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INSTRUCTION
for medical use

MEZACAR®

Composition:
active ingredient: carbamazepine;
5 ml of suspension contain carbamazepine 100 mg;
excipients: xanthan gum; hypromellose; potassium sorbate; citric acid, monohydrate; propylene glycol; sorbitol solution, non-crystallizing (E 420); sucrose; sunset yellow FCF (E 110); flavor "Orange"; flavor "Vanilla"; purified water.

Pharmaceutical form. Oral suspension.
Main physical and chemical properties: viscous suspension of orange color with a specific odor.

Pharmacotherapeutic group.
Antiepileptic drugs. ATC code N03A F01.

Pharmacological properties.
Pharmacodynamics.
Carbamazepine exhibits antiepileptic, neurotropic and psychotropic activity. As an *anticonvulsant agent*, carbamazepine is effective in partial seizures (simple and complex) with and without secondary generalization; generalized tonic-clonic seizures, as well as in combination of these types of seizures. The mechanism of action of carbamazepine has only been partially determined. Carbamazepine stabilizes the membranes of hyperexcited nerve fibers, inhibits recurrent neuronal discharges, and reduces synaptic propagation of excitatory impulses. It has been found that the main mechanism of action of the drug is the prevention of repeated formation of sodium-dependent action potentials in depolarized neurons through blockade of sodium channels. The anticonvulsant effect of the drug is mainly due to the decrease of glutamate release and stabilization of neuron membranes, while the anti-manic effect may be due to the suppression of dopamine and noradrenaline metabolism. When using carbamazepine as monotherapy in patients with epilepsy (especially children), a psychotropic effect has been marked, which was partly manifested by a positive effect on the symptoms of anxiety and depression, as well as decreased irritability and aggression. According to several studies, the effect of carbamazepine on cognitive function and psychomotor performance was dose-dependent and was either dubious or negative. In the course of other studies, a positive effect of carbamazepine on indicators that characterize attention, learning ability, and memorization, has been marked.
As a *neurotropic agent,* carbamazepine is effective in a number of neurological disorders. For example, it prevents pain episodes in idiopathic and secondary trigeminal neuralgia. Moreover, the drug should be used for relief of neurogenic pain in a variety of conditions, including tabes dorsalis, post-traumatic paresthesias, and post-herpetic neuralgia. In alcohol withdrawal syndrome, the drug increases the convulsion threshold (which is lowered in this condition) and reduces the severity of clinical manifestations of the syndrome, such as excitability, tremor, impaired gait. In patients with central diabetes insipidus, the drug reduces diuresis and thirst.

As a *psychotropic agent*, the drug proved effective in affective disorders, namely: as treatment for acute mania, for maintenance treatment of bipolar affective (manic-depressive) disorders (as monotherapy or in combination with neuroleptics, antidepressants, or lithium preparations).

Pharmacokinetics.

Absorption.

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. After a single administration of a conventional tablet, the maximum plasma concentration (C_{max}) is reached after 12 hours, and in liquid form – after 2 hours. There is no clinically significant difference between oral dosage forms with respect to the amount of active substance absorbed. After a single administration of 400 mg carbamazepine (tablets), the mean peak concentration of unchanged carbamazepine in the plasma is approximately 4.5 mcg/ml.

The bioavailability of carbamazepine in various oral forms was shown to be within the range of 85-100 %.

Food intake has no significant effect on the rate and extent of absorption regardless of the dosage form of carbamazepine.

Steady plasma concentrations of carbamazepine are attained within about 1-2 weeks depending on the individual autoinduction of carbamazepine and heteroinduction of other agents – enzyme-inducers, as well as of the pre-treatment status, dosage, and duration of treatment.

Bioavailability of different preparations of carbamazepine may vary; in order to avoid the effect of bioavailability reduction, the risk of convulsions, or excessive adverse reactions, it may be advisable not to replace the drug with a different one.

Distribution

Carbamazepine is bound to serum proteins within the range of 70-80%. The concentration of unchanged substance in the cerebrospinal fluid and saliva reflects the non-protein bound portion in blood 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 expected volume of distribution varies 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, forming the main metabolites, a derivative of 10,11-trans-diol and glucuronide.

It has been determined that cytochrome P450 3A4 is the major isoform responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine. Human microsomal epoxide hydrolase was identified as the enzyme responsible for the formation of a 10,11-transdiol derivative from carbamazepine-10,11-epoxide. 9-hydroxymethyl-10-carbamoyl acridan is a secondary metabolite of this path. After a single dose of carbamazepine, about 30% appears in the urine as end products of the epoxide pathway.

Other important biotransformation pathways of carbamazepine lead to various monohydroxylated compounds, as well as N-glucuronide of carbamazepine, which is formed by UGT2B7.

Elimination

The elimination half-life of unchanged carbamazepine averages approximately 36 hours following a single dose, whereas after repeated administration the half-life averages only 16-24 hours (autoinduction of the hepatic mono-oxygenase system), depending on the duration of treatment. In patients receiving concomitant treatment with other liver enzyme-dependent drugs (e.g. phenytoin, phenobarbital), the elimination half-life averages 9-10 hours.

The mean elimination half-life of the 10,11-epoxide metabolite in blood plasma is approximately 6 hours following a single dose of epoxide.

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

Indices in patients.

Significant intraindividual differences in stable state concentrations have been observed within the therapeutic range: in most patients these values vary between 4 and 12 mcg/ml (17-50 μmol/l). The

concentration of carbamazepine-10,11-epoxide (pharmacologically active metabolite) is approximately 30% of the level of carbamazepine.
Pharmacokinetics in certain groups of patients.
Children. Due to increased excretion of carbamazepine, to maintain the therapeutic concentration children may need higher doses of carbamazepine (in mg/kg) than adults.
Elderly patients. There are no data indicating that the pharmacokinetics of carbamazepine changes in elderly patients (compared to young adults).
Patients with renal or hepatic impairment. So far there are no data on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

Clinical characteristics.
Indications.
Epilepsy: generalized tonic-clonic and partial seizures.
Paroxysmal pain in trigeminal neuralgia.
Prevention of manic-depressive psychosis in patients with no therapeutic effect of lithium preparations.

Contraindications.
Hypersensitivity to carbamazepine or chemically similar drugs (e.g. 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).
Concomitant use with monoamine oxidase (MAO) inhibitors.

Interaction with other medicinal products and other types of interaction.
Cytochrome P450 3A4 (CYP3A4) is the main enzyme that catalyzes the formation of the active metabolite carbamazepine-10,11-epoxide. Concomitant use of CYP3A4 inhibitors or inhibitors of epoxide hydrolase with carbamazepine may increase the concentration of carbamazepine or carbamazepine-10,11-epoxide in blood plasma respectively, which in turn may induce adverse reactions. The dosage of the drug Mezacar®, oral suspension, should be adjusted accordingly and/or the plasma levels should be monitored. Concomitant use of CYP3A4 inducers may increase the metabolism of carbamazepine, which potentially decreases plasma carbamazepine concentrations and the therapeutic effect. Similarly, discontinuation of enzyme CYP3A4 inducers may reduce the rate of carbamazepine metabolism leading to an increase in its plasma concentration.
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 other medications mainly metabolized by CYP3A4 by induction of their metabolism.
Human microsomal epoxide hydrolase is an enzyme responsible for the formation of 10,11-transdiol derivatives from carbamazepine-10,11-epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased concentrations of carbamazepine-10,11-epoxide in blood plasma.
Contraindicated drug combinations.
The drug Mezacar®, oral suspension, is contraindicated in combination with MAO inhibitors, before starting the drug, the MAO inhibitor should be discontinued (at least 2 weeks before or earlier, if the patient's condition so permits).
Drugs that may increase plasma carbamazepine levels.
Since raised plasma carbamazepine levels may induce adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of the drug Mezacar®, oral suspension, should be adjusted accordingly and/or the plasma levels should be monitored when used concomitantly with the following drugs.
Analgesics, anti-inflammatory drugs: dextropropoxyphene, ibuprofen.
Androgens: danazole.
Antibiotics: macrolide antibiotics (e.g. erythromycin, troleandomycin, josamycin, clarithromycin), ciprofloxacin.

Antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine, trazodone, viloxazine.
Antiepileptics: stiripentol, vigabatrin.
Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole).
Alternative antiepileptic drugs may be recommended in patients treated with voriconazole or itraconazole.
Antihistamines: loratadine, terfenadine.
Antipsychotics: olanzapine, loxapine, quetiapine.
Antituberculous drugs: isoniazid.
Antiviral drugs: protease inhibitors for HIV (e.g. ritonavir).
Carbonic anhydrase inhibitors: acetazolamide.
Cardiovascular drugs: diltiazem, verapamil.
Gastrointestinal drugs: cimetidine, omeprazole.
Muscle relaxants: oxybutynin, dantrolene.
Platelet aggregation inhibitors: ticlopidine.
Other substances: grapefruit juice, nicotinamide (when used in adults, only in high doses).
Drugs that may raise the active metabolite carbamazepine-10, 11-epoxide plasma levels
Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, somnolence, ataxia, diplopia), the dose of the drug Mezacar®, oral suspension, should be adjusted accordingly and/or its plasma levels should be monitored when used concomitantly with the following substances:
Antiepileptics: quetiapine, progabide, valproic acid, valnoctamide, valpromide, primidone, brivaracetam.
Drugs that may decrease plasma carbamazepine levels.
Dose adjustment may be necessary for the drug Mezacar®, oral suspension, in case of concomitant use with the following drugs.
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 mcg/ml before starting treatment with carbamazepine) and fosphenytoin, primidone, and clonazepam (although the data regarding it are contradictory).
Antineoplastic drugs: cisplatin or doxorubicin.
Antituberculous drugs: rifampicin.
Bronchodilators or antiasthmatic drugs: theophylline, aminophylline.
Dermatological drugs: isotretinoin.
Interaction with other substances: herbal preparations containing St John's wort (*Hypericum perforatum*).
Mefloquine may exhibit antagonistic properties regarding the antiepileptic effect of carbamazepine. Accordingly, the dose of the drug Mezacar®, oral suspension, should be adjusted.
Isotrenoin, as it has been reported, changes the bioavailability and/or clearance of carbamazepine and carbamazepine-10,11-epoxide; plasma concentrations of carbamazepine should be controlled.
The effect of the drug Mezacar®, oral suspension, on plasma levels of concomitantly administered drugs.
Carbamazepine may decrease plasma levels of some drugs and decrease or neutralize their effects. Dose adjustment may be necessary for the following drugs in accordance with the clinical requirements.
Analgesics, anti-inflammatory drugs: buprenorphine, methadone, paracetamol (prolonged use of carbamazepine with paracetamol (acetaminophen) may be associated with the development of hepatotoxicity), phenazone (antipyrine), tramadol.
Antibiotics: doxycycline, rifabutin.

Anticoagulants: oral anticoagulants (e.g. warfarin, phenprocoumon, dicoumarol and acenocoumarol, rivaroxaban, dabigatran, apixaban, edoxaban).

Antidepressants: bupropion, citalopram, nefazodone, mianserin, 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. In order to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine, it is recommended to adjust the plasma phenytoin concentration to 13 mcg/ml before adding carbamazepine to the treatment regimen. There were reports of an increase in the plasma level of phenytoin due to the action of carbamazepine, as well as of its decrease, and, in isolated cases, of an increase of the plasma levels of mephenytoin.
Antifungals: itraconazole, voriconazole, ketoconazole. Alternative antiepileptic drugs may be recommended in patients treated with voriconazole or itraconazole.
Anthelmintics: praziquantel, albendazole.
Antineoplastic drugs: imatinib, cyclophosphamide, lapatinib, temsirolimus.
Neuroleptics: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone.
Antiviral drugs: protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).
Anxiolytics: alprazolam, midazolam.
Bronchodilators or anti-asthmatic drugs: theophylline.
Hormonal contraceptives (CYP3A4 substrates):
Carbamazepine is a potent inducer of CYP3A4. Carbamazepine may increase the metabolism of some hormonal contraceptives (by CYP3A4 induction) such as oral and subcutaneous implant contraceptives leading to significantly lower blood concentrations of the hormones. This may cause contraceptive failure or breakthrough bleeding. Alternatives to oral and subcutaneous implant contraceptives, which are significantly affected by CYP3A4 induction, should be considered; or alternatives to the medicinal product carbamazepine should be considered (see section "Administration details").
Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, quinidine, propranolol, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.
Corticosteroids: corticosteroids (namely prednisolone, dexamethasone).
Drugs used in erectile dysfunction: tadalafil.
Immunosuppressants: cyclosporin, everolimus, tacrolimus, sirolimus.
Thyroid drugs: levothyroxine.
Interaction with other substances: products containing estrogens and/or progesterones (alternative contraceptive methods should be considered); buprenorphine, gestrinone, tibolone, toremifene, mianserin, sertraline.
Drug combinations that require separate consideration.
Concomitant use of carbamazepine and levetiracetam may increase carbamazepine toxicity.
Concomitant use of carbamazepine and isoniazid may increase isoniazid hepatotoxicity.
Concomitant use of carbamazepine and lithium preparations may lead to increased neurotoxicity even in the presence of therapeutic plasma levels of lithium. Concomitant use of carbamazepine and metoclopramide or neuroleptics (haloperidol, thioridazine) may increase neurological adverse reactions.
Combination therapy with the drug Mezacar®, oral suspension, and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.
Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g. pancuronium). The dose of these drugs may need to be increased, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.
Like other psychoactive drugs, carbamazepine may reduce alcohol tolerance, therefore, patients are advised to abstain from alcohol.
Concomitant use of carbamazepine with direct oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) may lead to reduced plasma concentrations of direct oral anticoagulants, and thus increase the risk of thrombosis. Therefore, if concomitant use is necessary, patients should be closely monitored for signs and symptoms of thrombosis.
Effect on serological testing.

Carbamazepine may give a false-positive result regarding the concentration of perphenazine, determined by the method of high-performance liquid chromatography (HPLC analysis).
Carbamazepine and 10,11-epoxide may give a false-positive result regarding the concentration of tricyclic antidepressants determined by the method of fluorescence polarization immunoassay.

Administration details.
Mezacar®, oral suspension, should be prescribed only under medical supervision, only after critical benefit/risk assessment and under close monitoring in patients with a history of cardiac, hepatic, or renal damage upon use of other drugs, or interrupted courses of therapy with carbamazepine.
It is recommended to conduct a urinalysis and determine the level of blood urea nitrogen at the beginning and at a certain frequency during therapy. Mezacar®, oral suspension, has a mild anticholinergic activity, therefore, patients with increased intraocular pressure should be warned and advised on possible risk factors.
Possible activation of hidden psychosis, and, with regard to elderly patients – possible activation of confusion and agitation, should be kept in mind.
The drug is usually ineffective in absence seizures (petit mal seizures) and myoclonic seizures. Individual cases indicate that increased seizures are possible in patients with atypical absence seizures.
Hematological effects.
The use of carbamazepine has been associated with agranulocytosis and aplastic anemia; however, due to the very low incidence of these conditions, meaningful risk estimates for Mezacar®, oral suspension, are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons/1000000 per year for agranulocytosis and 2 persons/1000000 per year for aplastic anemia.
Decreased platelet or white blood cell counts may occur during treatment with carbamazepine. Blood tests, including platelet and reticulocyte counts, as well as serum iron, should be performed before initiating treatment with carbamazepine and periodically during the treatment.
Patients and their relatives should be informed about the early signs of carbamazepine therapy toxicity and the symptoms of possible hematological, dermatological, and hepatic disorders. The patient should be warned to immediately seek medical attention in case of reactions such as fever, sore throat, skin rashes, ulcers in the mouth, bruises that occur easily, pinpoint bleeding, or hemorrhagic purpura.
If the white blood cell or platelet count decreases significantly during therapy, the patient's condition should be carefully monitored and a continuous, complete blood count performed. Mezacar®, oral suspension, should be discontinued if the patient develops leukopenia, which is serious, progressive, or accompanied by clinical manifestations, such as fever or sore throat. Mezacar®, oral suspension, should be discontinued if signs of bone barrow suppression occur.
Transient or persistent 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 unlikely to signal the onset of aplastic anemia or agranulocytosis. Blood tests, including platelet counts (as well as, possibly, reticulocyte counts and hemoglobin level), should be performed before initiating treatment with carbamazepine and periodically during the treatment.
Renal function.
It is recommended to perform a urinalysis and determine blood urea nitrogen at the beginning and periodically during treatment with carbamazepine.
Hepatic function.
Assessment of liver function should be conducted before the start and periodically throughout therapy with carbamazepine, especially in patients with history of liver disease and in elderly patients. Carbamazepine should be discontinued immediately in case of exacerbation of chronic liver disorders or in the event of acute liver disease.
Some liver function 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 lead to modest elevations in alkaline phosphatase. This increase in the functional activity of hepatic metabolism is not an indication for the discontinuation of carbamazepine.

Severe hepatic reactions during carbamazepine use occur very rarely. In case of symptoms of liver dysfunction or acute active liver disease, the patient should be examined immediately and treatment with Mezacar®, oral suspension, should be suspended until the results of the examination are obtained.
Suicidal ideations and behaviour.
The risk of suicidal ideations and behaviour has been reported in patients receiving antiepileptic drugs. The mechanism of this risk is not known, and the available data do not exclude the possibility of this risk for therapy with carbamazepine. Therefore, patients should be monitored for suicidal ideations and behaviour, and appropriate treatment should be prescribed if necessary. Patients and their caregivers should be advised to seek medical advice should signs of suicidal ideations or behaviour emerge.
Serious dermatological reactions.
Serious dermatological reactions, including toxic epidermal necrolysis (TEN or 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 lethal. Most of the SJS/TEN cases develop in the first few months of treatment with carbamazepine. These reactions are estimated to occur in 1-6 per 10,000 new patients in countries with predominantly Caucasian populations, however, the risk may be 10 times higher in some Asian countries. If signs and symptoms suggestive of severe dermatological reactions (e.g. SJS, Lyell's syndrome/TEN) appear, the drug Mezacar®, oral suspension, should be discontinued immediately and alternative therapy should be considered.
Pharmacogenomics.
There is growing evidence of the impact of different HLA alleles on the patient's predisposition to adverse reactions associated with the immune system.
<u>Association with (HLA)-B*1502.</u>
Retrospective studies in patients of Han Chinese origin have shown a strong correlation between carbamazepine-associated SJS/TEN skin reactions and the presence of the human leukocyte antigen (HLA), allele (HLA)-B*1502 in these patients. The frequency of this allele HLA-B*1502 is 2% to 12% in Han Chinese patients and around 8% in Thailand. The highest frequency of reports of SJS development is characteristic of some Asian countries (such as Taiwan, Malaysia, and Philippines), where allele (HLA)-B*1502 is more prevalent in the population. The number of carriers of this allele among the Asian population is over 15% in the Philippines, Thailand, Hong Kong and Malaysia, about 10% – in Taiwan, almost 4% – in North China, about 2% to 4% – in South Asia (including India) and less than 1% – in Japan and Korea. (HLA)-B*1502 allele frequency is insignificant in people of European and African descent, in the native American population and Latin American population.
Patients who are considered as genetically belonging to risk groups should be tested for the (HLA)-B*1502 allele before initiating treatment with the drug Mezacar®, oral suspension. If the patient tests positive for the presence of the (HLA)-B*1502 allele, treatment with the drug Mezacar®, oral suspension, should not be started, unless there are no other options of therapeutic treatment. Patients who test negative for the presence of (HLA)-B*1502 have a low rick of SJS, although such reactions may still very rarely occur.
Due to lack of data, it is currently not known whether all the people of Southeast Asian origin have risks.
The allele (HLA)-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other antiepileptic drugs associated with the development of SJS/TEN. Therefore, other drugs associated with SJS/TEN should be avoided in patients that have the allele (HLA)-B*1502 if alternative therapies can be applied. Genetic screening is not generally recommended in patients from populations in which the prevalence of the allele (HLA)-B*1502 is low. Screening is generally not recommended in patients already receiving Mezacar®, oral suspension, as the risk of SJS/TEN development is largely confined to the first few months of therapy, regardless of the patient's (HLA)-B*1502 status.
There is no relation between the (HLA)-B*1502 allele and the development of SJS in Caucasian patients.
<u>Association with (HLA)-A*3101.</u>

The human leukocyte antigen (HLA)-A*3101 may be a risk factor for the development of adverse cutaneous reactions such as SJS, TEN, drug rash with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), maculopapular rash. If the screening reveals the presence of the HLA-A*3101 allele, the use of the drug Mezacar®, oral suspension, should be avoided.
Retrospective studies in Japanese and Northern European populations have demonstrated an association between severe skin reactions (SJS/TEN, DRESS, AGEP and maculopapular rash) associated with carbamazepine use and the carriers of the HLA-A*3101 allele of the human leukocyte antigen (HLA).
The frequency of this allele may vary widely between different ethnic groups: about 2-5% in European populations, about 10% in Japanese populations. The presence of the HLA-A*3101 allele may increase the risk for carbamazepine-induced cutaneous reactions (mostly less severe) from 5.0% in the general population to 26.0% among subjects of Northern European ancestry, whereas its absence may in turn reduce the risk from 5.0% to 3.8%.
There are insufficient data supporting a recommendation for HLA-A*3101 allele screening before starting carbamazepine treatment.
In patients of European or Japanese descent with confirmed presence of the HLA-A*3101 allele, carbamazepine should only be used if the benefits of the therapy exceed the potential risks.
Limitations of genetic screening
The results of genetic screening should not substitute for appropriate clinical supervision and treatment of patients. Other possible factors, such as dosage of the antiepileptic drug, adherence to the therapy regimen, concomitant therapy, play a role in the development of these serious cutaneous adverse reactions.
Other dermatological reactions.
Transient and non-hazardous mild skin reactions, e.g. isolated macular or maculopapular exanthema, can also occur. They usually disappear within a few days or weeks, either during the continued course of treatment or following dose reduction. However, since it may be difficult to differentiate the early signs of more serious dermatological reactions from mild transient reactions, the patient should be kept under close supervision in order to immediately discontinue the drug should the reaction worsen with continued use.
The presence of the HLA-A*3101 allele in the patient is associated with the development of less serious adverse cutaneous reactions to carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular rash).
The presence of the HLA-B*1502 allele in the patient is not a risk factor of less serious cutaneous reactions to carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular rash).
Hypersensitivity.
Carbamazepine may trigger hypersensitivity reactions, including drug rash with eosinophilia and systemic symptoms (DRESS), reactivation of HHV6 associated with the DRESS syndrome, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, abnormal liver function tests, and vanishing bile duct syndrome (including the destruction and disappearance of the intrahepatic bile ducts), which may occur in various combinations. Other organs may also be affected (lungs, kidneys, pancreas, myocardium, colon).
The presence of the HLA-A*3101 allele in the patient is associated with the development of less serious adverse cutaneous reactions to carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular rash).
In general, if symptoms suggestive of hypersensitivity reactions occur, the drug Mezacar®, oral suspension, should be discontinued immediately.
Patients with hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of such patients may experience hypersensitivity reactions with oxcarbazepine. Cross-hypersensitivity can occur when using carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone, and phenobarbital).
Seizures.

Mezacar®, oral suspension, should be used with caution in patients with mixed seizures which include absence seizures (typical or atypical). In such conditions, the drug may provoke seizures. If seizures are provoked, the drug Mezacar®, oral suspension, should be discontinued immediately. An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.

Dose reduction and drug withdrawal.

Abrupt withdrawal of the drug Mezacar®, oral suspension, may provoke seizures, therefore, carbamazepine withdrawal should be gradual. If treatment has to be withdrawn abruptly in a patient with epilepsy, the switch to the new antiepileptic drug should be done under the cover of an appropriate drug (e.g. intravenous diazepam, rectal or intravenous phenytoin).

Women of childbearing age

Carbamazepine may cause fetal harm if used by a pregnant woman (see section "Use during pregnancy or breastfeeding"). Pregnancy registries and epidemiological data suggest a potential association between carbamazepine use during pregnancy and serious congenital malformations, including neural tube defects and defects of other body systems (e.g., craniofacial defects and cardiovascular defects). These available data indicate that, compared to monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. In animal studies, the use of carbamazepine in clinically significant doses during pregnancy resulted in developmental toxicity, including an increase in the incidence of fetal malformations.

Women who may become pregnant should be informed about the potential increased risk of serious birth defects with carbamazepine during pregnancy. The risks and benefits of carbamazepine should be evaluated and discussed with the patient to determine whether alternative treatment should be considered.

If, after careful consideration of alternative treatment options, the benefit cannot be judged to outweigh the risks, carbamazepine should not be used in women of childbearing age. Pregnancy testing should be considered in women of childbearing age before the initiation of treatment with carbamazepine.

Women of childbearing age should use highly effective contraception during treatment and for at least two weeks after stopping the treatment. Carbamazepine may decrease the effectiveness of hormonal contraceptives. Women of childbearing potential should be counselled regarding the use of effective non-hormonal contraception or barrier methods during the use of the drug carbamazepine (see section “Interaction with other medicinal products” and “Use during pregnancy or breastfeeding”).

Women of childbearing age should consult their doctor as soon as they are planning a pregnancy in order to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see section “Use during pregnancy or breastfeeding”). Women of childbearing age should be advised to contact the doctor immediately if they become pregnant or think they might be pregnant and are taking carbamazepine.

Endocrine effects.

Breakthrough bleeding has been reported in women taking carbamazepine while using hormonal contraceptives. The reliability of hormonal contraceptives is adversely affected by carbamazepine due to liver enzyme induction, therefore, women of childbearing age taking Mezacar®, oral suspension, should use alternative methods of contraception.

Patients taking Mezacar®, oral suspension, and requiring hormonal contraception should receive a preparation containing not less than 50 mcg estrogen, or use of alternative non-hormonal methods of contraception should be considered in such patients.

Monitoring of plasma drug concentrations.

Although correlations between the dosage and the plasma levels of carbamazepine, as well as between the plasma levels of carbamazepine and the clinical efficacy or tolerability are rather tenuous, monitoring of the drug plasma levels may be reasonable in the following situations: dramatic increase in seizure frequency, verification of patient compliance, during pregnancy, when treating children; in suspected absorption disorders, in suspected toxicity, when more than one drug is being used.

Hyponatremia.

Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium levels or in patients treated concomitantly with sodium-lowering medicinal products (such as diuretics, medicinal products associated with inappropriate antidiuretic hormone secretion), blood sodium levels should be measured prior to initiating treatment and, thereafter, after approximately 2 weeks and then at monthly intervals for the first 3 months during therapy, or according to the clinical need. This applies to elderly patients in particular. If hyponatremia is observed according to clinical indications, water restriction should be used.

Hypothyroidism.

Carbamazepine may reduce the concentrations of thyroid hormones, therefore, an increase in the dose of thyroid hormone replacement therapy is required in patients with hypothyroidism. Thyroid function monitoring should be performed to adjust the dosage of thyroid hormone replacement therapy.

Anticholinergic effects.

Carbamazepine demonstrates mild anticholinergic activity. Therefore, patients with increased intraocular pressure and urinary retention should be closely observed during therapy.

Psychiatric effects.

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

Interaction.

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

Co-administration of CYP3A4 inducers with carbamazepine may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of CYP3A4 inducers may increase carbamazepine plasma concentrations. Carbamazepine dose adjustment may be required.

Carbamazepine is a potent inducer of CYP3A4 isoenzyme and other phase I and phase II enzyme systems in the liver and may reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism (see section “Interaction with other medicinal products and other types of interaction”).

Female patients of childbearing age should be warned that concurrent use of carbamazepine with hormonal contraceptives may render the latter ineffective. Alternative non-hormonal forms of contraception are recommended when using Mezacar®, oral suspension (see section “Interaction with other medicinal products and other types of interactions” and “Use during pregnancy or breastfeeding”).

Use in elderly patients.

Due to drug interactions and different pharmacokinetics of antiepileptic drugs, the dose of Mezacar®, oral suspension, should be selected with caution in elderly patients.

Falls.

Carbamazepine treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, or lethargy (see “Adverse reactions”), which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or those using medications that could exacerbate these effects, complete and regular risk assessment of fall should be considered in case of long-term treatment with *carbamazepine.*

Photosensitivity. Patients should avoid exposure to sunlight during carbamazepine treatment due to the risk of photosensitivity.

Excipients.

The drug contains azo dye sunset yellow FCF which may cause allergic reactions. In case of intolerance to some sugars, the patient should consult a doctor before taking this drug as it contains sorbitol solution and sucrose.

Use during pregnancy or breastfeeding.

Pregnancy

Overall risk associated with the use of antiepileptic drugs (AED)

Medical advice regarding the potential risks to the fetus caused both by seizures and antiepileptic treatment should be given to all women of childbearing age receiving antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.
Sudden discontinuation of AED therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.
Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations.
Risks associated with carbamazepine
Carbamazepine crosses the placental barrier. Prenatal exposure to carbamazepine may increase the risks for congenital malformations and other adverse development outcomes. Carbamazepine exposure during pregnancy is associated with an incidence of severe congenital malformations that is 2–3 times higher than in the general population, with an incidence of 2–3%. The reported congenital malformations include neural tube defects, craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadia, finger hypoplasia and other anomalies involving various body systems in fetuses of mothers who used carbamazepine during pregnancy. Specialized antenatal surveillance for these malformations is recommended. Neurodevelopmental disorders have been reported in the offspring of women with epilepsy who used carbamazepine as monotherapy or in combination with other AEDs. Studies of the risks of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are questionable and the risk cannot be excluded.
Carbamazepine should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative treatment options. The woman should be fully informed of and understand the risks of taking carbamazepine during pregnancy.
Evidence suggests that the risk of congenital malformations with carbamazepine may be dose-dependent. If, based on careful risk/benefit assessment, no alternative treatment option is suitable, and treatment with carbamazepine is continued, monotherapy and the lowest effective dose of carbamazepine should be used, and monitoring of plasma levels is recommended. The plasma concentration can be maintained in the lower side of the therapeutic range from 4 to 12 mcg/ml, provided that seizure control is maintained.
Some AEDs, such as carbamazepine, have been reported to decrease serum folate levels. This deficiency may contribute to the increased incidence of congenital malformations in the offspring of women with epilepsy. Folic acid supplementation is recommended before and during pregnancy. In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1 be given to the mother during the last weeks of pregnancy as well as to the newborn.
If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking carbamazepine, she should be referred to a specialist to reassess the treatment and consider alternative treatment options.
Women of childbearing age
Carbamazepine should not be used in women of childbearing age unless the potential benefits/risks outweigh the alternative treatment options. The woman should be fully informed of and understand the risk of potential harm to the fetus if carbamazepine is taken during pregnancy, therefore, any pregnancy should be planned beforehand. Pregnancy testing in women of childbearing age should be considered prior to initiating treatment with carbamazepine.
Women of childbearing age should use highly effective contraception during treatment and for at least two weeks after stopping the treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives (see section “Interaction with other medicinal products and other types of interaction”), therefore, women of childbearing age should be counselled regarding the use of other effective contraceptive methods. At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

Newborns.
In order to prevent bleeding disorders in newborns, it has also been recommended that vitamin K_1 be prescribed to the mother during the last weeks of pregnancy as well as to the newborn.
Several cases of neonatal seizures and/or respiratory depression, as well as several cases of vomiting, diarrhea and/or appetite disorders have been reported in association with the use of carbamazepine and other anticonvulsants by the mother. These reactions may represent a neonatal withdrawal syndrome.
Breastfeeding.
Carbamazepine passes into breast milk (about 25-60% of the plasma concentrations). The benefits of breastfeeding with a delayed possibility of adverse reactions in the infant should be weighed carefully. Mothers receiving carbamazepine may breastfeed, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reactions). There have been some reports of cholestatic hepatitis in newborns exposed to carbamazepine during the antenatal period and or during breastfeeding. Therefore, breastfed newborns of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects.
Fertility.
There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

Effect on reaction rate when driving motor transport or using other mechanisms.
The ability of the patient receiving carbamazepine to react (especially at the start of treatment or during dose adjustment) may be impaired by the medical condition resulting in seizures as well as by adverse reactions associated with the use of the drug Mezacar®, oral suspension, including dizziness, somnolence, ataxia, diplopia, impaired accommodation, and blurred vision. Patients should therefore exercise due caution when driving a vehicle or operating other mechanisms.

Dosage and administration.
The drug may be taken during or after a meal, or between meals with a small amount of liquid.
Mezacar®, oral suspension, is used orally. Shake before use.
The dose is usually divided into 2-3 doses.
As the maximum concentration level of carbamazepine when receiving the drug in the form of suspension is higher compared to the same dose of the drug in the tablet form, it is recommended to start using the suspension with low doses and gradually increase them (to avoid CNS adverse reactions, such as dizziness and somnolence).
When replacing the tablet formulation with suspension, the same dose should be administered, however it should be divided into smaller single doses, and the number of intakes should be increased accordingly.
Before initiating treatment, patients of certain ethnic groups (Chinese, Thai) should be screened for HLA-B*1502 as the presence of this allele strongly predicts the risk of severe carbamazepine-associated Stevens-Johnson syndrome.
Epilepsy.
The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate seizure control. Determination of carbamazepine 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 mcg/ml (17 to 50 μmol/l).
Adults.
A gradually increasing dosage scheme, which should be adjusted to suit the needs of each individual patient, is recommended for all formulations of carbamazepine.
For adults, the initial dose of the drug is 100-200 mg 1-2 times a day. Then the dose is slowly raised to achieve the optimal effect; it is usually achieved at a dose of 800-1200 mg per day, divided into 2 or more doses. In some patients the dose may need to be increased to 1600-2000 mg/day.
Elderly patients
Due to the increased interaction with other medicinal products, carbamazepine dosage should be carefully selected in elderly patients.
Children.

A gradually increasing dosage scheme, which should be adjusted to suit the needs of each individual patient, is recommended for all formulations of carbamazepine.
The usual daily dose of the drug is 10-20 mg/kg bodyweight, which should be divided into several doses.
The following daily doses are recommended for different ages (table 1).

Table 1.

Age	*Daily dose, mg*	*Daily dose, ml*
Up to 1 year	100-200 mg	5-10 ml
1 to 5 years	200-400 mg	10-20 ml
5 to 10 years	400-600 mg	20-30 ml
10 to 15 years	600-1000 mg	30-50 ml
Above 15 years	800-1200 mg	40-60 ml

The following maximum daily doses are recommended for different ages (table 2).

Table 2.

Age	*Maximum daily dose*
Up to 6 years	35 mg/kg/day
6 to 15 years	1000 mg/day
Above 15 years	1200 mg/day

When possible, antiepileptic drugs should be prescribed separately (as monotherapy), however, when used in polytherapy, the same incremental dosage pattern is advised. When Mezacar®, oral suspension, is added to the existing antiepileptic therapy, the dose of the drug should be increased gradually while maintaining or, if necessary, adjusting the dose of the currently used antiepileptic drug(s) (see section *"Interaction with other medicinal products and other types of interaction"*).
Trigeminal neuralgia.
The initial dose of carbamazepine is 200-400 mg daily. It should be raised slowly until pain disappears (normally up to 600-800 mg daily, divided into 3-4 doses). In some instances, doses of 1600 mg daily may be needed. When pain is reduced, the dosage should then be gradually reduced to the lowest possible maintenance level. The maximum recommended daily dose is 1200 mg. When pain relief has been obtained, attempts should be made to gradually discontinue carbamazepine therapy, until another attack occurs.
Elderly patients
Due to the increased interaction with other medicinal products, the dosage of carbamazepine should be selected with caution in elderly patients.
In elderly patients, the recommended initial dose is 200 mg daily, divided into 2 doses. This dose should be slowly raised daily until pain disappears (normally up to 600-800 mg daily, divided into 3-4 doses). Once pain is reduced, the dosage should then be gradually reduced to the lowest possible maintenance level. The maximum recommended daily dose is 1200 mg. When pain relief has been obtained, attempts should be made to gradually discontinue carbamazepine therapy, until another attack occurs.
Prevention of manic-depressive psychosis in patients unresponsive to lithium therapy.
The initial dose is 400 mg daily, divided into several single doses. The dose should be gradually increased until control of symptoms is achieved or until the daily dose of 1600 mg, divided into several doses, is reached. The usual daily dose is 400-600 mg, divided into several doses.
Special patient groups
Renal/hepatic impairment

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

Children.
Treatment of bipolar disorder and pain in trigeminal neuralgia
The safety and efficacy of carbamazepine use in children have not been established.
Treatment of epilepsy
The safety and efficacy of carbamazepine use in children for the treatment of partial seizures, generalized tonic-clonic seizures and combinations of these seizures have been determined (see sections "Indications" and "Dosage and administration").
Oral suspension Mezacar® can be used in children from birth.

Overdose.
Symptoms. The signs and symptoms that develop in case of overdosage involve the central nervous, cardiovascular, respiratory systems, as well as the adverse drug reactions mentioned in section "Adverse reactions".
Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucinations, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, hyperreflexia (initially), hyporeflexia (later); convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.
Respiratory system: respiratory depression, pulmonary edema.
Cardiovascular system: tachycardia, hypotension, sometimes 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 reports of individual cases of rhabdomyolysis associated with carbamazepine toxicity.
Urinary system: urinary retention, oliguria or anuria; fluid retention; water intoxication due to the effect of carbamazepine similar to the action of the antidiuretic hormone.
Changes in laboratory findings: hyponatremia, possible metabolic acidosis, hyperglycemia, increased muscle creatine phosphokinase.
Treatment. No specific antidote is available. Initially, treatment should be based on the clinical condition of the patient; admission to the hospital is indicated. Carbamazepine plasma concentration is determined to confirm the poisoning with this agent and to assess the degree of overdose.
Evacuation of the stomach, gastric lavage, and administration of activated charcoal are carried out. Delay in evacuating the stomach may result in delayed absorption, leading to the recurrence of intoxication symptoms during recovery. Symptomatic supportive treatment is used in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.
Special recommendations. In case of hypotension, intravenous dopamine or dobutamine is indicated; in case of heart rhythm disorders, treatment should be selected individually; in case of convulsions, benzodiazepines (e.g. diazepam) or other anticonvulsants such as phenobarbital (with caution due to increased risk of respiratory depression) or paraldehyde are administered; in case of hyponatremia (water intoxication), introduction of fluid is restricted and a slow, careful intravenous infusion of 0.9% sodium chloride solution is performed. These measures can be useful in preventing cerebral edema.
It is recommended to conduct hemosorption using coal sorbents. Hemodialysis and peritoneal dialysis have been reported to be effective in overdose with carbamazepine.
It is necessary to consider the possibility of aggravation of overdose symptoms on the 2nd and 3rd day after its onset, due to the delayed absorption of the drug.

Adverse reactions.
At the start of treatment with carbamazepine, or if the initial dose is too high, or when treating elderly patients, certain types of adverse reactions occur commonly or uncommonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, somnolence, fatigue, diplopia), gastrointestinal disturbances

(nausea, vomiting), or allergic skin reactions.
Dose-dependent adverse reactions usually abate within a few days, either spontaneously or after a transient dose reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuations in plasma concentrations of the active ingredient. In such cases it is advisable to monitor the plasma levels of the active ingredient and divide the daily dose of the drug into smaller (i.e. 3–4) individual doses.
Adverse reactions were observed with the following frequency: very common (> 1/10) common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (> 1/10000, < 1/1000); very rare (< 1/10000), including individual cases.
Blood and lymphatic system disorders: very common – leukopenia; common – thrombocytopenia, eosinophilia; rare – lymphadenopathy, leukocytosis; very rare – agranulocytosis, aplastic anemia, pancytopenia, pure red cell aplasia, anemia, megaloblastic anemia, reticulocytosis, hemolytic anemia.
Immune system disorders: rare – delayed multi-organ hypersensitivity disorder with fever, skin rash, vasculitis, lymphadenopathy; pseudolymphoma; arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, and abnormal liver function tests, and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), which may occur in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon); very rare – aseptic meningitis with myoclonus and peripheral eosinophilia; anaphylactic reaction, angioedema, hypogammaglobulinemia.
Endocrine system disorders: common – edema, fluid retention, weight gain, hyponatremia, and lowered plasma osmolarity due to the effect similar to the action of the antidiuretic hormone, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, and neurological disorders, convulsions, disorientation, perceptual disturbances, visual disturbances, or encephalopathy (syndrome of inappropriate antidiuretic hormone secretion, SIADH); very rare – increased blood prolactin levels accompanied or not accompanied by such manifestations as galactorrhea, gynecomastia, bone metabolism disorders (decrease in plasma calcium and 25-hydroxy-cholecalciferol levels), leading to osteomalacia/osteoporosis; in individual cases – increased cholesterol concentrations, including high density lipoproteins and triglycerides.
Metabolism and nutrition disorders: rare – folate deficiency, decreased appetite; very rare – acute porphyria (acute intermittent porphyria and variegate porphyria), non-acute porphyria (porphyria cutanea tarda); unknown – hyperammonemia.
Psychiatric disorders: rare – hallucinations (visual or auditory), depression, loss of appetite, restlessness, aggression, agitation, confusional state; very rare – activation of psychosis.
Nervous system: very common – dizziness, ataxia, somnolence, fatigue; common – headache, diplopia, eye accommodation disorders (e.g. blurred vision); uncommon – abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus; rare – orofacial dyskinesia, eye movement disorders, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, peripheral neuropathy, paresthesia, muscle weakness, and paresis; very rare – taste disturbance, neuroleptic malignant syndrome (NMS), aseptic meningitis with myoclonia and peripheral eosinophilia, dysgeusia.
Organs of vision: common – accommodation disorders (e.g. blurred vision); very rare – lens opacification, conjunctivitis, increased intraocular pressure.

Ear and labyrinth disorders: very rare – hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, pitch perception disturbances.
Cardiovascular disorders: rare – intracardiac conduction disorder; hypertension or hypotension; very rare – bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, coronary artery disease aggravated, thrombophlebitis, thromboembolism (e.g. pulmonary embolism), vasculitis.
Respiratory, thoracic and mediastinal disorders: very rare – pulmonary hypersensitivity reactions characterized by fever, dyspnea, pneumonitis, or pneumonia.
Gastrointestinal disorders: very common – nausea, vomiting; common – dry mouth; uncommon – diarrhea or constipation; rare – abdominal pain; very rare – glossitis, stomatitis, pancreatitis.

Hepatobiliary disorders: very common – elevated gamma-glutamyl transferase levels (due to liver enzyme induction), which is usually clinically insignificant; common – elevated blood alkaline phosphatase levels; uncommon – elevated transaminase levels; rare – hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice; very rare – granulomatous hepatitis, hepatic failure.
Skin and subcutaneous tissue disorders: very common – allergic dermatitis, pruritus, urticaria, sometimes severe; uncommon – exfoliative dermatitis, erythroderma; rare – systemic lupus erythematosus, pruritus; very rare – Stevens-Johnson syndrome (in some Asian countries this adverse reaction was reported as "rare"), toxic epidermal necrolysis, photosensitivity, erythema multiforme and erythema nodosum, skin pigmentation disorder, purpura, acne, increased sweating, increased hair loss, hirsutism.
Musculoskeletal, connective tissue and bone disorders: rare – muscle weakness, very rare – arthralgia, myalgia, muscle spasms, bone metabolism disorders (decrease in plasma calcium and 25-hydroxy-cholecalciferol levels), leading to osteomalacia/osteoporosis.
Renal and urinary system disorders: very rare – tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, hematuria, oliguria, blood urea increased/azotemia), urinary frequency, urinary retention.
Reproductive system disorders: very rare – sexual dysfunction/impotence/erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility).
There have been very rare reports of fertility disturbances and/or abnormal spermatogenesis in men.
General disorders: very common – fatigue.
Abnormal laboratory and instrumental findings: very common – elevated gamma-glutamyl transferase levels (due to liver enzyme induction), which is usually clinically insignificant, common – elevated blood alkaline phosphatase levels, uncommon – elevated transaminase levels, very rare – increased intraocular pressure, increased blood cholesterol levels (including high density lipoproteins and triglycerides), increased blood triglyceride levels, abnormal thyroid function parameters: decreased L-thyroxine levels (free thyroxine (FT_4), thyroxine (T_4), triiodothyronine (T_3)), and increased blood thyroid stimulating hormone (TSH), usually without clinical manifestations; increased blood prolactin levels, hypogammaglobulinemia.
Injury, poisoning, and procedural complications: falls (carbamazepine therapy was associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedative effect) (see section "Administration details")
Adverse reactions based on spontaneous reports (frequency unknown).
Information on the following adverse reactions has been obtained from spontaneous reports and publications during the post-marketing use of the drug. Since the reports are spontaneous, it is impossible to identify the exact number of patients and adequately assess the frequency of adverse reactions, therefore, their frequency is classified as "unknown".
Infections and infestations: reactivation of human herpesvirus VI.
Blood and lymphatic system disorders: bone marrow failure.
Nervous system disorders: lethargy, sedation, memory impairment.
Gastrointestinal disorders: colitis.
Immune system disorders: drug rash with eosinophilia and systemic symptoms (DRESS).
Skin and subcutaneous tissue disorders: acute generalized exanthematous pustulosis (AGEP) lichenoid keratosis, onychomadesis.
Musculoskeletal, connective tissue and bone disorders: fractures.
Abnormal laboratory and instrumental findings: decreased bone mineral density.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorization of the medicinal product is an important procedure. It allows continued monitoring of the benefit/risk balance of this medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system and to the applicant via the feedback form at the website: https://kusum.ua/pharmacovigilance/.

Shelf life. 3 years.

Storage conditions.
Store at a temperature not more than 25 °C.
Keep out of reach of children.
After the first opening of the bottle, store the drug for no more than 4 weeks.

Package.
100 ml of suspension are in a bottle, one bottle with a dosing cup is in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str., 54.

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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