce the plasma level of bupropion and increase that of the metabolite hydroxybupropion, thus reducing the clinical effectiveness and safety of bupropion.

Carbamazepine can reduce the plasma level of trazodone, but appears to increase the antidepressant effect of trazodone.

Carbamazepine can possibly accelerate the metabolism of Zotepine.

<u>Decreased plasma concentration of Carbamazepine</u>
Carbamazepine is by the cytochrome P-450 System (mainly by the isoenzyme CYP3A4), which is metabolized. Inducers of CYP3A4 may, therefore, Carbamazepine metabolism increase and this may result in a reduction in Carbamazepine plasma concentration and therapeutic effect. Conversely, it could after discontinuation of a CYP3A4 Inducer, reduced metabolism of Carbamazepine and an increase in Carbamazepine plasma concentration. A reduction in Carbamazepine plasma concentration is, for example, is possible through the following substances (according to substance classes, sorted):

- Other anticonvulsants: Felbamate, Ethosuximide, Oxcarbazepine, Phenobarbital, Phensuximide, Phenytoin (a Phenytoin intoxication, and result in subtherapeutic concentrations of Carbamazepine to avoid, it is recommended that the plasma concentration of Phenytoin to 13 micrograms/ml, before the additional treatment with Carbamazepine is added), Fosphenytoin, primidone, Progabide and may (here, data are partly contradictory) Clonazepam, Valpromide
- Tuberculosis Agents: Rifampicin
- Bronchodilators, Anti-Asthmatics: Theophylline, Aminophylline
- Dermatology: Isotretinoin
- Cytostatic Drugs: Cisplatin, Doxorubicin
- Other: St. John's wort (*hypericum perforatum*)

On the other hand, the plasma concentrations of the pharmacologically active metabolite Carbamazepine-10,11-epoxide by valproic acid, and primidone increases.

By administration of Felbamate the plasma levels of Carbamazepine are reduced and the of Carbamazepine-10,11-epoxide increased, at the same time, the felbamate levels are reduced.

Due to the interaction, in particular, in the case of simultaneous administration of multiple anti-epileptic drugs, it is recommended that the plasma levels to control the dosage of Carbamazepine, if necessary, adjusted.

Increased plasma concentration of Carbamazepine and/or Carbamazepine-10,11-epoxy

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

Increased plasma levels of Carbamazepine are able to in section 4.8 above-mentioned symptoms (e.g., dizziness, drowsiness, unsteadiness, double vision) lead.

Therefore, should the Carbamazepine plasma concentration in the case of occurrence of such symptoms checked and the dose, if necessary, be reduced.

The plasma concentration of Carbamazepine, for example, by the following substances (according to substance classes) will be increased:
- 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, Viloxazin, may also desipramine
- Other Anticonvulsants: Stiripentol, Vigabatrin
- Antifungals: from Antifungals (such as Itraconazole, ketoconazole, fluconazole, voriconazole). For patients with voriconazole or Itraconazole to be treated, are alternative anticonvulsants is recommended.
- Antihistamines: Terfenadine
- Tuberculosis Agents: Isoniazid
- Antiviral agents: protease inhibitors for the treatment of HIV e.g., Ritonavir
- Carbonic Anhydrase Inhibitors (Diuretics): Acetazolamide
- Calcium Antagonists: Diltiazem, Verapamil
- Muscle Relaxants: Oxybutynin, Dantrolene
- Neuroleptics: Loxapine, Olanzapine, Quetiapine
- Platelet Aggregation Inhibitors: Ticlopidine
- Ulcer drugs: omeprazole, possibly cimetidine
- Other interactions: grapefruit juice, nicotinamide (only in high dosage)

Agents that may raise the active metabolite Carbamazepine-10,11-epoxide plasma levels:
The human microsomal epoxide Hydrolase was used as the enzyme identified, the formation of the 10,11-trans-diol of Carbamazepine-10,11-epoxide causes. The co-administration of inhibitors of human microsomal epoxide hydrolase may, therefore, increased plasma concentrations of Carbamazepine-10,11-epoxy lead.

Increased plasma concentrations of Carbamazepine-10,11-epoxide in section 4.8 above-mentioned symptoms (e.g., dizziness, light-headedness, unsteadiness of gait, double vision) lead. Therefore, the plasma concentration in the case of occurrence of such symptoms checked and the dose adjusted if necessary, when the following substances are at the same time to be given:

Loxapine, quetiapine, primidone, Progabide, valproic acid, Valnoctamide, and Brivaracetam.

Other interactions, with special attention:
Concomitant use of Carbamazepine and levetiracetam may increase Carbamazepine toxicity.

The concomitant use of Carbamazepine and lithium, or metoclopramide and neuroleptics (haloperidol, thioridazine), on the other hand, the occurrence of neurological side effects favor. In patients with neuroleptic - treated, is to make sure that Carbamazepine plasma levels of this drug to be reduced and thus a deterioration of the disease can cause. A dose adjustment of the respective neuroleptic agent may be required to be.

It is noted that, in particular, the simultaneous application of lithium and Carbamazepine, the neurotoxic effect of both compounds, even in the presence of therapeutic lithium levels, intensify can. Therefore, a careful monitoring of the blood levels of both. Prior treatment with neuroleptics should longer than 8 weeks ago and not even at the same time. On the following signs of neurotoxic symptoms is to pay attention to: Unsteady gait, ataxia, horizontal nystagmus, increased muscle reflexes, muscle twitching (muscle fasciculations).

The combined administration of Carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia lead.

The effectiveness of non-depolarizing muscle relaxants such as Pancuronium, can by Carbamazepine are affected. This is a quicker abolition of the neuromuscular blockade is possible. Patients with muscle relaxants treated to be, should be monitored and the dose of these medicinal products, where appropriate, be increased.

Carbamazepine, like other psychoactive substances, the alcohol tolerance of the patients to decrease it. The patient should drink during the treatment, no alcohol.

The concomitant administration of Carbamazepine and direct-acting oral anticoagulants (Rivaroxaban, Dabigatran, Apixaban, and Edoxaban) may lead to reduced plasma levels of the direct-acting oral anticoagulants lead. For more details, please refer to the following table:

Direct-acting oral Anticoagulants (NOAC)	Recommendations for the concomitant use of NOAC and Carbamazepine
Apixaban	• In the prophylaxis of venous thromboembolism (VTE) to elective hip or knee replacement surgery, in the Prophylaxis of Strokes and systemic embolism in patients with nonvalvular atrial fibrillation, as well as in the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (LE) should be the simultaneous use with caution. • In the treatment of DVT or PE and should the simultaneous application are avoided.
Rivaroxaban	The concomitant use should be avoided, unless, the patient should be closely monitored for signs and symptoms of thrombosis monitored.
Dabigatran	The concomitant use should be avoided will be.
Edoxaban	The concomitant use should be with caution and be done.

In the literature there are indications that the additional intake of Carbamazepine in the case of pre-existing neuroleptic therapy, the risk for the occurrence of a malignant neuroleptic syndrome or Stevens-Johnson syndrome are increased.
In the case of co-administration of Isotretinoin (the active ingredient for acne treatment) and Carbamazepine should Carbamazepine plasma levels are controlled. The co-administration of Carbamazepine with Paracetamol can the bioavailability of Paracetamol may decrease.
Carbamazepine seems to be the elimination of thyroid hormones to increase and the demand for these in patients with underactive thyroid to increase. Therefore, in such patients, the substitution therapy, at the beginning and at the end of a therapy with Carbamazepine of the thyroid parameters to determine. Where appropriate, a dose adjustment of thyroid hormone preparations to make. In particular, the simultaneous treatment with Carbamazepine and other anticonvulsants (e.g., Phenobarbital) can the thyroid function change.
The co-administration of the antidepressants on the type of Serotonin reuptake inhibitors (e.g., fluoxetine) can cause a toxic Serotonin syndrome.
It is recommended that Carbamazepine in combination with nefazodone (for depression resolving agent) to be applied, as Carbamazepine to a significant reduction in the nefazodone plasma levels to the effect of the loss may cause. In addition, in the case of co-administration of nefazodone and Carbamazepine of Carbamazepine plasma levels increased and that of its active degradation product of Carbamazepine-10,11-epoxide decreased.
By concomitant use of Carbamazepine and antiarrhythmic drugs, cyclic antidepressants, or Erythromycin increases the risk for cardiac conduction abnormalities.

Impairment of serological testing
By interference in the HPLC analysis, Carbamazepine false positive

Perphenazine concentrations of lead.
Carbamazepine and its 10,11-epoxide metabolite in fluorescence polaris decoration immunoassays false positive concentrations of tricyclic antidepressants lead.

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 about the risks of possible harm to the fetus if Carbamazepine is taken during pregnancy and understand the importance of planning a pregnancy. A pregnancy test should be considered before initiating 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 may result in 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 contraceptive methods. 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 a contraceptive method, you should: In each case, the individual circumstances are assessed and the patient is included in the discussion.

Pregnancy
Risk associated with antiepileptic drugs in general
All women of childbearing potential receiving antiepileptic treatment, and especially women planning to become pregnant or already pregnant, should receive specialist medical advice about the potential risks to the fetus caused by both seizures and antiepileptic treatment.

Sudden discontinuation of antiepileptic drugs should be avoided as this may lead to seizures, which could have serious consequences for the woman and the unborn child.
For the treatment of epilepsy in pregnancy, monotherapy is preferred whenever possible because therapy with multiple antiepileptic drugs, particularly polytherapy with valproate, may be associated with a higher risk of congenital malformations than monotherapy, depending on the specific antiepileptic drug.

Risks associated with Carbamazepine
In humans, Carbamazepine crosses the placenta. Prenatal exposure to Carbamazepine may increase the risk of congenital malformations and other adverse developmental effects. In humans, Carbamazepine exposure during pregnancy is associated with a 2 to 3 times higher incidence of major malformations than in the general population, where the incidence is 2 to 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 abnormalities affecting various body systems have been reported in the offspring of women who have taken Carbamazepine during pregnancy. Special prenatal monitoring is recommended for these malformations. Neurodevelopmental disorders have been reported in children of women with epilepsy who used Carbamazepine alone or in combination with other antiepileptic drugs during pregnancy. Studies on the risk of neurodevelopmental disorders in children exposed to Carbamazepine during pregnancy are conflicting and a risk cannot be excluded.
Carbamazepine should not be used during pregnancy unless the benefits outweigh the risks after careful consideration of alternative appropriate treatment options. The woman should be fully informed of and understand the risks of taking Carbamazepine during pregnancy.
Data suggest that the risk of malformations with Carbamazepine may be dose-related. If after careful benefit-risk consideration 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. Plasma concentrations could be maintained at the lower end of the therapeutic range of 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 an increased incidence of birth defects in the offspring of treated women with epilepsy. Folic acid supplementation before and during pregnancy is recommended. To prevent bleeding disorders in the offspring, it is also recommended that phytomenadione (vitamin K1) be given to the mother in the last weeks of pregnancy and to the newborn.
If a woman plans a pregnancy, every effort should be made to switch to an appropriate alternative treatment before conception and before stopping contraception. If a woman becomes pregnant while taking Carbamazepine, she should be referred to a specialist who will reassess Carbamazepine treatment and consider alternative treatment options.
During the first three months of pregnancy, when malformations are most prevalent, and especially between days 20 and 40 after conception, the lowest effective dose should be used, since malformations are likely to be caused by high plasma concentrations. Monitoring of plasma levels is recommended. They should be in the lower end of the therapeutic range (3 to 7 micrograms/ml). At a dose of < 400 mg Carbamazepine per day, the malformation rates are lower than at higher doses.
A few cases of convulsions and/or respiratory depression in newborns have been reported in association with the use of Carbamazepine and other antiepileptic drugs, as well as some cases of vomiting, diarrhoea and/or reduced food intake. These could be signs of withdrawal syndrome in the newborn.

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

Fertility
There have been isolated cases of sexual dysfunction, such as: impotence or decreased libido. Reduced male fertility and/or abnormal spermatogenesis have been reported very rarely.

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

4.8 Undesirable effects
The following frequencies are used to evaluate side effects:
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 (frequency cannot be estimated from available data)

The side effects observed occurred less frequently when Carbamazepine was administered alone (monotherapy) than when other antiepileptic drugs were administered at the same time (combination therapy).

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

Dose-dependent side effects usually disappear on their own within a few days or after a temporary dose reduction. Therefore, Carbamazepine should be dosed as gradually as possible. Central nervous system disorders may be a sign of relative overdose or large fluctuations in plasma levels; therefore, in these cases it is advisable to determine the plasma levels.

Adverse reactions are listed according to organ class according to MedDRA terminology. Within the organ classes, side effects are listed in descending order of severity.

Infections and infestations	
Not known**	Reactivation of human herpesvirus 6 infection.
Blood and lymphatic system disorders	
Very common:	Leukopenia. According to the literature occurs at the most common is a benign leukopenia, in about 10 % of the cases, temporarily, in 2 % persistent, on. A benign leukopenia occurs mainly within the first four therapy months.
Common:	Thrombocytopenia, eosinophilia.
Rare:	Leukocytosis, lymphadenopathy.
Very rare:	Agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia. bone marrow depression.
Not known**	Bone marrow insufficiency.
Immune system disorders	
Rare:	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 (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon)
Very rare:	Acute allergic general reactions, anaphylactic reactions, oedema angioedema, hypogammaglobulinemia.
Not known**	Rash with eosinophilia and systemic symptoms (Drug Rash with Eosinophilia and Systemic Symptoms [DRESS]).
Endocrine Disorders	
Common:	Oedema, fluid retention, weight gain, hyponatremia, and decreased plasma osmolality due to an antidiuretic hormone-like effect, leading in rare cases to water intoxication with lethargy, vomiting, headache, confusional state and other neurological disorders.
Very rare:	Galactorrhoea and gynecomastia.
Metabolism and nutrition disorders	
Rare:	Folic acid deficiency, decreased appetite.
Very rare:	Acute porphyria (acute intermittent porphyria, variegate porphyria), non-acute porphyria (porphyria cutanea tarda).
Not known**:	Hyperammonemia.
Psychiatric Disorders	
Uncommon:	In older patients, confusion, and restlessness (agitation).
Rare:	Hallucinations (visual and acoustic), depression, restlessness, aggressive behaviour.
Very rare:	Activation of latent psychosis, mood changes, such as phobic disorders, difficulty thinking, loss of drive.
Nervous system disorders	
Very common:	Dizziness, ataxia (ataxic and cerebellar disorders),

	somnolence, sedation, drowsiness.
Common:	Headache, diplopia.
Uncommon:	Abnormal involuntary movements such as tremor, asterixis, dystonia, or tics and disorders of the eye accompanied by nystagmus.
Rare:	Dyskinetic disorders such as orofacial dyskinesia, choreoathetosis (involuntary movements of the mouth area of the face, such as grimacing, screw-down movements), speech disorders (e.g., dysarthria, slurred speech), polyneuropathy, peripheral neuritis, peripheral neuropathy, paraesthesia, paresis.
Very rare:	Neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
Not known**	Memory disorder.

There is evidence that Carbamazepine may cause multiple sclerosis symptoms to worsen. As with other medications for seizure disorders, Carbamazepine may lead to an increase in seizures; Absences in particular can become more severe or appear new.

Diseases of the eye	
Common:	Accommodation disturbances (e.g., blurred vision).
Very rare:	Lens opacity, conjunktivitis. Retinotoxicity was reported in two patients in association with long-term Carbamazepine therapy, which resolved after discontinuation of Carbamazepine.
Ear and labyrinth disorders	
Very rare:	Hearing disorders, such as tinnitus and hyper – and hypoacusis as well as change the perception of pitch.
Cardiac disorders	
Rare:	Conduction disturbances, atrioventricular block, in individual cases with syncope.
Very rare:	Bradycardia, cardiac arrhythmias, congestive heart failure, worsening of a pre-existing coronary heart 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 in the lung with fever, dyspnea and pneumonitis or pneumonia (alveolit iden), single cases of pulmonary fibrosis have been described in the literature.
Gastrointestinal disorders	
Very common:	Nausea, vomiting.
Common:	Loss of appetite, dryness of the mouth.
Uncommon:	Diarrhoea, constipation.
Rarely:	Abdominal pain.
Very rare:	Inflammation of the mucous membrane in the mouth and throat area (stomatitis, gingivitis, glossitis), pancreatitis.
Not known**	Colitis.
Hepatobiliary disorders	
Rare:	Various forms of hepatitis (cholestatic, hepatocellular, and mixed), vanishing bile duct syndrome, jaundice, life-threatening acute hepatitis, in particular within the first

	therapy months, liver failure.
Very rare:	Granulomatous liver disease.
Skin and subcutaneous tissue disorders	
Very common:	Allergic skin reactions with and without fever, such as, for example, urticaria (also severe).
Uncommon:	Exfoliative dermatitis, erythroderma.
Rare:	Systemic lupus erythematosus, pruritus.
Very rare:	Stevens-Johnson Syndrome*, Lyell's syndrome (Toxic epidermal necrolysis), photosensitivity, erythema multiforme et nodosum, change in skin pigmentation, Purpura, acne, increased sweating, alopecia; hirsutism, and vasculitis have been very rarely reported, but the causal connection is unclear.
Not known**	Acute generalized exanthema of pustulosis (AGEP), lichenoid keratosis, onychomadesis.

There is increasing evidence linking genetic markers to the occurrence of skin adverse drug reactions such as SJS, TEN, DRESS, AGEP and maculopapular rash. An association between these reactions and the use of Carbamazepine in the presence of the HLA-A*3101 allele has been reported in Japanese and European patients. Another marker, the HLA-B*1502 allele, has been shown to be strongly associated 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:	Muscle weakness.
Very rare:	Bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.
Not known**:	Fractures.

There are case reports of the decrease in bone density with the appearance of osteoporosis and even 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 disorders	
Uncommon:	Renal dysfunction (e.g., albuminuria, hematuria, oliguria, increased urea nitrogen in the blood/azotemia).
Very rare:	Tubulointerstitial nephritis, renal failure, other urinary symptoms (frequent urination, dysuria, pollakiuria, urinary retention).
Reproductive system disorders	
Very rare:	Sexual dysfunction, decreased libido, erectile dysfunction, decreased male fertility and/or abnormal spermatogenesis (decreased sperm count and/or motility).
General disorders and administration site conditions	
Very common:	Fatigue.
Investigations	
Very common:	Increase in γ-GT values (due to hepatic enzyme induction), is usually not clinically relevant.
Common:	Increase in alkaline phosphatase in the blood.
Uncommon:	Increase in transaminases.
Very rare:	Increased intraocular pressure, increased cholesterol levels, including HDL cholesterol and triglyceride levels, altered

	thyroid function parameters: reduced L-thyroxine (free thyroxine, thyroxine, triiodothyronine) and increased TSH in the blood, usually without clinical symptoms, increase of free cortisol in serum, increased prolactin levels 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 the Carbamazepine treatment induced ataxia, dizziness, somnolence, hypotension, confusion, and sedation (see section 4.4)).

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

Additional side effects from spontaneous reports (frequency not known)
During post-marketing experience with Carbamazepine, side effects were reported through spontaneous reports and literature. Since the reports were voluntary and from an unknown population size, the frequency cannot be estimated based on 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 ″Arpimed″ LLC by going to www.arpimed.com and fill out the appropriate form ″Report an adverse reaction or inefficiency of drug″. Hotline number: (+374 55) 05 79 86. And by using ″Centre of Drug and Medical Technology Expertise″ SNPO, going to the site: www.pharm.am in ″Report about adverse effect of medicine″ section and fill out the ″Report of adverse reaction or manufacturing problem of medicinal product″.
Hotline numbers: +37410200505; +37496220505.

4.9 Overdose

Signs and symptoms
The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under section 4.8.
Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.
Respiratory system: Respiratory depression, pulmonary oedema.
Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.
Gastro-intestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.
Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with Carbamazepine toxicity.
Renal function: Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of Carbamazepine.
Laboratory findings: Hyponatremia, possibly metabolic acidosis, possibly hyperglycemia, increased muscle creatine phosphokinase.

Treatment
There is no specific antidote.
Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm Carbamazepine poisoning and to ascertain the size of the overdose.

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

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

5. Pharmacological properties

5.1 Pharmacodynamic Properties

Therapeutic class: Antiepileptics. Carboxamide derivatives. Carbamazepine. (ATC Code: N03 AF01).
As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalization; generalized tonic-clonic seizures, as well as combinations of these types of seizures.

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

Whereas reduction of glutamate release and stabilization of neuronal membranes may account 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 absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400mg Carbamazepine (tablets) the mean peak concentration of unchanged Carbamazepine in the plasma is approx. 4.5µg/ml.

The bioavailability of Carbamazepine in various oral formulations has been shown to lie between 85-100%. Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Carbamazepine.
Steady-state plasma concentrations of Carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by Carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment. Different preparations of Carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.
Distribution
Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels. Carbamazepine crosses the placental barrier. Assuming complete absorption of Carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.
Biotransformation
Carbamazepine is metabolized in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of Carbamazepine 10, 11-epoxide from Carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from Carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of Carbamazepine about 30% appears in the urine as end-products of

the epoxide pathway. Other important biotransformation pathways for Carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of Carbamazepine produced by UGT2B7.

Elimination

The elimination half-life of unchanged Carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (autoinduction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g., phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found. The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

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

Characteristics in patients

The steady-state plasma concentrations of Carbamazepine considered as "therapeutic range" vary considerably inter-individually; for the majority of patients a range between 4-12µg/ml corresponding to 17-50µmol/l has been reported. Concentrations of Carbamazepine 10, 11epoxide (pharmacologically active metabolite): about 30% of Carbamazepine levels. Owing to enhanced Carbamazepine elimination, children may require higher doses of Carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, 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 two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence to date that these observations are of any relevance to the therapeutic use of Carbamazepine in humans.

Reproductive toxicity

In animals studies in mice, rats and rabbits oral administration of Carbamazepine during organogenesis led to increased embryo-fetal mortality and fetal growth retardation at daily doses which were associated with maternal toxicity (above 200mg/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 reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

Fertility

In chronic toxicity studies dose related testicular atrophy and spermatogenesis occurred in rats receiving Carbamazepine. The safety margin for this effect is not known.

6. Pharmaceutical particulars

6.1 List of excipients

Carbamazepine Tablets:

Each tablet contains microcrystalline cellulose, aerosil 200, carmellose sodium, magnesium stearate.

6.2 Incompatibilities

None known

6.3 Shelf life

3 years

6.4 Special precautions for storage
Store at a temperature below 25^0C, out of the reach of children.

6.5 Nature and contents of container
10 tablets are packed into PVC-Aluminum blister packet (inside package)
5 blister packet with 10 tablets in each and leaflet inserted in the cardboard box (outer package).

10 tablets are packed into PVC-Aluminum blister packet (inside package)
4 blister packet with 10 tablets in each and leaflet inserted in the cardboard box (outer package).

6.6 Special precautions for disposal and other handling
None

7. Marketing authorisation holder
"ARPIMED" LLC
Kotayk Marz, Abovyan, 2204, 2nd Micro-District, 19 Building, Republic of Armenia
Tel.: (374) 222 21703
Fax: (374) 222 21924

8. Date of first authorisation/renewal of the authorization
12.07.2004 (Date of first authorisation)

9. Date of revision of the text