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INSTRUCTION
For medical use

MEZACAR®

Composition:
active substance: carbamazepine;
1 tablet contains 200 mg of carbamazepine;
excipients: microcrystalline cellulose, hypromellose E5, croscarmellose sodium, colloidal silicon dioxide anhydrous, magnesium stearate.

Pharmaceutical form. Tablets.
Main physicochemical properties: white to off-white round tablets with beveled breakline on one side and embossed "K" on the other side

Pharmacotherapeutic group.
Antiepileptics. ATC code: N03A F01.

Pharmacological properties.
Pharmacodynamics.
As an anticonvulsant, antiepileptic drug Mezacar® is effective at partial seizures (simple and complex) with and without secondary generalization; generalized tonic-clonic seizures, as well as combinations of these types of seizures.
In clinical studies carbamazepine given as monotherapy to patients with epilepsy (in particular children and adolescents) has been reported to exert a psychotropic action, which was partly manifested by positive effect on symptoms of anxiety and depression as well as a decrease in irritability and aggressiveness.
As a neurotropic agent carbamazepine is effective in a number of neurological disorders. Thus, for example, it prevents paroxysmal attacks of pain in idiopathic and secondary trigeminal neuralgia. In addition, carbamazepine is used for the relief of neurogenic pain in a variety of conditions. In alcohol-withdrawal syndrome it raises convulsion threshold (which is lowered in this condition) and improves withdrawal symptoms (e.g. hyperexcitability, tremor, impaired gait).
As a *psychotropic* agent, carbamazepine proved to have clinical efficacy in affective disorders, i.e. as treatment for acute mania as well as for maintenance treatment of (manic-depressive) bipolar affective disorders, when given either as monotherapy or in combination with neuroleptics, antidepressants, or lithium drugs.
Pharmacokinetics.
Absorption.
Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations (C_{max}) within 12 hours following single oral doses.

The bioavailability of various oral formulations of carbamazepine has been shown to be within 85–100%. Ingestion of food has no significant influence on the rate and extent of carbamazepine absorption.
For doses up to 300 mg carbamazepine about 75% of the total amount absorbed reaches the general blood circulation within 6 hours after application. The result has led to the recommendation that the maximal daily dose be limited to 250 mg q.i.d.
Plasma concentrations. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400 mg carbamazepine (tablets), the average value of C_{max} of the unchanged active substance reaches about 4.5 μg/mL.
The steady-state plasma concentrations of carbamazepine considered as 'therapeutic range' vary considerably interindividually: for the majority of patients a range between 4 to 12 μg/mL (17 to 50 μmol/L) has been reported. Concentrations of carbamazepine-10,11-epoxide (pharmacologically active metabolite) are about 30% of carbamazepine levels.
Steady-state plasma concentrations of carbamazepine are attained within about 1–2 weeks, depending individually upon specific metabolism (liver enzyme systems auto-induction by carbamazepine, hetero-induction by other drugs that are used simultaneously) as well as on pre-treatment status of a patient, dosage, and duration of treatment.
Distribution. Carbamazepine is bound to serum proteins to the extent of 70% to 80%. The concentration of unchanged carbamazepine in cerebrospinal fluid and saliva reflects the non-protein bound portion in the plasma (20% to 30%). Concentrations of carbamazepine in breast milk were found to be equivalent to 25% to 60% of the corresponding plasma levels. Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.
Metabolism. Carbamazepine is metabolized in the liver, where the epoxide pathway is the most important one, yielding the 10,11-transdiol derivative and its conjugate with glucuronic acid. In the first stage, oxidation to the carbamazepine-10,11-epoxide, preferably via isoenzyme of cytochrome P450 3A4 occurs. Human microsomal epoxide-hydrolysis is considered to be responsible for the formation of a pharmacologically active carbamazepine-10,11-epoxide, which is almost completely transformed into a derivative of 10,11-transdiol and its glucuronides. As a result of these metabolic reactions, 9-hydroxy-methyl-10-carbamoyl acridan, a minor metabolite, is also formed. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway. Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by uridine diphosphate glucuronosyltransferase (UGT2B7).
Carbamazepine induces its own metabolism.
Elimination. The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages 16–24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9–10 hours have been found.
The mean elimination half-life of the 10,11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.
After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% – in the feces. Almost 2% of the administered dose is excreted with the urine as unchanged drug and about 1% as the pharmacologically active 10,11-epoxide metabolite, and approximately 30% – as carbamazepine-10,11-transdiol and other inactive metabolites.
Pharmacokinetics in special populations.
Elderly. There is no indication of altered pharmacokinetics of carbamazepine in elderly patients (as compared with young adults).
Patients with hepatic or renal impairment. No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

Clinical particulars.
Indications.
- Epilepsy:
  - complex or simple partial seizures (with or without loss of consciousness) with or without

secondary generalization;
- generalised tonic-clonic seizures;
- mixed forms of seizures.

Mezacar® is suitable for both monotherapy and combination therapy.

Carbamazepine is usually not effective in absences (petit mal) and myoclonic seizures (see "Special warnings and precautions for use" section).

- Acute mania; maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.
- Alcohol-withdrawal syndrome.
- Idiopathic trigeminal neuralgia and trigeminal neuralgia in disseminated sclerosis (either typical or atypical).
- Idiopathic glossopharyngeal neuralgia.

Contraindications.

Mezacar® is contraindicated:

- with known hypersensitivity to carbamazepine and oxcarbazepine or chemically related drugs (e.g. tricyclic antidepressants) or any other component of the formulation;
- with atrioventricular block;
- in patients with a history of bone marrow depression;
- in patients with a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda);
- in co-administration with monoamine oxidase inhibitors (MAO).

Interactions with other medicinal products and other forms of interaction.

Cytochrome P450 3A4 (CYP3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine-10,11-epoxide. Co-administration of inhibitors of CYP3A4 or epoxide hydrolase inhibitors with carbamazepine may result in increased carbamazepine plasma concentrations which could induce adverse reactions. Therefore, the dose of Mezacar® should be adjusted and blood levels in plasma should be monitored. Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to potential decreases in the carbamazepine serum level and reduced therapeutic effect. Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels. Therefore, it may be necessary to adjust the dose of Mezacar®.

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 comedications mainly metabolized by CYP3A4 by induction of their metabolism.

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

Co-administration of carbamazepine with oral direct-acting anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) may lead to a decrease in the concentration of direct-acting oral anticoagulants in blood plasma and, thus, to an increased risk of thrombosis. Therefore, if co-administration is necessary, patients should be closely monitored for signs and symptoms of thrombosis.

Agents that may raise carbamazepine plasma levels.

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

Analgesics, anti-inflammatory drugs: dextropropoxyphene, ibuprofen.

Androgens: danazol.

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 anticonvulsants may be recommended in patients treated with voriconazole or itraconazole.
Antihistamines: loratadine, terfenadine.
Antipsychotics: olanzapine, loxapine, quetiapine.
Antituberculosis: isoniazid.
Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir).
Carbonic anhydrase inhibitors: acetazolamide.
Cardiovascular drugs: diltiazem, verapamil.
Gastrointestinal drugs: cimetidine, omeprazole.
Muscle relaxants: oxybutynin, dantrolene.
Antiplatelet drugs: ticlopidine.
Other interactions: grapefruit juice, nicotinamide (in adults, only in high dosage).
Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels.
Since raised plasma active metabolite carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Mezacar® should be adjusted accordingly and/or the carbamazepine plasma levels monitored when used concomitantly with the following drugs: loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide, brivaracetam.
Agents that may decrease carbamazepine plasma levels.
The dose of Mezacar® may have to be adjusted when used concomitantly with the substances described below.
Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbital, phensuximide, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 μg/mL before starting carbamazepine treatment) and fosphenytoin, primidone, and clonazepam (although the data are partly contradictory).
Antineoplastics: cisplatin or doxorubicin.
Antituberculosis: rifampicin.
Bronchodilators or anti-asthma drugs: theophylline, aminophylline.
Dermatological drugs: isotretinoin.
Other interactions: herbal preparations containing St. John's wort (*Hypericum perforatum*).
Mefloquine may antagonize anticonvulsant effect of carbamazepine. Therefore, the dosage of Mezacar® should be adjusted respectively.
Isotretinoin is reported to change bioavailability and/or clearance of carbamazepine and carbamazepine-10,11-epoxide; carbamazepine plasma concentrations should be monitored.
Effect of Mezacar® on plasma levels of concomitant agents.
Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement.
Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), phenazone (antipyrine), tramadol.
Antibiotics: doxycycline, rifabutin.
Anticoagulants: oral anticoagulants (e.g. warfarin, phenprocoumon, dicoumarol, acenocoumarol, rivaroxaban, dabigatran, apixaban, edoxaban).
Antidepressants: bupropion (carbamazepine may lower blood plasma levels of bupropion and increase the level of its metabolite hydroxybupropion, thereby reducing the clinical efficacy and safety of bupropion), citalopram, mianserin, nefazodone, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine). The use of Mezacar® in combination with monoamine oxidase (MAO) inhibitors is contraindicated. The use of MAO inhibitors should be discontinued at least 2 weeks before the administration of Mezacar® (and if the clinical situation permits, even earlier).
Antiemetics: aperpitant.
Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, eslicarbazepine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. There have been reported of either increase or decrease of plasma level of phenytoin caused by carbamazepine action and there have been rare reports of an increase in plasma mephenytoin levels. To avoid phenytoin intoxication and

subtherapeutic concentrations of carbamazepine, the recommended plasma phenytoin concentration should not exceed 13 μg/ml before initiation of carbamazepine therapy. There are some reports of an increase in the concentration of mefenitoin in blood plasma against carbamazepine intake, which in rare cases caused confusion and even coma.
Antifungals: itraconazole, voriconazole, ketoconazole. Alternative anticonvulsants may be recommended in patients treated with voriconazole or itraconazole.
Antihelmintics: praziquantel, albendazole.
Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.
Antipsychotics: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, paliperidone.
Antivirals: protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).
Anxiolytics: alprazolam, midazolam.
Bronchodilators or anti-asthma drugs: theophylline.
Hormonal contraceptives (CYP3A4 substrates).
Carbamazepine is a strong inducer of CYP3A4. Carbamazepine can increase the metabolism of certain hormonal contraceptives (through CYP3A4 induction) such as oral and subdermal implant contraceptives, leading to significantly lower plasma concentrations of hormones. This can cause contraceptive failure or breakthrough bleeding. Consider alternatives to oral and subdermal implant contraceptives that are significantly affected by induction of CYP3A4; or consider alternatives to carbamazepine (see "Special warnings and precautions for use" and "Use in special populations" sections).
Cardiovascular drugs: calcium channel blockers (dihydropyridine group), e.g. felodipine, isradipine, digoxin, quinidine, propranolol, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.
Corticosteroids, including prednisolone, dexamethasone.
Drugs used in erectile dysfunction: tadalafil.
Immunosuppressants: cyclosporin, everolimus, tacrolimus, sirolimus.
Thyroid agents: levothyroxine. Carbamazepine is believed to promote the elimination of thyroid hormones and increase the need for them in patients with hypothyroidism. Therefore, thyroid function should be checked in patients having replacement therapy, both at the beginning and at the end of Mezacar® treatment.
If necessary, the dose of thyroid hormones should be adjusted. Thyroid function may change, in particular if carbamazepine and other anticonvulsants (e.g. phenobarbital) are used concomitantly.
Other drug interactions: drugs containing estrogens and/or progesterones (alternative methods of contraception should be considered); buprenorphine, gestrinone, tibolone, toremifene, mianserin, sertraline.
Drug combinations that require specific consideration.
Concomitant use of carbamazepine and levetiracetam can increase carbamazepine-induced toxicity.
Concomitant use of carbamazepine and isoniazid can increase isoniazid-induced hepatotoxicity.
Concomitant use of carbamazepine and lithium drugs or metoclopramide, as well as carbamazepine and neuroleptics (haloperidol, thioridazine) may result in the increase of neurological adverse reactions (in the case of the latter combination – even in case of therapeutic plasma levels). Therefore, clinical symptoms should be closely monitored. At least 8 weeks must elapse after completion of previous treatment with neuroleptics. Concomitant treatment should also be avoided. Patients should be monitored for the following neurotoxic symptoms: unsteady gait, ataxia, horizontal nystagmus, increased proprioceptive muscle reflexes, muscle cramps (fasciculations).
According to the published literature, the addition of carbamazepine to current neuroleptic therapy may increase the risk of malignant neuroleptic syndrome or Stevens-Johnson syndrome.
Concomitant medication with Mezacar® and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatremia.
Carbamazepine may antagonize the effects of non-depolarizing muscle relaxants (e.g. pancuronium). The dosage of these drugs may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.
Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance, therefore it is advisable for the patient to abstain from alcohol.

Concomitant use of carbamazepine with oral direct-acting oral anticoagulants (rivaroxaban, dabigatran, apixaban, edoxaban) may lead to a decrease in the concentration of direct-acting oral anticoagulants in blood plasma and consequently to an increased risk of thrombosis. Therefore, if coadministration is necessary, patients should be closely monitored for signs and symptoms of thrombosis.

Interactions resulting in a contraindication.

Since carbamazepine is structurally similar to the tricyclic antidepressants, the use of Mezacar® is contraindicated in combination with monoamine-oxidase inhibitors (MAO); before administering it, MAO inhibitors should be discontinued (for a minimum of 2 weeks, or longer if the clinical situation permits).

Interference with serological testing.

Carbamazepine may result in false positive perphenazine concentrations in HPLC (high-performance liquid chromatography) analysis to determine the concentration of perphenazine.

Carbamazepine and 10,11-epoxide can give false positive result of fluorescence polarized immunoassay method to determine the concentration of tricyclic antidepressants.

Special warnings and precautions for use.

General precautions.

Mezacar® should be taken exceptionally under medical supervision, only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic, or renal damage, adverse hematological reactions to other drugs, impaired sodium metabolism or interrupted courses of therapy with Mezacar®.

It is recommended to conduct urinalysis and determine blood urea nitrogen at the beginning and at regular intervals during therapy.

Mezacar® has shown mild anticholinergic activity, so patients with increased intraocular pressure should therefore be warned and advised on possible risk factors.

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

The drug is not usually effective in absences (petit mal) and myoclonic seizures. Some cases evidence that seizure exacerbation may occur in patients with atypical absences.

Hematological effects.

Agranulocytosis and aplastic anemia have been associated with the administration of the drug; however, due to the very low incidence of these conditions, meaningful risk estimates for Mezacar® are difficult to obtain. The overall risk in the population that has not been treated with carbamazepine has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anemia.

Patients should be advised of early toxic signs and symptoms of a potential hematological problem, as well as symptoms of dermatological or hepatic reactions.

In case such reactions as fever, sore throat, groin infection, skin rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage appear, the patient should be advised to consult a physician immediately.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored. Treatment with Mezacar® should be discontinued if the patient develops leukopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Mezacar® should be discontinued if any evidence of significant bone-marrow depression appears.

Transient or persistent decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Mezacar®. However, in the majority of cases these effects prove transient and are unlikely to signal the onset of either aplastic anemia or agranulocytosis. Complete pre-treatment blood counts, including platelets (and possibly reticulocyte count, hemoglobin level, and serum iron level), should be obtained at baseline, and periodically thereafter.

Serious dermatologic reactions.

Serious dermatologic reactions, including toxic epidermal necrolysis (TEN), also known as Lyell's syndrome, and Stevens-Johnson syndrome (SJS), have been reported very rarely with Mezacar®. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-

threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with Mezacar®. These reactions are estimated to occur in 1 to 6 per 10000 new users in countries with mainly Caucasian populations. However, in patients of some Asian countries, the risk may increase by approximately 10 times. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, Mezacar® should be withdrawn at once and alternative therapy should be considered.

Pharmacogenomics.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions.

Association with (HLA)-B*1502.

Retrospective studies in Han Chinese patients have demonstrated strong correlation between SJS/TEN skin reactions associated with carbamazepine and the presence in these patients of the Human Leukocyte Antigen (HLA)-B*1502 allele. The prevalence of HLA-B*1502 allele is about 2% to 12% in Han Chinese and 8% in patients from Thailand. Higher reporting rates of SJS (rather rarely than very rarely) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the population. The prevalence of this allele among Asian population is above 15% (in the Philippines and in some Malaysia populations). In Korea and India, the prevalence of this allele among the population was registered from 2% to 6%, respectively. The prevalence of allele (HLA)-B*1502 is negligible among European, African peoples, as well as among the Native American and Hispanic populations (<1%).

The prevalence of allele specified in this document represents the percentage of chromosomes in certain populations that have the corresponding allele. Therefore, the percentage of patients who have a copy of the allele with at least one of its two chromosomes (i.e., "carrier frequency"), is almost twice the prevalence of the allele. Therefore, the percentage of patients at risk is almost twice the prevalence of the allele.

Testing for the presence of HLA-B*1502 allele should be considered in those patients with ancestry in genetically at-risk populations, prior to initiating treatment with Mezacar®. The use of Mezacar® should be avoided in tested patients who are found to be positive for HLA-B*1502 unless there are no other options for therapeutic treatment. When assessing risk, it should be remembered that the HLA-B*1502 allele is also a risk factor for other antiepileptic drugs. Patients that were screened and received a negative result on (HLA)-B*1502, have a low risk of SJS, although such reactions may occur very rarely.

It has been found that identifying patients with the HLA-B*1502 allele and refusing carbamazepine in such patients of the Han ethnic group reduces the incidence of SJS/TEN cases caused by carbamazepine.

Currently, due to the lack of data it is not known exactly whether all Southeast Asians are exposed to risk.

HLA-B*1502 allele may be a risk factor for the development of SJS/TEN in Chinese patients taking other antiepileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoiding use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Genetic screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low. Screening is generally not recommended for any current Mezacar® users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

The results of genetic screening should not replace adequate clinical supervision, since many HLA-B*1502 carriers do not produce SJS/TEN, while in other patients without genetic risk factors for SJS/TEN it may develop for other reasons. The situation is similar for HLA-A*3101 allele carriers receiving Mezacar® treatment. These patients do not necessarily have SJS/TEN, DRESS, AGEP, or maculopapular rash. However, serious skin reactions may occur in patients without the HLA-A*3101 allele on other reasons. To date, no studies have been conducted regarding that how other factors (such as doses, regimen adherence, concomitant medications, and comorbidities) contribute to the development of these serious dermatological reactions.

There is no association between (HLA)-B*1502 allele and development of SJS in European patients.

Association with HLA-A*3101.

Human Leukocyte Antigen may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, drug rush with eosinophilia and systemic symptoms (DRESS), acute generalized

exanthematous pustulosis (AGEP) and maculopapular rash. The use of Mezacar® should be avoided in patients who are found to be positive for HLA-A*3101 allele.
Data of retrospective analysis in patients of Japanese nationality and northern Europeans demonstrated an association between severe skin lesions (Stevens-Johnson syndrome, Lyell's syndrome, drug rush with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, and maculopapular rash) in carriers of the HLA-A*3101 allele of the human leukocyte antigen (HLA) gene and the use of carbamazepine.
The prevalence of this allele may vary across ethnic groups: about 2–5% in the European population, about 10% in Japanese. Allele prevalence is less than 5% in the population of Australia, Asia, Africa, and North America. For the population of Western Europe, the prevalence of the HLA-A*3101 allele is estimated to be up to 6.7% depending on the geographical region. Exceptions range from 5% to 12%. Prevalence of more than 15% is established in some ethnic groups of South America (Argentina and Brazil), indigenous people of North America (the Navajo and Siox tribes, in Mexico – Sonora Seri), Southern India (Tamil Nadu).
The allele prevalence indicated in this document represents the percentage of chromosomes in certain populations that have the corresponding allele. Therefore, the percentage of patients who have a copy of the allele with at least one of its two chromosomes (ie, "carrier frequency") is almost twice the prevalence of the allele. Therefore, the percentage of patients at risk is almost twice the prevalence of the allele.
Before initiating treatment with Mezacar®, possible HLA-A*3101 allele carriers (for example, Japanese patients, Caucasians, Native Americans, Latinos, South Indian peoples, and Arabs) are recommended to be appropriately screened for this allele (see "Administration and dosage" section). The drug should only be used in carriers of this allele if the benefit from the therapy outweighs the potential risk. Screening for HLA-A*3101 allele is generally not required in patients who have already received Mezacar® for a long time, since SJS/TEN, AGEP, DRESS, and maculopapular rash are usually observed only during the first few months of therapy.
Limitation of genetic screening
Genetic screening results must never substitute for appropriate clinical vigilance and patient management. The role in the development of these severe cutaneous adverse reactions is played by other possible risk factors such as dosing of antiepileptic drug, adherence to therapy, concomitant therapy. The influence of other diseases and the level of skin disorders monitoring were not studied.
Other dermatologic reactions.
Mild skin reactions, e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment with carbamazepine or following a decrease in dosage. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing the drug should the reaction worsen with continued use.
The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However, The HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions.
Hypersensitivity.
Mezacar® may trigger hypersensitivity reactions, including drug rush with eosinophilia and systemic symptoms (DRESS), a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may manifest in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium and colon).
The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption).
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of these patients may experience hypersensitivity reactions with

oxcarbazepine. Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone, and phenobarbital).
In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Mezacar® should be withdrawn immediately.
Seizures.
Since carbamazepine can cause or intensify absences, Mezacar® should be used with caution in patients with mixed seizures including absences, either typical or atypical. In all these conditions, the drug may exacerbate seizures. In the event of exacerbation of seizures, Mezacar® should be immediately discontinued.
An increase in seizure frequency may occur during switchover from an oral formulation of drug to suppositories.
Hepatic function.
Baseline and periodic evaluations of hepatic function must be performed during drug treatment, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or active liver disease.
Renal function.
Baseline and periodic kidney function test and BUN determinations are recommended during treatment.
Hyponatremia.
Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate antidiuretic hormone secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, they should be measured after approximately two weeks and then with an interval of one month for the first three months during therapy, or according to clinical need. This applies especially to elderly patients. In this case water restriction is an important counter-measurement.
Hypothyroidism.
Carbamazepine may reduce serum concentrations of thyroid hormones. Therefore, increasing the dose of thyroid hormone replacement therapy for patients with hypothyroidism is required. Accordingly, it is recommended to monitor the thyroid function to determine the dose of hormone replacement therapy.
Anticholinergic effects.
Mezacar® has shown mild anticholinergic activity. Patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy.
Psychiatric effects.
The possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.
Suicidal ideation and behaviour.
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents. A meta-analysis of data from placebo-controlled studies of antiepileptic drugs has also shown a slight increase in the risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk of suicidal ideation and behaviour with the use of carbamazepine.
Therefore, patients should be monitored for signs of suicidal ideation and behaviours and, if necessary, appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Pregnancy.
Congenital malformations may occur if carbamazepine is used during pregnancy. For the treatment of epilepsy during pregnancy carbamazepine should therefore only be taken if the potential benefit justifies the potential risks. Carbamazepine should not be used for psychiatric indications and neuropathic pain and patients should instead be switched to more suitable alternative treatments.
Pregnant women and women planning to conceive potential should be adequately advised on potential teratogenic risk for unborn infants.
Women of childbearing potential should use reliable contraception during treatment with carbamazepine and for 2 weeks after the last dose.
Women of childbearing potential.

Carbamazepine can cause fetal harm when administered to a pregnant woman. Pregnancy registries and epidemiological data suggest a potential association between prenatal exposure to carbamazepine and the risks for major congenital malformations and other adverse development outcomes, including neural tube defects and malformations involving other body systems (e.g. craniofacial defects and cardiovascular malformations) (see "Pregnancy and lactation" section). In animal studies, administration of carbamazepine at clinically relevant doses during pregnancy resulted in developmental toxicity, including increased incidences of fetal malformations.
Carbamazepine should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.
Women of childbearing potential should be fully informed of the potential risk to the fetus if they take carbamazepine during pregnancy.
Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.
Women of childbearing potential should use effective contraception during treatment and for two weeks after stopping treatment.
Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see "Interactions with other medicinal products and other forms of interaction" and "Pregnancy and lactation" sections).
Women of childbearing potential should be counselled regarding the need to consult her physician as soon as she is planning pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see "Pregnancy and lactation" section).
Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking carbamazepine.
Endocrinological effects.
Due to liver enzyme induction, Mezacar® may result in a failure of the therapeutic effect of drugs containing estrogen and/or progesterone. This can lead to a reduction of effective contraception, recurrence of symptoms or breakthrough bleeding or spotting. Patients taking Mezacar® and requiring hormonal contraception should receive a preparation containing not less than 50 μg estrogen or use of some alternative effective and reliable non-hormonal method of contraception should be considered during therapy with Mezacar®.
Monitoring of plasma levels.
Although correlations between dosage and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous, monitoring of the plasma levels may be useful in the following situations: dramatic increase in seizure frequency, verification of patient compliance, during pregnancy, when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used.
Dose reduction and withdrawal.
Abrupt withdrawal of Mezacar® may precipitate seizures. If treatment with Mezacar® has to be withdrawn abruptly in a patient with epilepsy, the switch to the new antiepileptic compound should be made under cover of a suitable drug.
Dose reduction and withdrawal syndrome.
Abrupt withdrawal of the drug may precipitate seizures therefore carbamazepine should be withdrawn gradually over a 6-month period. If treatment with carbamazepine has to be withdrawn abruptly in a patient with epilepsy, the switch to the new antiepileptic compound should be made under cover of a suitable drug (e.g. diazepam i.v., rectal; or phenytoin i.v.).
Falls.
Mezacar® treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see "Adverse reactions" section) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently in case of long-term treatment with Mezacar®.
During carbamazepine treatment, patients should avoid the effects of strong sunlight due to the risk of photosensibilization.

Pediatric use.
The safety and effectiveness of carbamazepine in the treatment of bipolar disorder and pain of trigeminal neuralgia have not been established in pediatric patients.
Safety and effectiveness of carbamazepine in pediatric patients for the treatment of partial seizures, generalized tonic-clonic seizures, and mixed seizure patterns have been established (see "Indications" and "Administration and dosage" sections).

Pregnancy and lactation.
Pregnancy.
Risk related to antiepileptic drugs (AED) in general
Specialist medical advice regarding the potential risks to a fetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.
Sudden discontinuation of AED therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.
Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy.
Risks related to carbamazepine
Carbamazepine crosses the placenta. Prenatal exposure to carbamazepine may increase the risks for congenital malformations and other adverse developmental outcomes. Carbamazepine exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 2–3%. Malformations such as neural tube defects, craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias, hypoplasia of the fingers, and other anomalies involving various body systems, have been reported in the offspring of women who used carbamazepine during pregnancy. Specialized antenatal surveillance for these malformations is recommended. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used carbamazepine alone or in combination with other AEDs during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are contradictory and a risk cannot be excluded.
Carbamazepine should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.
The woman should be fully informed of and understand the risks of taking carbamazepine during pregnancy.
Evidence suggests that the risk of malformation with carbamazepine may be dose-dependent. If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with carbamazepine is continued, monotherapy and the lowest effective dose of carbamazepine should be used, and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 μg/mL provided seizure control is maintained.
Some AED, such as carbamazepine, have been reported to decrease serum folate levels. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy. In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.
If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking carbamazepine, she should be referred to a specialist to reassess carbamazepine treatment and consider alternative treatment options.
Women of childbearing potential
Carbamazepine should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risk of potential harm to the fetus if carbamazepine is taken during pregnancy and therefore the importance of planning any pregnancy. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with carbamazepine.

Women of childbearing potential should use effective contraception during treatment and for two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives (see "Interactions with other medicinal products and other forms of interaction" section), therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods. At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.
In the neonate. In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.
There have been a few cases of neonatal seizures and/or respiratory depression in the neonates, a few cases of vomiting, diarrhea and/or decreased feeding associated with maternal carbamazepine and other concomitant anticonvulsant drug use.
Breast-feeding. In studies in rats, side effects were observed in the offspring of female rats administered carbamazepine. Carbamazepine passes into the breast milk (about 25% to 60% of plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. The benefits of breast-feeding tend to outweigh the risk of adverse effects. Breast-feeding should be discontinued if the baby is gaining weight poorly, is too drowsy, or has allergic skin reactions. In children receiving carbamazepine antenatally or with breast milk, cases of cholestatic hepatitis have been described, and such children should be monitored for the diagnosis of side effects from the hepatobiliary system. Mothers taking Mezacar® may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).
Fertility.
There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis. However, a causal link between these disorders and carbamazepine has not yet been established.

Effects on the ability to drive and use machines.
The patient's ability to react quickly during Mezacar® therapy (especially at the start of treatment or in connection with dose adjustments) may be reduced both by convulsions caused by the disease and by adverse effects associated with the use of carbamazepine such as dizziness, drowsiness, ataxia, diplopia, impaired accommodation, and impaired vision. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

Administration and dosage.
Mezacar® is given orally, usually the daily dose of the drug should be divided into two or three doses. The drug may be taken during, after or between meals, with a little liquid, e.g. a glass of water.
Before deciding to initiate treatment, patients that are potential HLA-A*3101 allele carrier should whenever possible be screened for this allele as it strongly predicts the risk of severe reactions, such as skin reactions.
Epilepsy.
Initially, the dosage should be low and then slowly raised. The drug dose should be adjusted to the needs of the individual patient.
Determination of plasma levels of the drug may help in establishing the optimum dosage.
Especially in case of combination therapy the therapeutic dose should be calculated on the basic determination of plasma carbamazepine and effectiveness.
Based on the experience, the therapeutic level of carbamazepine is in the range from 4 to 12 μg/mL.
Adults: initially 100–200 mg of the drug once or twice daily is recommended. This may be followed by a slow increase until the best response is obtained; often the daily dose is 400 mg two or three times a day (corresponding to 800–1200 mg). For some patients 1600 mg or even 2000 mg of Mezacar® daily may be necessary; although these high doses should be avoided because of the higher incidence of adverse events.
Elderly: due to the potential for drug interactions, the dosage of Mezacar® should be selected with caution in elderly patients. The recommended starting dose is 100 mg twice a day. The recommended starting dose is 100 mg twice a day.

Children: therapy may begin with 100 mg/day, increasing at weekly intervals by 100 mg.
Usual dosage is 10–20 mg/kg bodyweight daily taken in several divided doses.

Child age	Daily dosage
6–10 years old	400–600 mg (2–3 divided doses)
11–15 years old	600–1000 mg (3 divided doses)

For children aged 15 and over the dosage is same as in adults.
Wherever possible, Mezacar® should be prescribed as monotherapy, but if used in combination with other drugs the same incremental carbamazepine dosage pattern is advised.
When Mezacar® is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the carbamazepine dosage of the other antiepileptic(s).
Acute mania and maintenance treatment of bipolar affective disorders
Dosage range: about 400 to 1600 mg daily, the usual dosage being 400 to 600 mg daily given in 2 to 3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for maintenance therapy of bipolar disorders in order to ensure optimal tolerability.
Alcohol-withdrawal syndrome
Average dosage: 200 mg 3–4 times daily. In severe cases, it can be raised during the first few days (e.g. to 400 mg 3 times daily (1200 mg/day). The dose is then slowly reduced, and the therapy is gradually discontinued. At the start of treatment for severe withdrawal manifestations, Mezacar® should be given in combination with sedative-hypnotic drugs (e.g. clomethiazole, chlordiazepoxide), following the abovementioned instructions for dosage. After the acute stage has abated, Mezacar® can be continued as monotherapy.
Idiopathic trigeminal neuralgia and trigeminal neuralgia in disseminated sclerosis (either typical or atypical). Idiopathic glossopharyngeal neuralgia.
The initial dosage of Mezacar® is 200 to 400 mg daily (100 mg twice daily for elderly). It should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). For majority of patients the carbamazepine dosage 200 mg 3 to 4 times daily is enough for maintenance of painless condition. In some instances, 1600 mg of carbamazepine daily may be necessary. After freedom from pain is achieved the dosage should then be gradually reduced to the lowest possible maintenance level. The maximum recommended dose is 1200 mg/day. The dose is then slowly reduced, and the therapy is gradually discontinued.

Children.
Owing to enhanced carbamazepine elimination, children may require higher doses of the drug (in mg/kg of body weight) than adults. Mezacar® can be administered in children aged 6 and older.

Overdose.
Symptoms. The presenting signs and symptoms of overdose usually involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under “Adverse reactions” section.
Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.
Respiratory system: respiratory depression, pulmonary oedema.
Cardiovascular system: tachycardia, hypotension, at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest, accompanied by loss of consciousness.
Gastrointestinal system: vomiting, delayed gastric emptying, reduced bowel motility.
Musculoskeletal system: there have been some cases, which reported rhabdomyolysis in association with carbamazepine toxicity.
Urinary system: retention of urine, oliguria, or anuria; fluid retention, water intoxication due to an ADH-like effect of carbamazepine.

Laboratory findings: hyponatremia, possibly metabolic acidosis, hyperglycemia, increased muscle creatine phosphokinase.
Management. There is no specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level is done to confirm carbamazepine poisoning and to ascertain the size of the overdose.
Evacuation of the stomach, gastric lavage, and administration of activated charcoal is performed. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication.
Symptomatic supportive treatment in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance is maintained.
Special recommendations. If hypotension is observed intravenous administration of dopamine or dobutamine is indicated; in case of arrhythmia the treatment is selected individually; if seizures are observed – administration of benzodiazepines (e.g. diazepam) or other anticonvulsants, e.g. phenobarbital (with caution because of an increased risk of respiratory depression) or paraldehyde; if hyponatremia is observed (water intoxication) – water restriction, slow, careful intravenous infusion of 0,9% sodium chloride solution. These measures may be useful for the prevention of cerebral edema.
Charcoal hemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose. Forced diuresis, hemodialysis and peritoneal dialysis are reported to be not effective.
Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated.

***Adverse reactions*.**
Particularly at the start of treatment with Mezacar®, or if the initial carbamazepine dosage is too high, or when treating elderly patients, certain types of adverse reaction occur often or not often, e.g. central nervous system adverse reactions (dizziness, headache, ataxia, somnolence, general weakness, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.
The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient carbamazepine dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation of active substance in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3–4) fractional doses.
Adverse reactions occurred 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 isolated cases.
Blood and lymphatic system disorders: very common – leukopenia (11%), persistent in 2% of cases; common – thrombocytopenia, eosinophilia; rare – lymphadenopathy, folic acid deficiency; very rare – leukocytosis, agranulocytosis, aplastic anemia, pancytopenia, pure red cell aplasia, anemia, megaloblastic anemia, acute intermittent porphyria, variegate porphyria, late cutaneous porphyria, reticulocytosis, hemolytic anemia, bone marrow failure.
Immune system disorders: rare – a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy; pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring 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 disorders: common – edema, fluid retention, weight increase, hyponatremia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders convulsions, disorientation, impaired perception, visual impairment or encephalopathy ("syndrome of inappropriate antidiuretic hormone secretion", SIADH); very rare – increased blood prolactin, accompanied or not accompanied by such reactions as galactorrhea, gynecomastia, bone metabolism disorders (decrease in plasma calcium and 25-hydroxycholecalciferol) leading to osteomalacia/osteoporosis; in isolated cases – cholesterol increased (incl. high-density lipoprotein

cholesterol and triglycerides.
Metabolism and nutrition disorders: rare – folate deficiency, decreased appetite; very rare – acute porphyria (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda); not known – hyperammonemia.
Psychiatric disorders: rare – hallucinations (visual or auditory), depression, decreased appetite, restlessness, aggression, agitation, confusional state; very rare – activation of psychosis.
Nervous system disorders: very common – dizziness (10–50%), ataxia (children 10.4%, adults 50%), somnolence, fatigue; common – headache, diplopia, accommodation disorders (e.g. blurred vision); uncommon – abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus; rare – orofacial dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, peripheral neuropathy, paraesthesia, muscle weakness and paresis; very rare – taste disorders, neuroleptic malignant syndrome (NMS), aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
Eye disorders: common – accommodation disorders (e.g. blurred vision); very rare – lenticular opacities, conjunctivitis, increased intraocular pressure.
Ear and labyrinth disorders: very rare – hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac and vascular disorders: rare – cardiac conduction disorders; hypertension or hypotension; very rare – bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, cardiac failure congestive, recrudescence of coronary artery disease, thrombophlebitis, thrombembolia (e.g. pulmonary embolism), vasculitis.
Respiratory, thoracic, and mediastinal disorders: very rare – pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia.
Gastrointestinal disorders: very common – nausea, vomiting (both 8%); common – dry mouth; uncommon – diarrhea or constipation; rare – abdominal pain; very rare – glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders: very common – increased gamma-glutamyl transferase (due to hepatic enzyme induction, usually not clinically relevant); common – increased blood alkaline phosphatase; uncommon – increased transaminases; 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 (which may be severe); uncommon – exfoliative dermatitis, erythroderma; rare – systemic lupus erythematosus, pruritus; very rare – Stevens-Johnson syndrome (reported as rare in some Asian countries), toxic epidermal necrolysis, photosensitivity reaction, multiforme and nodular erythema, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.
Musculoskeletal, connective tissue and bone disorders: rare – muscular weakness; very rare – arthralgia, myalgia, muscle spasms, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol, leading to osteomalacia and osteoporosis).
Renal and urinary disorders: very rare – tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, hematuria, oliguria, and increased blood urea / azotemia), urinary frequency, urinary retention.
Reproductive system: very rare – sexual dysfunction, impotence, erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility).
There have been very rare reports of impaired male fertility and/or impaired spermatogenesis.
General disorders: very rare – fatigue.
Deviations in laboratory and instrumental examinations: very common – increased gamma-glutamyl transferase (caused by liver enzymes induction, which is usually not of clinical significance); common – increase in the level of alkaline phosphatase in the blood; uncommon – increased transaminases, increased intraocular pressure, increased blood cholesterol (including increased levels of high density lipoproteins and triglycerides), increased triglycerides in the blood, changes in thyroid function: decreased L-thyroxine (free thyroxine (FT_4), thyroxine (T_4), triiodothyronine (T_3)) and increased thyroid-stimulating hormone (TSH), which is usually not accompanied by clinical manifestations; increase in blood prolactin levels, hypogammaglobulinemia.
<u>List of adverse drug effects from spontaneous reports (frequency not known).</u>
The following adverse effects have been identified from post-marketing spontaneous reports and

publications. Because these reactions are reported spontaneously, it is not possible to establish the exact number of patients and to reliably state the true frequency of adverse reactions, therefore their frequency is classified as “unknown”.
Infections and infestations: reactivation of human VI herpesvirus.
Blood and lymphatic system disorders: bone marrow failure.
Nervous system disorders: 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 and connective tissue disorders: fracture.
Investigations: bone density decreased.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf life. 4 years.

Storage.
Store below 25°C.
Keep out of reach of children.

Package.
10 tablets in blister; 5 blisters in a carton box.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

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