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The Order of Ministry of
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INSTRUCTION
for medical use

MEZACAR®

Composition:
active substance: carbamazepine;
5 ml of suspension contain carbamazepine 100 mg;
excipients: xanthan gum; hypromellose; potassium sorbate; citric acid, monohydrate; propylene glycol; sorbitol solution, which does not crystallize (E 420); sucrose; sunset yellow FCF (E 110); flavor "Orange"; flavor "Vanilla"; purified water.

Pharmaceutical form. Oral suspension.
Basic physico-chemical properties: viscous suspension of orange color with a specific odor.

Pharmacotherapeutic group.
Antiepileptic drugs. Code ATC N03A F01.

Pharmacological properties.
Pharmacodynamics.
Carbamazepine shows antiepileptic, neurotropic and psychotropic activity. As *anticonvulsant agent* carbamazepine is effective in partial seizures (simple and complex) with secondary generalization and without it; generalized tonic-clonic convulsions, as well as in combination of these types of convulsion. The mechanism of action of carbamazepine is only partially determined. Carbamazepine stabilizes membranes hyperactive nerve cells, inhibits repetitive neuronal discharges, reduces synaptic propagation of excitatory impulses. It has been found that the main mechanism of action of the preparation is prevention of repeated formation of sodium dependent action potentials in depolarized neurons through blockade of sodium channels. Anticonvulsant effect of the drug is mainly due to the decrease of glutamate release and stabilization of neuron membranes, while anti-maniac effect may be due to the suppression of dopamine and noradrenaline metabolism.
When using carbamazepine as monotherapy in patients with epilepsy (especially children) psychotropic effect has been marked, this was partly manifested by positive effect on symptoms of anxiety and depression, as well as decreased irritability and aggressiveness. According to a number of studies, the effect of carbamazepine on cognitive function and psychomotor performance depended on the dose and was either dubious or negative. In course of other studies a positive effect of carbamazepine on indicators that characterize attention, learning ability and memorization has been marked.
As *neurotropic agent* carbamazepine is effective in some neurological diseases. For example, it prevents pain episodes in idiopathic and secondary trigeminal neuralgia. Besides, the drug should be used for relief of neurogenic pain in various states, including amyelotrophy, posttraumatic paresthesia and postherpetic neuralgias. In alcohol withdrawal syndrome, the drug increases the threshold of

convulsive readiness (which is decreased in this condition) and reduces the severity of clinical manifestations of the syndrome, such as excitability, tremor, gait impairment. In patients with diabetes insipidus of central origin the drug reduces diuresis and thirst.
It has been confirmed that as *psychotropic agent* the drug is effective in affective disorders, that is: for treatment of acute manic states, for supportive treatment of bipolar (manic-depressive) affective disorders (as monotherapy, as well as in combination with neuroleptic agents, antidepressants or lithium).
Pharmacokinetics.
Absorption.
Carbamazepine is completely, but relatively slowly absorbed from tablets. After a single administration of conventional tablet, the maximum plasma concentration (C_{max}) is reached after 12 hours, and in a liquid form – after 2 hours. There is no clinically significant difference between oral dosage forms in the amount of active substance absorbed. After a single administration of 400 mg of carbamazepine (tablets) mean maximum plasma concentration of unchanged carbamazepine is approximately 4.5 μg/ml.
It has been shown that bioavailability of carbamazepine in various oral forms is 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.
Sustained 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 reducing the bioavailability, the risk of convulsions or excessive adverse effects; it may be advisable not to replace the drug with another.
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Distribution.
Carbamazepine is bound to plasma proteins within the range of 70–80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the percentage of substance unbound to plasma proteins (20–30%). Concentrations were found in breast milk, they are 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 route 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 derivative of carbamazepine-10, 11-epoxide, 10, 11-trans-diol. 9 hydroxymethyl-10-carbamoyl acridan is a secondary metabolite of this path. After a single dose of carbamazepine, about 30% is detected in the urine end products of epoxide path.
Other important paths of biotransformation of carbamazepine lead to various monohydroxylated compounds, as well as N-glucuronide of carbamazepine, which is formed by UGT2B7.
Excretion

The half-life of unchanged carbamazepine averages about 36 hours after a single dose, after repeated administration the half-life averages only 16-24 hours (autoinduction of hepatic mono-oxygenase system) depending on the duration of treatment. In patients receiving concomitant treatment with other enzyme-dependent drugs (e.g. phenytoin, phenobarbital), the half-life averages 9-10 hours.
The average half-life of 10,11-epoxide metabolite in plasma is approximately 6h after administration of the dose of epoxide.
After 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 appears unchanged 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 µg/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 therapeutic concentration children may need higher doses of carbamazepine (in mg/kg), than adults.
Elderly patients. There are no data indicating that pharmacokinetics of carbamazepine changes in elderly patients (compared to young adults).
Patients with impaired function of kidneys or liver. So far there are no data about pharmacokinetics of carbamazepine in patients with impaired function of kidneys or liver.

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

Contraindications.
Hypersensitivity to carbamazepine or chemically similar drugs (e.g. tricyclic antidepressants) or any other component of the drug.
Atrioventricular block.
Bone marrow suppression in the anamnesis.
Hepatic porphyria (e.g. acute intermittent porphyria, mixed porphyria, late skin porphyria) in the anamnesis.
Concomitant use with moniamineoxidase (MAO) inhibitors.

Drug interactions and other types of interactions.
Cytochrome P450 3A4 (CYP3A4) is the main enzyme that catalyzes formation of the active metabolite carbamazepine-10,11-epoxide. Concomitant use of CYP3A4 inhibitors or inhibitors of carbamazepine epoxide hydrolyzate may cause increase in the concentration of carbamazepine in blood plasma, which in its turn may bring on adverse reactions. Concomitant use of CYP3A4 inducers may increase metabolism of carbamazepine, which causes potential decrease in serum carbamazepine concentration and therapeutic effect. Similarly, discontinuation of the enzyme CYP3A4 inducers may reduce the speed of metabolism of carbamazepine and lead to an increase in its plasma concentration.
Carbamazepine is a potent inducer of CYP3A4 and other enzyme systems of the phases I and II in the liver, therefore it may decrease plasma concentrations of other preparations, which are mostly metabolized by CYP3A4 through induction of their metabolism.
Human microsomal epoxide hydrolases is an enzyme responsible for the formation of 10,11-transdyl derivatives of carbamazepine-10,11-epoxide. The simultaneous administration of inhibitors of human microsomal epoxy hydrolases may result in increased concentrations of carbamazepine-10,11-epoxide in plasma.
Contraindicated interaction.

Mezacar®, an oral suspension, is contraindicated in combination with monoamine oxidase inhibitors (MAO); Before starting the drug, you must stop taking the MAO inhibitor (at least 2 weeks or earlier, if the patient's condition so permits).

Drugs that may increase the level of carbamazepine in the blood plasma.

Since the increase in the level of carbamazepine in blood plasma may cause adverse reactions (such as dizziness, somnolence, ataxia, diplopia), the dosage of the drug Mezacar®, oral suspension, should be adjusted accordingly and/or its plasma levels should be controlled when concomitant use with the following drugs.

Analgesics, anti-inflammatory drugs: dekstropropoxyfen, ibuprofen.

Androgens: diazole.

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

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

Antiepileptic agents: stiripentol, vigabatrin.

Antifungal agents: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole).

Patients receiving treatment with voriconazole or itraconazole may be recommended alternative antiepileptic drugs.

Antihistamine agents: loratadine, terfenadine.

Antipsychotic agents: olanzapine, loxapine, quetiapine.

Antituberculous agents: isoniazid.

Antiviral agents: protease inhibitors for HIV (e.g. ritonavir).

Carbonic anhydrase inhibitors: acetazolamide.

Cardiovascular agents: diltiazem, verapamil.

Drugs for treatment of gastrointestinal tract diseases: cimetidine, omeprazole.

Myorelaxants: oxybutynin, dantrolene.

Antiaggregant agents: ticlopidine.

Other substances: grapefruit juice, nicotinamide (when using in adults, only in high doses).

Drugs that may increase the level of active metabolite carbamazepine-10,11-epoxide in blood plasma.

Since the increased plasma level of active metabolite carbamazepine-10,11-epoxide may cause adverse reactions (e.g., dizziness, drowsiness, ataxia, diplopia), the dosage of the drug Mezacar® oral suspension, should be accordingly adjusted and/or plasma level of the drug should be controlled, if Mezacar®, oral suspension, is taken concomitantly with such drugs: loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Drugs that may decrease the level of carbamazepine in blood plasma.

Dosage adjustment might be necessary for the drug Mezacar®, oral suspension, in case of concomitant use with the following drugs.

Antiepileptic agents: felbamate, metsuximide, oxcarbazepine, phenobarbitone, phensuccimide, phenytoin (to avoid intoxication with phenytoin and subtherapeutic concentrations of carbamazepine, it is recommended to adjust plasma concentration of phenytoin to 13 µg/ml before starting treatment with carbamazepine) and fosphenytoin, primidone and clonazepam (though the data on it are controversial).

Anitumoral agents: cisplatin or doxorubicin.

Antituberculous agents: rifampicin.

Bronchodilators or antiasthmatic agents: theophylline, aminophylline.

Dermatologic agents: isotretinoin.

Interaction with other substances: preparations of medicinal herbs containing St. John's wort (*Hypericum perforatum*).

Mefloquine may exhibit antagonistic properties regarding antiepileptic effect of carbamazepine. Accordingly, the dose of the drug Mezacar®, oral suspension, should be adjusted.

Isotrenoin, as it has been reported, changes bioavailability and/or clearance of carbamazepine andcarbamazepine-10,11-epoxide; plasma concentrations of carbamazepine should be controlled.

Effect of the drug Mezacar®, oral suspension, on plasma level of concomitantly administered drugs.

Carbamazepine may decrease plasma level of some drugs and decrease or neutralize their effects. Dosage 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, dicumarol and acenocumarol).
Antidepressants: bupropion, citalopram, nefazodone, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, smitriptyline, nortriptiline, clomipramine).
Antiemetic agents: aprepitant.
Antiepileptic agents: 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 phenytoin concentration in plasma to 13 μg / ml before adding carbamazepine to the treatment regimen. It was reported as an increase in the level of phenytoin in the blood plasma due to the action of carbamazepine, and on its decrease, and on isolated cases of increased levels of mefenitoin in blood plasma.
Antifungal agents: itraconazole, voriconazole, ketoconazole. Alternative antiepileptic agents may be recommended to patients receiving treatment with voriconazole or itraconazole.
Anthelmintic agents: praziquantel, albendazole.
Anitumoral agents: imatinib, cyclophosphamide, lapatinib, temsirolimus.
Neuroleptic agents: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone.
Anti-viral agents: protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).
Anxiolytic agents: alprazolam, midazolam.
Bronchodilators or antiasthmatic agents: theophylline.
Contraceptive agents: hormonal contraceptives (the possibility of using alternative methods of contraception should be considered).
Cardiovascular agents: calcium channel blockers (dihydropyridine group), e.g. felodipine, digoxin, quinidine, propranolol, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.
Corticosteroids: corticosteroids (in particular prednisone, dexamethasone).
Agents used for treatment of erectile dysfunction: tadalafil.
Immunosuppressant agents: cyclosporine, everolimus, tacrolimus, sirolimus.
Thyroid agents: levothyroxine
Interaction with other drugs: preparations containing estrogen and/or progesterone (alternative methods of contraception should be considered); buprenorphine, gestrinone, tibolone, toremifene, mianserine, sertraline.
Combinations of drugs that require special consideration.
Concomitant use of carbamazepine and levetiracetam may lead to increased toxicity of carbamazepine.
Concomitant use of carbamazepine and isoniazid may lead to increased hepatotoxicity of isoniazid.
Concomitant use of carbamazepine and lithium or metoclopramide, as well as carbamazepine and neuroleptics (haloperidol, thioridazine) may lead to increased adverse neurological effects.
Combined 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. pancuronia). It may be necessary to increase doses of these drugs, and the patients require close monitoring because of the possibility of a faster than expected completion of neuromuscular blockade.
Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance, therefore, patients are advised to abstain from alcohol.
Effect on serologic examination.
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 polarization fluorescence immunoassay.

Peculiarities of use.

Mezacar®, oral suspension should be administered only under medical supervision, only after a critical evaluation of the benefit / risk ratio and with careful monitoring of patients with heart, liver or kidney disorders, with side effects (in the history) of the blood side when used with other drugs and Interrupted courses of carbamazepine therapy.

It is recommended to conduct a general analysis of urine and determine the level of urea nitrogen in the blood 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 advised and advised on possible risk factors.

It should be remembered about the possible activation of hidden psychosis, and with regard to the elderly - about the possible activation of confusion and anxiety.

The drug is usually ineffective in absences (small epileptic seizures) and myoclonic attacks. Separate cases indicate that increased attacks are possible in patients with atypical absenches.

Hematological effects.

The development of agranulocytosis and aplastic anemia is associated with the drug, however due to the extremely low incidence of these states it is impossible to evaluate the significant risk when using the drug Mezacar®, oral suspension. The overall risk for people who are not receiving treatment, is 4.7 persons/1,000,000 per year for the development of agranulocytosis and 2 persons/1 million a year for the development of aplastic anemia.

With carbamazepine therapy, the number of platelets or leukocytes may decrease. Prior to initiating carbamazepine therapy and periodically during the course of it, blood tests should be performed, including determination of platelet count, reticulocytes and iron content in blood serum.

Patients and their relatives should be informed about the early signs of toxicity and symptoms of the possible hematological disorders, as well as about the symptoms of dermatological and hepatic reactions. The patient should be warned that in case of such reactions as fever, sore throat, skin rashes, sores in the mouth, bruises that occur easily, pinpoint bleeding or hemorrhagic purpura, they should immediately seek medical attention. If the number of leukocytes or platelets significantly decreases during therapy, the condition of the patient should be carefully monitored and a continuous, common blood test. Treatment with Mezacar®, an oral suspension, should be stopped if the patient develops leukopenia, which is serious, progressive, or accompanied by clinical manifestations, such as fever or throat pain. The use of Mezacar®, an oral suspension, should be discontinued if signs of inhibition of bone marrow function occur.

Periodically or often there is a temporary or persistent decrease in the number of platelets or white blood cells due to the administration of carbamazepine. However, for most of these cases, their temporality is confirmed and they do not indicate the development of aplastic anemia or agranulocytosis. Prior to initiating carbamazepine therapy and periodically during the course of the test, a blood test, including platelet count (and, possibly, reticulocyte count and hemoglobin levels) should be performed.

Kidney function.

It is recommended to conduct a general analysis of urine and determine the level of urea nitrogen in the blood at the beginning and at a certain frequency during carbamazepine therapy.

Liver function.

The assessment of liver function should be performed prior to the initiation of carbamazepine therapy and periodically during therapy, especially in patients with history of liver disease and in elderly patients. Reception of carbamazepine should be stopped immediately in case of exacerbation of chronic disorders of the liver function or in the event of an acute liver disease.

Some laboratory parameters of liver function in patients receiving carbamazepine may go beyond the norm, in particular gamma glutamyltransferase (GGT). This is probably due to the induction of hepatic enzymes. The induction of enzymes can also lead to a moderate increase in alkaline phosphatase levels. Such an increase in the functional activity of the hepatic metabolism is not an indication for the abolition of carbamazepine.

Severe side-effects of the liver when used with carbamazepine are observed very rarely. In case of symptoms of liver dysfunction or acute active liver disease, the patient should be urgently examined, while treatment with Mezacar®, oral suspension, should be suspended until the results are obtained.
Suicidal thoughts and behavior.
There was a risk of suicidal thoughts and behavior in patients receiving antiepileptic drugs. The mechanism of this risk is unknown, and the available data do not exclude it in the case of carbamazepine therapy. Therefore, patients need to be checked for suicidal thoughts and behaviors and, if necessary, prescribed appropriate treatment. Patients and persons caring for patients should be advised to seek medical advice if signs of suicidal thoughts and behavior develop.
Serious dermatological reactions.
Serious dermatological reactions, including toxic epidermal necrolysis (TEN or Lyell's syndrome) and Stevens-Johnson syndrome (SJS), occur very rarely when using carbamazepine. Patients with severe dermatological reactions may require hospitalization, as these conditions can be life threatening and lethal. Most cases of SJS / TEN develop during the first few months of treatment with carbamazepine. In the development of symptoms indicating severe dermatological reactions (such as SDS, Lyell / Tenen syndrome), taking Mezacar®, an oral suspension, should be stopped immediately and alternative therapy should be prescribed.
Pharmacogenomics.
There is more evidence of the impact of different HLA alleles on patient's predisposition to adverse reactions associated with the immune system.
Relation with (HLA)-B*1502.
There are data concerning the pronounced correlation between skin reactions SJS/TEN associated with carbamazepine and the presence of human leukocyte antigen (HLA), allele (HLA)-B*1502 in patients. Greater frequency of reports of SJS development is characteristic of some Asian countries (such as Taiwan, Malaysia and Philippines), where allele (NLA)-B*1502 is prevalent in population. The number of carriers of this allele among the Asian population is over 15% in the 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 European, African people, in native American population and Latin-American population.
In those patients who are considered as genetically belonging to risk groups before treatment with the drug Mezacar®, oral suspension, a test for the presence of (HLA)-B*1502 allele should be carried out. If the patient's test for the presence of (HLA)-B*1502 allele gives positive result, treatment with the drug Mezacar®, oral suspension, should not be started, except the cases when other variants of therapeutic treatment are absent. The patients who have been examined and obtained negative result on (HLA)-B*1502 have low rick of SJS, though very rare, such reactions are still possible.
Currently, due to lack of data is not known whether all the people of South-East Asian origin have risks.
(NLA)-B*1502 allele may be a risk factor for SSD/TEN in Chinese patients receiving other antiepileptic drugs that may be associated with the development of SSD/TEN. Therefore, the use of other drugs that may be associated with the development of SSD/TEN in patients who have (NLA)-B*1502 allele should be avoided if another, alternative therapy may be used. Usually it is not recommended to conduct genetic screening in patients of the nationalities, whose representatives have low coefficient of (HLA)-B*1502 allele. Usually it is not recommended to conduct genetic screening in patients already receiving Mezacar®, since the risk of SSD/TEN is significantly limited by the first few months, regardless of the presence of (HLA)-B*1502 allele in the patient's gens.
In Caucasian patients the relation between (HLA)-B*1502 allele and the development of SJS is absent.
Relation with (HLA)-A*3101.
Human leukocyte antigen may be a risk factor for the development of skin adverse reactions, such as SJS, TEN, drug-induced rash with eosinophilia and systemic symptoms (DRESJS), acute generalized exanthematous pustulosis (AGEP), maculopapular rash. If the analysis reveals the presence of HLA-A*3101 allele, it is recommended to abstain from using the drug Mezacar®, oral suspension.
Limitations of genetic screening

The results of genetic screening should not replace appropriate clinical supervision and treatment. The role in the occurrence of these serious skin adverse reactions is played by other possible factors, such as dosage of the antiepileptic drug, adherence to the therapy regimen, concomitant therapy.
Other dermatologic reactions. The development of transient and non-life-threatening mild dermatologic reactions, e.g. macular or maculopapular isolated exanthema, is possible. They usually disappear after a few days or weeks at constant dosing, as well as after dose reduction. Along with this, since the early signs of more serious dermatologic reactions may be very difficult to distinguish from mild transient reactions, the patient should be under careful supervision in order to stop the drug immediately, if the reaction worsens with its continuation.
The presence of HLA-A*3101 allele in patient is associated with the appearance of less serious adverse skin reactions to carbamazepine, such as syndrome of hypersensitivity to anticonvulsant agents or insignificant rash (maculopapular rash).
The presence of HLA-A*3101 allele in patient is not a risk factor of less serious skin reactions to carbamazepine, such as s syndrome of hypersensitivity to anticonvulsant agents or insignificant rash (maculopapular rash).
Hypersensitivity. Carbamazepine may trigger the development of hypersensitivity reactions, including drug-induced rash with eosinophilia and systemic symptoms (DRESJS), multiple slow type hypersensitivity reaction with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly, altered liver function parameters and vanishing bile ducts syndrome (including destruction and disappearance of intrahepatic bile ducts), that may present in various combinations. Also, the effect on other organs is possible (lungs, kidneys, pancreas, myocardium, colon).
The presence of HLA-A*3101 allele in patient is associated with the appearance of less serious adverse skin reactions to carbamazepine, such as syndrome of hypersensitivity to anticonvulsant agents or insignificant rash (maculopapular rash).
In general, if symptoms suggest a hypersensitivity, the use of the drug Mezacar®, the oral suspension should be stopped immediately.
Patients with hypersensitivity reactions to carbamazepine should be informed that about 25-30% of such patients may have hypersensitivity reactions to oxcarbamazepine. When using carbamazepine and phenytoin, the development of cross-reactive hypersensitivity is possible.
Seizures.
Mezacar®, oral suspension should be used with caution in patients with mixed seizures which include absences (typical or atypical). In such circumstances, the drug can provoke seizures. In case of provoking seizures, the use of the drug Mezacar®, oral suspension, should be stopped immediately. Increased of frequency of seizures is possible when transition from oral forms of the drug to suppositories.
Dose reduction and drug withdrawal.
Abrupt discontinuation of Mezacar®, an oral suspension, may provoke an attack, so stopping the carbamazepine melting should be gradual. If necessary, the sudden withdrawal of therapy with the drug for patients with epilepsy, the transition to a new antiepileptic drug should be carried out against the background of therapy with an appropriate medicinal product (such as intravenous diazepam, rectal or intravenous phenytoin).
Endocrinal effects.
Breast bleeding has been reported in women taking carbamazepine and hormonal contraceptives. Due to the induction of liver enzymes, carbamazepine reduces the effectiveness of hormonal contraceptives, therefore, women of childbearing age taking Mezacar ® oral suspension should use alternative contraceptive methods.
Female patients taking Mezacar®, oral suspension, for whom hormonal contraception is necessary, should receive preparation containing at least 50 µg of estrogen, or for such patients alternative non-hormonal methods of contraception should be considered.
Monitoring of drug level in blood plasma.
Although the correlation between dosage and plasma levels of carbamazepine, as well as between plasma levels of carbamazepine and clinical efficacy and tolerability is unreliable, monitoring of the drug plasma level may be appropriate in such cases: sudden increase in the frequency of seizures,

check of patient's compliance, during pregnancy, when treating children; suspected absorption disorder, suspected toxicity and when using more than one drug.

Hyponatremia.

There have been cases of hyponatremia in the use of carbamazepine. In patients with pre-existing renal impairment associated with reduced sodium levels or in patients with concomitant treatment with sodium reducing agents (such as diuretics, drugs that are associated with inadequate antidiuretic hormone secretion), before treatment it is necessary to determine the level of sodium in the blood, then every 2 weeks, then - at intervals of 1 month during the first 3 months of treatment or according to clinical need. This is especially true for the elderly. If hyponatremia is observed according to clinical indications, the amount of water intake should be limited.

Hypothyroidism.

Carbamazepine may reduce the concentration of thyroid hormones, therefore, an increase in the dose of thyroid hormone replacement therapy for patients with hypothyroidism is required. Monitoring of thyroid function should be performed to adjust the dose of thyroid hormones substitution therapy.

Anticholinergic effects.

Carbamazepine has a moderate anticholinergic activity. Thus, patients with increased intraocular pressure and urinary retention should be closely monitored during therapy.

Mental effects.

It is necessary to remember about the possibility of activating latent psychosis, in patients of the elderly - confusion of consciousness or anxiety.

Application to elderly patients.

Given drug interactions and different pharmacokinetics of antiepileptic drugs, the elderly dose of Mezacar®, oral suspension should be carefully selected.

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 because the drug contains sorbitol solution and sucrose.

Use during pregnancy or breast feeding.

In children, whose mothers suffer from epilepsy, a disposition to the emergence of pathologies, including congenital malformations, is observed. Carbamazepine-associated fetal abnormalities and congenital malformations, including spinal cord and other congenital anomalies, have been reported, such as maxillo-facial defects such as lip / palate cleavage, cardiovascular malformations, hypospadias, and abnormalities in the development of various systems of the body. Patients should be advised about the possibility of increasing the risk of developmental defects and enable them to have prenatal screening.

The following data should be kept in mind:

- the use of the drug Mezacar®, oral suspension, in pregnant women with epilepsy requires special attention;
- if a woman receiving carbamazepine is pregnant, planning a pregnancy or during pregnancy, the need for carbamazepine is used, the potential benefit of the drug should be weighed against the risk (especially in the 1st trimester of pregnancy);
- for women of reproductive age, if possible, carbamazepine should be prescribed as monotherapy, since the incidence of congenital anomalies in women who received treatment with a combination of antiepileptic drugs is higher than that of mothers who received these drugs as monotherapy. The risk of developing developmental malformations after the use of carbamazepine in polytherapy may vary depending on the drugs used and may be higher in those combination of polytherapy, which includes valproate;
- it is recommended to prescribe the minimum effective dose of the drug and monitor the plasma concentration of carbamazepine. Concentration of the drug in blood plasma can be maintained at a lower therapeutic range of 4 to 12 mg / ml, while maintaining control over attacks. There is evidence to suggest that the risk of developmental defects caused by carbamazepine may

be dose-dependent, that is, at doses <400 mg per day, the incidence of developmental malformations will be lower than at higher doses of carbamazepine;
- patients should be informed about the possibility of increasing the risk of birth defects in the child and should provide them with an opportunity for antenatal screening;
- during effective pregnancy, effective antiepileptic therapy should not be interrupted, as the exacerbation of the disease will endanger the health of both the mother and the child.

Observation and prevention.
It is known that during pregnancy, folic acid deficiency may develop. Antiepileptic drugs may increase the level of folic acid deficiency. This deficiency can help increase the number of birth defects in children whose mothers receive treatment for epilepsy, so an additional folic acid is recommended before and during pregnancy.
Newborns.
To prevent blood clotting disorders in newborns it is recommended to prescribe Vitamin K_1 to women during the last weeks of pregnancy and to newborn child.
There are several cases of seizures and/or respiratory depression in newborns, several cases of vomiting, diarrhea and/or poor appetite in newborns known, which are associated with the use of carbamazepine and other anticonvulsants by the mother. These reactions may be manifestations of neonatal withdrawal syndrome.
Breast feeding.
Carbamazepine is excreted into the breast milk (25-60% of the plasma concentration). The benefits of breast feeding and delayed possibility of adverse effect in the infant should be weighed carefully.
Mothers who receive carbamazepine can breastfeed with the condition that the baby is observed with regard to the development of possible adverse reactions (e.g. excessive drowsiness, allergic skin reactions). Several reports have been received on the development of cholestatic hepatitis in newborns who have been exposed to carbamazepine during the antenatal period or during breastfeeding. Therefore, newborns who are breast-fed and mothers receiving carbamazepine therapy should be closely monitored for the development of undesirable effects from the liver and bile passages.
Fertility.
Very rarely reported cases of malformation in males and / or deviations from the norm of spermatogenesis.

Effect on reaction rate when driving motor transport or operating other mechanisms.
The ability of a patient taking carbamazepine to respond to a rapid reaction (especially at the beginning of therapy or during the dose selection) may be affected by dizziness, drowsiness, ataxia, diplopia, abnormal accommodation and fuzzy vision, especially at the beginning of treatment or due to Dose adjustment. Therefore, when driving a car or working with other mechanisms the patient should be careful.

Administration and dosage.
The drug may be taken during or after meal, or between meals with a small amount of liquid.
Mezacar®, oral suspension, is used orally. Shake before use.
The usual dose is divided in 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 in the form of tablet, it is recommended to start using suspension with low doses and gradually increase them (to avoid adverse reactions of the CNS, such as dizziness and drowsiness).
When replacing the tablet formulation by suspension, the same dose should be administered, but it should be divided into smaller single doses, and the number of intakes should be increased accordingly.
For people belonging to certain ethnic groups (Chinese, Thai) before the start of treatment it is advisable to perform screening of HLA-B * 1502, as the presence of this allele is a predictor of possible risk of severe Stevens-Johnson syndrome associated with carbamazepine.

Epilepsy.

The dose of carbamazepine should be tailored individually to each patient in order to achieve adequate control of convulsive attacks. Determining the concentration of carbamazepine in blood plasma can help in choosing the optimal dose. In the treatment of epilepsy, carbamazepine dosage usually requires the achievement of a total concentration of carbamazepine in plasma from 4 to 12 μg / ml (from 17 to 50 μmol / L).

Adults.

For all carbamazepine dosage forms, a gradual increase dose is recommended, which should be adjusted to suit the needs of each individual patient.

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 treatments. Some patients may need to increase the dose to 1600-2000 mg / day.

Elderly patients

Due to the increased interaction with other drugs for the elderly, carbamazepine dosage should be carefully selected.

Children.

For all carbamazepine dosage forms, a gradual increase dose is recommended, which should be adjusted to suit the needs of each individual patient.

Typically, the daily dose of the drug is 10-20 mg / kg body weight, which should be distributed to several methods.

For the different ages the following daily doses are recommended (table 1).

Table 1.

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

For the different ages the following maximum daily allowances are recommended (table 2).

Table 2.

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

If possible, antiepileptic drugs should be administered separately (in the form of monotherapy), but when used in the composition of polytherapy, the same mode of increasing dosage is recommended. When administering a suspension of oral Mezacar®, in addition to current antiepileptic therapy, the dose of the drug should be gradually increased without changing the dose of the current anti-epileptic drug(s) used or, if necessary, correcting it (see section *"Interaction with other medicines and other types of interactions").*

Trigeminal neuralgia.

The initial dose of the drug carbamazepine is 200-400 mg. It is slowly increased until the disappearance of painful sensations (usually to a dose of 600-800 mg, divided into 3-4 doses). In some cases a dose of 1600 mg per day may be necessary. After pain decreases, the dosage should be gradually reduced to the lowest possible supportive level. The maximum recommended daily dose is 1200 mg. When the pain disappears, one should try to slowly stop carbamazepine therapy until the next attack occurs.

Elderly patients

Due to the increased interaction with other drugs for the elderly, carbamazepine dosage should be carefully selected.

The recommended starting dose for elderly patients is 200 mg per day, divided into 2 doses. It should be slowly raised until pain disappears (usually up to a dose of 600-800 mg per day, distributed in 3-4 doses). After pain decreases, the dosage should be gradually reduced to the lowest possible supportive level. The maximum recommended daily dose is 1200 mg. When the pain disappears try to slowly stop carbamazepine therapy until the next attack occurs.

Prevention of manic-depressive psychosis in patients with no therapeutic effect of lithium drugs.

The initial dose is 400 mg per day, divided into several single doses. It should be slowly raised to allow for control of the symptoms of the disease, or until a daily dose of 1600 mg distributed over several treatments is reached. Typically, the daily dose of the drug is 400-600 mg, distributed to several methods.

Special patient groups

Chronic kidney / liver function disorders

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

Children.

Oral Mezacar® suspension can be taken from birth by children.

Overdose.

Symptoms. Symptoms and complaints that arise during overdose, usually reflect lesions of the central nervous, cardiovascular and respiratory systems.

Central nervous system: suppression of CNS functions; Disorientation, depressed level of consciousness, drowsiness, excitement, hallucinations, coma; Blurred vision, indiscriminate speech, dysarthria, nystagmus, ataxia, dyskinesia, hyperreflexia (initially), hyporeflexia (later); Convulsions, psychomotor disorders, myoclonus, hypothermia, mydriasis.

Respiratory system: respiratory depression, pulmonary edema.

Cardiovascular system: tachycardia, arterial hypotension, sometimes - arterial hypertension, conduction impairment with expansion of the QRS complex; Syncope associated with cardiac arrest, accompanied by loss of consciousness.

Gastrointestinal tract: vomiting, food stomach in the stomach, decreased motility of the large intestine.

Musculoskeletal system: reported cases of rhabdomyolysis associated with the toxic effects of carbamazepine.

Urinary system: urinary retention, oliguria or anuria; fluid retention; hyperhydration, due to the effect of carbamazepine, similar to the action of the antidiuretic hormone.

Changes from laboratory parameters: hyponatremia, metabolic acidosis, hyperglycemia, and increased muscle fraction of creatinine phosphokinase.

Treatment. No specific antidote is available. Initially, treatment should be based on the clinical condition of the patient; hospitalization is shown. A determination of the concentration of carbamazepine in blood plasma is carried out to confirm the poisoning with this agent and to assess the degree of overdose.

Evacuation of the contents of the stomach, gastric lavage, and the use of activated charcoal are being carried out. Late evacuation of gastric contents may lead to delayed absorption and reoccurrence of symptoms of intoxication during recovery. Symptomatic supportive treatment in the intensive care unit, monitoring of cardiac function, and vigorous correction of electrolyte disorders are used.

Special recommendations. In the development of arterial hypotension, intravenous dopamine or dobutamine is indicated; in the development of heart rhythm disorders, treatment should be selected individually; in the development of the vessel - the administration of benzodiazepines (for example, diazepam) or other anticonvulsants, such as phenobarbital (with caution due to increased risk of respiratory depression) or paraldehyde; with the development of hyponatraemia (aqueous intoxication) - restriction of the introduction of fluid, slow, cautious intravenous infusion of 0.9% solution of sodium chloride. These measures can be useful in preventing brain edema.
It is recommended to conduct hemosorption on coal sorbents. The effectiveness of hemodialysis and peritoneal dialysis in overdose with carbamazepine has been reported.
It is necessary to consider the possibility of re-intensifying the symptoms of overdose on the 2nd and 3rd day after its onset, due to the slow absorption of the drug.

Adverse reactions.
At the beginning of treatment with carbamazepine or with the application of too much initial dose of the drug, or in the treatment of elderly patients, certain types of adverse reactions, for example, from the CNS (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal tract (Nausea, vomiting) or allergic skin reactions.
Dose-dependent adverse reactions usually last for several days both spontaneously and after a temporary decrease in the dose of the drug. Development of adverse reactions from the central nervous system may be the result of a relative overdose of the drug or significant changes in the concentrations of the active substance in the blood plasma. In such cases, it is recommended to monitor the level of the active substance in the blood plasma and distribute the daily dose of the drug into smaller individual doses (for example, 3-4).
Blood system and lymphatic system disorders: leukopenia; thrombocytopenia, eosinophilia, leukocytosis, lymphadenopathy, folic acid deficiency, agranulocytosis, aplastic anemia, pancytopenia, erythropocytic aplasia, anemia, megaloblastic anemia, acute intermittent porphyria, mixed porphyria, late porphyria, reticulocytosis, hemolytic anemia, bone marrow insufficiency.
Immune system: multiorgan hypersensitivity of the delayed type with fever, skin rashes, vasculitis, lymphadenopathy; Pseudolymphoma, arthralgia, leukopenia, eosinophilia, hepatosplenomegaly and altered liver function and bile duct disappearance syndrome (destruction and disappearance of intrahepatic bile ducts) that arise in various combinations.
There may be a violation of other organs (e.g., liver, lungs, kidneys, pancreas, myocardium, colon), aseptic meningitis with myoclonus and peripheral eosinophilia, anaphylactic reactions, medication rash with eosinophilia and systemic symptoms (DRESS), angioneurotic edema, hypogammaglobulinemia.
Endocrine system disorders: edema, fluid retention, weight gain, hyponatremia and decreased blood osmolality due to an effect similar to the action of antidiuretic hormone, that rarely leads to a overhydration accompanied by lethargy, vomiting, headache, mental confusion, and neurological disorders; increased prolactin levels, accompanied or not accompanied by such manifestations as galactorrhea, gynecomastia; changes in indices of thyroid function, reduced level of L-thyroxin (FT_4, T_4, T_3) and increased level of thyroid-stimulating hormone, which is usually not accompanied by clinical manifestations.
Metabolism and nutrition: lack of folate, appetite loss, acute porphyria (acute intermittent porphyria and mixed porphyria), obtuse porphyrya (late porphyria of the skin).
Mental disorders: hallucinations (visual or auditory), depression, loss of appetite, anxiety, aggressiveness, agitation, confusion of consciousness, activation of psychosis.
Nervous system: dizziness, ataxia, drowsiness, sedation, memory impairment, headache, diplopia, disturbance in the accommodation of the eye (e.g. blurred vision); abnormal involuntary movements (e.g. tremor, dystonia, asterixis, tick), nystagmus; orophasic dyskinesia, eye movement disorder, speech impairment (e.g. dysarthria or indiscriminate speech), choreatoathetosis, peripheral neuropathy, paresthesia, paresis; disturbance of taste sensations, malignant neuroleptic syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
Visual disorders: disturbance of accommodation (for example blurred vision), cloudy lens, conjunctivitis, increased intraocular pressure.

Organ of hearing and labyrinth: hearing disorders, such as ringing in the ears, increased auditory sensitivity, reduced auditory sensitivity, disturbance of perception of the height of the sound.
Cardiovascular system: intracardiac conduction impairment; Arterial hypertension or arterial hypotension; Bradycardia, arrhythmia, atrientricular blockade from syncope, circulatory collapse, congestive heart failure, exacerbation of ischemic disease, thrombophlebitis, thromboembolism (e.g. pulmonary embolism).
Respiratory system, the chest and mediastinum: hypersensitivity reactions from the lungs characterized by fever, shortness of breath, pneumonitis, or pneumonia.
Gastrointestinal tract: nausea, vomiting, dry mouth, diarrhea or constipation, abdominal pain, glossitis, stomatitis, pancreatitis, colitis.
Hepatobiliary system: increased gamma-glutamyltransferase (induced by liver enzymes, which usually has no clinical significance), increased levels of alkaline phosphatase in the blood, increased levels of transaminases, hepatitis cholestatic, parenchymal (hepatocellular) or mixed types, biliary disappearance syndrome, jaundice , granulomatous hepatitis, hepatic insufficiency.
Skin and subcutaneous tissue: allergic dermatitis, urticaria (sometimes severe), exfoliative dermatitis, erythroderma, systemic lupus erythematosus, lupus erythematosus, itching, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, multivariate and nodular erythema, Disorder of pigmentation of the skin, purpura, acne, increased sweating, increased hair loss, hirsutism, acute generalized existentious pustulosis (AGEP), lichenoid keratosis, onychomedesis.
Musculoskeletal system, connective tissue and bone tissue: muscle weakness, arthralgia, muscle pain, muscle spasm, bone metabolism disturbances (decreased calcium and 25-hydroxycholecalciferol in blood plasma, which may lead to osteomalacia or osteoporosis), fractures, decrease in mineral density of bone tissue.
Kidneys and the urinary system: tubulointerstitial nephritis, renal insufficiency, renal dysfunction (e.g. albuminuria, hematuria, oliguria, elevated blood urea / azotemia), frequent urination, urinary retention.
Reproductive system: sexual dysfunction, impotence, erectile dysfunction, impaired spermatogenesis (with decreased number and/or sperm motility).
General disorders: general weakness.
Rejection of the results of laboratory and instrumental studies: increased intraocular pressure, increased blood cholesterol levels, increased levels of high density lipoprotein, increased levels of triglycerides in the blood, increased levels of gammaglutamyltransferase, increased levels of alkaline phosphatase in the blood, decreased levels of L-thyroxine (free thyroxine, thyroxine , Tri-iodothyronine) and increased thyroid stimulating hormone in the blood, increased levels of prolactin in the blood.
Infections and invasions: reactivation of human herpesvirus VI type.

Shelf-life. 3 years.

Storage conditions.
Store at the temperature not more than 25 °C, out of reach of children.
Keep out of the reach of children.
Do not store the drug for longer than 4 weeks after the bottle is first open.

Package.
100 ml of suspension are in a bottle, one bottle with a dose-measuring cup is in a carton.

Conditions of supply.
On prescription.

Manufacturer.
“KUSUM PHARM” LTD.

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