INSTRUCTION
for medical use of the medicinal product
LEKTIL 200
CARBAMAZEPINE

Composition:
Active substance: carbamazepine;
1 tablet contains 200 mg carbamazepine;
Excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sodium laurilsulfate, gelatin.

Pharmaceutical form. Tablets.
Main physical and chemical properties: white or off-white, monolayer, round, bevelled-edged, scored tablets, with flat top and bottom surfaces. Upon fracture a relatively uniform structure is visible through a magnifying glass.

Pharmacotherapeutic group. Antiepileptics. Carbamazepine.
ATC code N03A F01.

Pharmacological properties.
Pharmacodynamic properties.
As *an antiepileptic agent.* As an antiepileptic agent Carbamazepine is effective at 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 – active substance of the medicinal product Carbamazepine, 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 blockade of sodium channels, that depends on duration of administration and voltage, is 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 the drug.
In clinical studies carbamazepine given as monotherapy to patients with epilepsy (in particular children and adolescents) has been reported to exert a psychotropic action, including a positive effect on symptoms of anxiety and depression as well as a decrease in irritability and aggressiveness. As regards cognitive and psychomotor performance, in some studies equivocal or negative effects, depending also upon dosages administered, were reported. In other studies, a beneficial effect of carbamazepine on attentiveness, cognitive performance/memory was observed.
As *a neurotropic agent*. Carbamazepine is effective in a number of neurological disorders: e.g. it prevents paroxysmal attacks of pain in idiopathic and secondary trigeminal neuralgia. In addition, the drug is used for the relief of neurogenic pain in a variety of conditions, including tabes dorsalis, post-traumatic paraesthesia, and post-herpetic neuralgia. In alcohol-withdrawal syndrome it raises the convulsion threshold (that is lowered in this state) and improves such withdrawal symptoms, as hyperexcitability, tremor, impaired gait. In diabetes insipidus centralis, Carbamazepine reduces the urinary volume and relieves the feeling of thirst.
As a *psychotropic agent* Carbamazepine proved to have clinical efficacy in affective disorders, i.e. as treatment for acute mania as well as for maintenance treatment of (manic-depressive) bipolar affective disorders, (when given either as monotherapy or in combination with neuroleptics, antidepressants, or lithium).
Pharmacokinetic properties.
Absorption. Carbamazepine is absorbed almost completely but relatively slowly from the tablets.

The conventional tablets yield mean peak plasma concentrations (C_{max}) within 12 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 400 mg carbamazepine tablets the mean C_{max} of unchanged active substance in the plasma is approx. 4.5 µg/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. The steady-state plasma concentrations of carbamazepine considered as therapeutic range vary considerably interindividually: for the majority of patients a range between 4 to 12 µg/ml (17 to 50 µmol/L) has been reported. Concentrations of carbamazepine-10,11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.
Different carbamazepine drugs 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. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg. Carbamazepine crosses the placental barrier. Carbamazepine is bound to serum proteins to the extent of 70 to 80%. The concentration of unchanged carbamazepine in cerebrospinal fluid and saliva reflects the non-protein bound portion in the plasma (20 to 30%). Concentrations of carbamazepine in breast milk were found to be equivalent to 25 to 60% of the corresponding plasma levels.
Metabolism. Carbamazepine is metabolized in the liver, where the epoxide pathway is the most important one, yielding the 10,11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of the pharmacologically active carbamazepine-10,11 epoxide from carbamazepine. 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 uridine diphosphate glucuronosyltransferase (UGT2B7).
Conclusion. 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 (auto-induction 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 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite.
Pharmacokinetics in special populations.
Paediatric patients. Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg of body weight) than adults to maintain therapeutic drug concentrations.
Elderly. There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.
Impaired renal or hepatic function. No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

Clinical characteristics.

Therapeutic indications.

- Epilepsy:
  - simple or complex partial seizures (with or without lost consciousness) with or without secondary generalized seizures;
  - generalised tonic-clonic seizures;
  - mixed seizures.

Carbamazepine can be used as monotherapy or in combination therapy.

- Acute mania; supportive therapy in bipolar affective disorders to prevent exacerbation or to relieve clinical manifestations of exacerbation.
- Alcohol-withdrawal syndrome.
- Idiopathic trigeminal neuralgia and trigeminal neuralgia in multiple sclerosis (typical and atypical).
- Idiopathic glossopharyngeal neuralgia.

Contraindications.

The drug should not be used in:

- hypersensitivity to carbamazepine or chemically similar drugs (such as tricyclic antidepressants) or to any other component of the drug;
- atrioventricular block;
- history of bone marrow suppression;
- history of hepatic porphyria (e.g., acute intermittent porphyria, mixed porphyria, late skin porphyria);
- combination with monoamine oxidase inhibitors (MAOIs).

Interactions with other medicinal products and other forms of interaction.

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

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism.

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

Agents that may raise carbamazepine plasma levels.

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

<u>Analgesics, anti-inflammatory drugs:</u> dextropropoxyphene, ibuprofen.

<u>Androgens:</u> danazol.

<u>Antibiotics:</u> macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin, ciprofloxacine).

<u>Antidepressants:</u> desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine.

<u>Antiepileptics:</u> stiripentol, vigabatrin.

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

Antihistamines: loratadine, terfenadine.
Antipsychotics: olanzapine, loxapine, quetiapine.
Antituberculosis: isoniazid.
Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir).
Carbonic anhydrase inhibitors: acetazolamide.
Cardiovascular drugs: diltiazem, verapamil.
Gastrointestinal drugs: cimetidine, omeprazole.
Muscle relaxants: oxybutynin, dantrolene.
Platelet aggregation inhibitors: ticlopidine.
Other interactions: grapefruit juice, nicotinamide (in adults, only in high dosage).

Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels.

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

Agents that may decrease carbamazepine plasma levels.

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

Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbital, phensuximide, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 μg/mL before adding carbamazepine to the treatment) and fosphenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam.
Antineoplastics: cisplatin or doxorubicin.
Antituberculosis: rifampicin.
Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.
Dermatological drugs: isotretinoin.
Other interactions: herbal preparations containing St John's wort *(Hypericum perforatum).*

Mefloquine may antagonize anticonvulsant effect of Carbamazepine. The dosage of Carbamazepine should be adjusted respectively.

As reported, isotretinoin changes bioavailability and/or clearance of carbamazepine and carbamazepine-10,11-epoxide; carbamazepine plasma concentrations should be monitored.

Effect of Carbamazepine on plasma levels of concomitant agents.

Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement.

Analgesics, anti-inflammatory drugs: buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), phenazone (antipyrine), tramadol.
Antibiotics: doxycycline, rifabutin.
Anticoagulants: oral anticoagulants (e.g. warfarin, phenprocoumon, dicoumarol and acenocoumarol).
Antidepressants: bupropion, citalopram, mianserin, nefazodone, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine).
Antiemetics: aprepitant.
Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. There have been reported of either increase or decrease of plasma level of phenytoin caused by carbamazepine action and there have been rare reports of an increase in plasma mephenytoin levels.
Antifungals: itraconazole, voriconazole, ketoconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.
Antihelmintics: praziquantel, albendazole.
Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.
Antipsychotics: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone.

Antivirals: protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).
Anxiolytics: alprazolam, midazolam.
Bronchodilatators or anti-asthma drugs: theophylline.
Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered).
Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g. felodipine, isradipine, digoxin, quinidine, propranolol, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.
Corticosteroids (e.g. prednisolone, dexamethasone).
Drugs used in erectile dysfunction: tadalafil.
Immunosuppressants: cyclosporine, everolimus, tacrolimus, sirolimus.
Thyroid agents: levothyroxine.
Interaction with other medicinal products: buprenorphine, gestrinone, tibolone, toremifene, mianserin, sertraline.
Combinations that require specific consideration.
Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.
Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced toxicity.
Combined use of carbamazepine and lithium or metoclopramide on the one hand, and carbamazepine and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of "therapeutic plasma levels").
Concomitant medication with Carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.
Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g. pancuronium). Their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.
Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol.
Interactions resulting in a contraindication.
Since carbamazepine is structurally similar to the tricyclic antidepressants, the use of carbamazepine is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits.
Interference with serological testing.
Carbamazepine may result in false positive perphenazine concentrations in HPLC (high-performance liquid chromatography) analysis due to interference to determine the concentration of perphenazine.
Carbamazepine-10,11-epoxide may result in false positive tricyclic antidepressant concentration in fluorescence polarized immunoassay method.

Special warnings and precautions for use.
Carbamazepine should be given only under medical supervision and prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with Carbamazepine.
It is recommended to conduct urinalysis and determine blood urea nitrogen at the beginning and at regular intervals during therapy.
Carbamazepine has shown mild anticholinergic activity, so patients with increased intraocular pressure should therefore be advised on possible risk factors.
The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.
The drug 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.
Haematological effects. Agranulocytosis and aplastic anaemia have been associated with the drug; however, due to the very low incidence of these conditions, meaningful risk estimates for

Carbamazepine are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia.
Patients should be made aware of early toxic signs and symptoms of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his physician immediately.
If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored. However, treatment with Carbamazepine should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Carbamazepine should be discontinued if any evidence of significant bone-marrow depression appears.
Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Carbamazepine. However, in the majority of cases these effects prove transient and are unlikely to signal the onset of either aplastic anaemia or agranulocytosis. Nonetheless, complete pre-treatment blood counts, including platelets (and possibly reticulocytes and haemoglobin), should be obtained at baseline, and periodically thereafter.
Serious dermatologic reactions. Serious dermatologic reactions, including toxic epidermal necrolysis (TEN), also known as Lyell's syndrome and Stevens-Johnson syndrome (SJS), have been reported very rarely with Carbamazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with Carbamazepine. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, Carbamazepine should be withdrawn at once and alternative therapy should be considered.
Pharmacogenomics.
There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.
Association with (HLA)-B*1502
Retrospective studies in Han Chinese patients showed a strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. Higher reporting rates of SJS are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the population. The frequency of this allele carrier is above 15% in the Philippines, Thailand, Hong Kong and Malaysia, around 10% – in Taiwan, almost 4% – in North China, around 2% to 4% – in South Asia (including India) and less than 1% – in Japan and Korea. The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous peoples of the Americas, Hispanic populations.
Whenever possible, these individuals should be screened for (HLA)-B*1502 allele before starting treatment with Carbamazepine. If these individuals test positive, Carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still very rarely occur.
Currently, due to the lack of data it is not known exactly whether all Southeast Asians are exposed to risk.
HLA-B*1502 allele may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs associated with SJS/TEN. Consideration should therefore be given to avoid other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low. Screening is generally not recommended for any current Carbamazepine users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.
Association between (HLA)-B*1502 allele and development of SJS in European patients is absent.
Association with HLA-A*3101
Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, drug rash with eosinophilia and systemic symptoms

(DRESS), acute generalised exanthematous pustulosis (AGEP) and maculopapular rash. The use of Carbamazepine should be avoided in patients who are found to be positive for HLA-A*3101 allele.
Limitation of genetic screening
Genetic screening results must never substitute for appropriate clinical vigilance and patient management. The role in the development of these severe cutaneous adverse reactions is played by other possible risk factors such as dosing of antiepileptic drug, adherence to therapy, concomitant therapy. The influence of other diseases, and monitoring of skin disorders have not been studied.
Other dermatologic reactions.
Mild skin reactions, e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.
The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However, the HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions.
Hypersensitivity. Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium and colon).
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30 % of these patients may experience hypersensitivity reactions with oxcarbazepine.
Cross-hypersensitivity can occur between carbamazepine and phenytoin.
In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Carbamazepine should be withdrawn immediately.
Seizures. Carbamazepine should be used with caution in patients with mixed seizures which includes absences, either typical or atypical. In all these conditions, Carbamazepine may exacerbate seizures. In the event of exacerbation of seizures, Carbamazepine should be discontinued.
An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.
Hepatic function. Baseline and periodic evaluations of hepatic function must be performed during treatment with the drug, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.
Some liver function laboratory tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase (GGT). This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.
Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with Carbamazepine suspended pending the outcome of the evaluation.
Renal function. Baseline and periodic complete urinalysis and BUN determinations are recommended.
Hyponatremia. Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at

monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If 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.
Anticholinergic effects. Carbamazepine has shown mild anticholinergic activity. Patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy.
Psychiatric disorders. The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.
Suicidal ideation and behaviour. Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. Meta-analysis of the data obtained during placebo-controlled studies of antiepileptic drugs also showed an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk of suicidal ideation and behaviour for carbamazepine.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Endocrine effects. Due to enzyme induction, Carbamazepine may result in a failure of the therapeutic effect of drugs containing estrogen and/or progesterone. This can lead to a reduction of effective contraception, recurrence of symptoms or breakthrough bleeding or spotting. Patients taking Carbamazepine and requiring hormonal contraception should receive a preparation containing not less than 50 µg estrogen or use of some alternative non-hormonal method of contraception should be considered.
Monitoring of plasma levels. Although correlations between dosage and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following situations: dramatic increase in seizure frequency/verification of patient compliance, during pregnancy, when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used.
Dose reduction and withdrawal effects. Abrupt withdrawal of Carbamazepine may precipitate seizures therefore carbamazepine withdrawal should be gradual for 6 months. If treatment with Carbamazepine has to be withdrawn abruptly in a patient with epilepsy, the switch to the new antiepileptic compound should be made under cover of a suitable drug.

Fertility, pregnancy and lactation.
In animals oral administration of carbamazepine caused the development of defects.
Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However, there are reports on developmental disorders and malformations, including spina bifida, and also other congenital anomalies e.g. craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with carbamazepine.
Taking these data into consideration:

- Pregnant women with epilepsy should be treated with Carbamazepine with special care;
- If women receiving carbamazepine become pregnant or plan to become pregnant, or if the problem of initiating treatment with Carbamazepine arises during pregnancy, the drug's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy;
- In women of childbearing potential carbamazepine should, wherever possible, be prescribed as monotherapy;

- Minimum effective doses should be given and monitoring of carbamazepine plasma levels is recommended;
- Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening;
- During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention. Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate deficiency. Folic acid supplementation has therefore been recommended before and during pregnancy.
In the neonate. In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.
There have been a few cases of neonatal seizures and/or respiratory depression, vomiting, diarrhoea and/or decreased feeding associated with maternal carbamazepine and other concomitant anticonvulsant drug use.
Breast-feeding. Carbamazepine passes into the breast milk (about 25 to 60% of plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking carbamazepine may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).
Fertility.
There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

Effects on ability to drive and use machines.
The patient's ability to react may be impaired by dizziness and drowsiness 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.

Posology and method of administration.
Carbamazepine is administered orally; the usual daily dose should be distributed into two or three doses. The drug can be taken with food, after a meal or between meals, with a small amount of liquid, such as a glass of water.
Prior to initiating therapy, testing for HLA-A*3101 should be performed in patients with ancestry in populations in which HLA-A*3101 may be present as it strongly predicts the risk of severe skin reactions.
Epilepsy
Initially, the dosage should be low and then slowly raised. The dose should be adjusted to the needs of the individual patient.
Determination of carbamazepine plasma levels may help in establishing the optimum dosage.
Especially in case of combination therapy the therapeutic dose should be calculated on the basic determination of plasma carbamazepine and effectiveness.
Adults: 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 of Carbamazepine daily may be necessary.
Elderly: due to the potential for drug interactions, the dosage of Carbamazepine should be selected with caution in elderly patients.
Paediatric patients: therapy may begin with 100 mg/day, increasing at weekly intervals by 100 mg. The usual dosage is 10 to 20 mg/kg daily in divided doses.

Child age	Daily dose
5-10 years old	400-600 mg (2-3 divided doses)
10-15 years old	600-1000 mg (2-5 divided doses)

The dosage for children aged 15 and over is the same as in adults.
Wherever possible, Carbamazepine should be prescribed as monotherapy, but if used in combination with other therapies 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).
Acute mania and supportive therapy in bipolar affective disorders
Dosage range: about 400 to 1600 mg daily, the usual dosage being 400 to 600 mg daily given in 2 to 3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for supportive therapy of bipolar disorders in order to ensure optimal tolerability.
Alcohol-withdrawal syndrome
Average dosage: 200 mg 3 times daily. In severe cases, it can be raised during the first few days (e.g. to 400 mg 3 times daily). At the start of treatment for severe withdrawal manifestations, Carbamazepine should be given in combination with sedative-hypnotic drugs (e.g. clomethiazole, chlordiazepoxide), following the above mentioned instructions for dosage. After the acute stage has abated, Carbamazepine can be continued as monotherapy.
Idiopathic trigeminal neuralgia and trigeminal neuralgia in disseminated sclerosis (either typical or atypical). Idiopathic glossopharyngeal neuralgia
The initial dosage of Carbamazepine is 200 to 400 mg daily (100 mg twice daily for elderly). It should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). For majority of patients the dosage 200 mg 3 to 4 times daily is enough for maintenance of painless condition. In some instances, 1600 mg of Carbamazepine daily may be necessary. When pain disappears, the dosage should then be gradually reduced to the lowest possible supportive level.

Children.
Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg of body weight) than adults to maintain therapeutic drug concentrations. Carbamazepine tablets can be used in children above 5 years of age.

Overdose.
Symptoms. The presenting signs and symptoms of overdosage usually involve the central nervous, cardiovascular, respiratory systems.
Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.
Respiratory system: respiratory depression, pulmonary oedema.
Cardiovascular system: tachycardia, hypotension, hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest, accompanied by loss of consciousness.
Gastrointestinal tract: vomiting, delayed gastric emptying, reduced bowel motility.
Musculoskeletal system: there have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.
Renal and urinary system: retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine.
Laboratory findings: hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, increased muscle 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: If hypotension is observed intravenous administration of dopamine or dobutamine is indicated; in case of arrhythmia the treatment is selected individually; if seizures are

observed – administration of benzodiazepines (e.g. diazepam) or other anticonvulsants, e.g. phenobarbital (with caution because of an increased risk of respiratory depression) or paraldehyde; if hyponatremia is observed (water intoxication) – water restriction, slow, careful intravenous infusion of 0,9% sodium chloride solution. These measures may be useful for the prevention of cerebral oedema.
Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis and peritoneal dialysis are not effective. Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

Undesirable effects.
Particularly at the start of treatment with Carbamazepine, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.
The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses.
Blood and lymphatic system disorders: leucopenia, thrombocytopenia, eosinophilia, leucocytosis, lymphadenopathy, folate deficiency, agranulocytosis, aplastic anaemia, pancytopenia, erythrocytic aplasia, anaemia, anaemia megaloblastic, acute intermittent porphyria, mixed porphyria, late skin porphyria, reticulocytosis, haemolytic anaemia, bone marrow depression.
Immune system disorders: 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); aseptic meningitis with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioedema, hypogammaglobulinemia, drug rash with eosinophilia and systemic symptoms (DRESS).
Endocrine system disorders: 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; increased blood prolactin, accompanied or not accompanied by such reactions as galactorrhoea, gynecomastia, one metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol, leading to osteomalacia and osteoporosis); blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased.
Metabolism disorders: folate deficiency, decreased appetite, porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).
Psychiatric disorders: hallucinations (visual or auditory), depression, restlessness, aggression, agitation, confusional state, activation of psychosis.
Nervous system disorders: dizziness, ataxia, somnolence, fatigue, headache, diplopia; abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus; orofacial dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, muscular weakness, paresis; taste disorders, neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia, sedation, memory impairment.
Eye disorders: accommodation disorders (e.g. blurred vision), lenticular opacities, conjunctivitis, increased intraocular pressure.
Ear and labyrinth disorders: hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac and vascular disorders: cardiac conduction disorders; hypertension or hypotension; bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, cardiac failure congestive, coronary artery disease aggravated, thrombophlebitis, thromboembolism (e.g. pulmonary embolism).

Respiratory, thoracic and mediastinal disorders: pulmonary hypersensitivity characterized e.g. by fever, dyspnoea, pneumonitis or pneumonia.
Gastrointestinal disorders: nausea, vomiting, dry mouth, diarrhoea or constipation; abdominal pain, glossitis, stomatitis, pancreatitis, colitis.
Hepatobiliary disorders: gamma-glutamyltransferase increased (due to hepatic enzyme induction, usually not clinically relevant), blood alkaline phosphatase increased, transaminases increased, hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice, granulomatous hepatitis, hepatic failure.
Skin and subcutaneous tissue disorders: dermatitis allergic, urticaria (which may be severe), dermatitis exfoliative, erythroderma, systemic lupus erythematosus, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism, acute generalized exanthematous pustulosis (AGEP), lichenoid keratosis, onychomadesis.
Musculoskeletal and connective tissue disorders: muscular weakness, arthralgia, myalgia, muscle spasms, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol, leading to osteomalacia and osteoporosis), fractures.
Renal and urinary disorders: tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and blood urea increased/azotaemia), urinary frequency, urinary retention.
Reproductive system disorders: sexual dysfunction, impotence, erectile dysfunction, spermatogenesis abnormal (with decreased sperm count and/or motility).
General disorders: general weakness.
Infections and infestations: reactivation of human herpesvirus Type VI.
Deviations in laboratory and instrumental examinations: gamma-glutamyltransferase increased (due to hepatic enzyme induction, usually not clinically relevant), blood alkaline phosphatase increased, transaminases increased, intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased, thyroid function test abnormal: decreased L-Thyroxin (FT_4, T_4, T_3) and increased blood thyroid stimulating hormone, usually without clinical manifestations; increased blood prolactin, hypogammaglobulinemia, bone mineral density decreased.

Shelf life. 3 years.

Storage.
Store in original packaging below 25 ^oC.
Keep out of the reach of children.

Package.
10 tablets in a blister; 5 blisters in a cardboard pack.
50 tablets in a container, 1 container in a cardboard pack.

Prescription status.
Rx

Manufacturer / applicant.
Group of Pharmaceutical Companies "Lekhim"
Private Joint Stock Company "Technolog"
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