

Summary of Product Characteristics

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1. NAME OF THE MEDICINAL PRODUCT

MEDAZAPINE 200 (Carbamazepine Tablets BP 200mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:

Carbamazepine BP 200mg

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Uncoated tablet

White to off white, round, flat, scored on one side, uncoated tablets with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Epilepsy – Generalised tonic – clonic and partial seizures.

Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences.

The paroxysmal pain of trigeminal neuralgia.

For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

4.2 Posology and Method of administration

Posology

Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated Stevens-Johnson Syndrome.

Epilepsy:

The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/ml (17 to 50 micromoles/litre).

Adults:

It is advised that with all formulations of Tegretol, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.

Carbamazepine should be taken in a number of divided doses although initially 100-200mg once or twice daily is recommended. This may be followed by a slow increase until the best response is obtained, often 800-1200mg daily. In some instances, 1600mg or even 2000mg daily may be necessary.

Elderly:

In elderly patients there is an increased potential for drug interactions. Therefore, the dose of carbamazepine should be selected with caution in this group of patients.

Paediatric population and adolescents:

It is advised that a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. It may be helpful to monitor the plasma concentration of carbamazepine to establish the optimum dose.

Usual dosage 10 – 20 mg/kg body weight daily in several divided doses.

For children less than 5 years old it is inappropriate to prescribe carbamazepine tablets, another formulation should be used.

5-10 years: 400 to 600 mg daily (2 – 3 x 200 mg tablets per day, to be taken in several divided doses).

10-15 years: 600 to 1000 mg daily (3 – 5 x 200 mg tablets per day, to be taken in several divided doses).

> 15 years of age: 800 to 1200 mg daily (same as adult dose).

Maximum recommendation dose

Up to 6 years of age: 35 mg/kg/day

6-15 years of age: 1000 mg/day

>15 years of age: 1200 mg/day

Trigeminal neuralgia:

Slowly raise the initial dosage of 200-400 mg daily (100 mg twice daily in elderly patients) until freedom from pain is achieved (normally at 200 mg 3-4 times daily). In the majority of patients a dosage of 200 mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, dosage of 1600 mg carbamazepine daily may be needed. However, once the pain is in remission, the

dosage should be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Elderly:

Dosage in Trigeminal neuralgia

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

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

For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy:

Initial starting dose of 400 mg daily in divided doses, increasing gradually until symptoms are controlled or a total daily dose of 1600 mg given in divided doses is reached. The usual daily dosage range is 400 – 600 mg, in divided doses.

Special populations

Renal impairment / Hepatic impairment

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

4.3 Contraindications

Known hypersensitivity to carbamazepine, or structurally related drugs, eg tricyclic anti-depressants. Patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda). Carbamazepine use is not recommended in combination with monoamine oxidase inhibitors (MAOIs).

4.4 Special warnings and precautions for use

Warnings

Agranulocytosis and aplastic anaemia have been associated with carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimate for carbamazepine are difficult to obtain. The overall risk in the general untreated population has been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 person per million per year for aplastic anaemia.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk with carbamazepine.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Serious dermatological reactions, including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) and Stevens Johnson syndrome (SJS) have been reported very rarely with carbamazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, carbamazepine should be withdrawn at once and alternative therapy should be considered.

Cutaneous reactions

Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1-6 per 10 000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher.

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

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first months of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, carbamazepine treatment should be discontinued.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of carbamazepine, carbamazepine must not be re-started in this patient at any time.

HLA-B* 1502 allele – in Han Chinese, Thai and other Asian populations

HLA-B*1502 in individuals of Han Chinese and Thai origin has been shown to be strongly associated with the risk of developing the severe cutaneous reactions known as SJS when treated with carbamazepine. The prevalence of HLA-B* 1502 carrier is about 10% in Han Chinese and Thai populations. Whenever possible, these individuals should be screened for this allele before starting

treatment with Carbamazepine. If these individuals test positive, carbamazepine should not be started unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still very rarely occur.

There are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations. Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.

The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%).

HLA-A*3101 allele – European descent and Japanese populations

There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash in people of European descent and the Japanese.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population.

The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in the general population to 26% among subjects of European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.

There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment.

If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks.

Other dermatologic reactions

Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous and usually disappear after a few days or weeks either during the course of the treatment or following a decrease in the dose. However, worsening of the rash or accompanying symptoms, and severe skin reactions are indications for the immediate withdrawal of carbamazepine. Patients should be kept under close surveillance since it may be difficult to differentiate the early signs of a more serious skin reaction from mild transient ones. Patients with serious dermatological reactions (such as SJS, TEN, also known as Lyell's syndrome) may require hospitalisation, as these conditions may be life-threatening and may be fatal.

The risk of less severe adverse cutaneous reactions such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption) is not predicted by the HLA-B*1502 allele.

Decreased platelet or white blood cell counts occur occasionally to frequently in association with use of carbamazepine. Complete blood counts including platelets, possibly reticulocytes and serum iron, and liver function tests should be performed before commencing treatment. Blood counts should then be repeated at weekly intervals during the first month of treatment and subsequently at regular intervals; liver function tests should also be undertaken before commencing treatment and periodically thereafter, especially in patients with a history of liver disease or in the elderly. In cases of aggravated liver dysfunction or acute liver disease, the drug should be withdrawn immediately.

Some liver function tests e.g. gamma glutamyl transferase, may be found to be abnormal, probably due to hepatic enzyme induction. Enzyme induction may also modestly elevate alkaline phosphatase levels. This is not a reason to withdraw treatment. However, rarely severe hepatic reactions to carbamazepine occur, if the signs and symptoms of liver dysfunction or active liver disease develop, treatment with carbamazepine should be suspended pending the outcome of the evaluation of these signs and symptoms.

Non-progressive or fluctuating asymptomatic leucopenia, which is quite often encountered, does not generally call for withdrawal of carbamazepine. If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and complete blood count should be closely monitored. However, treatment with carbamazepine should be discontinued if the patient develops leucopenia, which is severe, progressive or accompanied by clinical manifestations, eg fever or sore throat. Discontinue carbamazepine if there is significant evidence of bone marrow depression.

Patients and their relatives should be informed of the importance of contacting the doctor immediately should any of the following occur: fever, sore throat, rash, mouth ulcers, easy bruising, petechial or purpuric haemorrhage. These may be symptoms of a potential haematological, dermatological or hepatic reaction.

Hypersensitivity

Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon). If the signs and symptoms of hypersensitivity reactions occur, carbamazepine should be immediately withdrawn.

25-30 % of patients who exhibit hypersensitivity reactions to carbamazepine, may also experience them with oxcarbazepine.

In addition, cross-hypersensitivity may occur between carbamazepine and phenytoin.

Carbamazepine may exacerbate seizures in patients with mixed seizures, which include absences, either typical or atypical, and therefore should be used with caution in these conditions. Carbamazepine should be discontinued in cases where seizures are exacerbated.

Seizure frequency may be increased during the switchover from oral formulations to suppositories.

Dose reduction and withdrawal effects

Abrupt withdrawal of carbamazepine may precipitate seizures therefore carbamazepine withdrawal should be gradual. If treatment with carbamazepine has to be withdrawn abruptly in a patient with epilepsy, the changeover to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug.

Note: in keeping with current opinion it is suggested that the level of serum folic acid be observed during anti-convulsant therapy.

Endocrinological effects

Breakthrough bleeding has been reported in women taking carbamazepine while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by carbamazepine and women of childbearing potential should be advised to consider using alternative forms of birth control while taking carbamazepine.

Patients taking carbamazepine and requiring hormonal contraception should receive a preparation containing not less than 50 µg oestrogen or the use of some alternative non-hormonal method of contraception should be considered.

Monitoring of plasma levels

Although correlations between dosages 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 conditions: 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.

Precautions

Carbamazepine should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with carbamazepine.

In patients with severe cardiovascular diseases, or with hepatic or renal disorders and in elderly patients, the initial dosage should be small and the increments titrated against the patient's condition. Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hyponatremia

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

Hypothyroidism

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

Anticholinergic effects

Carbamazepine has shown mild anticholinergic activity; patients with increased intraocular pressure and urinary retention should therefore be closely observed during therapy.

Psychiatric effects

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

Interactions

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

Co-administration of CYP3A4 inducers with carbamazepine may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of carbamazepine may have to be adjusted.

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

Female patients of childbearing potential should be warned that the concurrent use of carbamazepine with hormonal contraceptives may render this type of contraceptive ineffective. Alternative non-hormonal forms of contraception are recommended when using carbamazepine.

4.5 Interaction with other medicinal products and other forms of interact.

Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalyzing formation of the active metabolite carbamazepine 10, 11-epoxide. Adverse reactions could be induced if inhibitors of CYP 3A4 were co-administered, resulting in increased carbamazepine plasma concentrations. In contrast, co-administration of CYP 3A4 inducers may lead to a decrease in the serum carbamazepine level and therapeutic effect, by increasing the rate of carbamazepine metabolism.

Furthermore, the rate of carbamazepine metabolism may be reduced by the discontinuation of a CYP3A4 inducer, leading to an increase in the plasma carbamazepine levels.

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

The formation of the 10, 11-transdiol derivative from carbamazepine 10, 11-epoxide is catalysed by human microsomal epoxide hydrolase. In a manner similar to that described above, increased plasma concentrations of carbamazepine-10, 11-epoxide may be the result of co-administration of human microsomal epoxide hydrolase inhibitors.

Interactions resulting in a contraindication

Carbamazepine is structurally related to tricyclic antidepressants. Therefore, carbamazepine should not be administered with, or within a minimum of two weeks of cessation of monoamine oxidase inhibitors (MAOI) therapy or longer if the clinical situation permits (see contraindications).

The effect of carbamazepine on the 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 therefore need 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), tramadol.

Antibiotics: doxycycline, rifabutin.

Anticoagulants: oral anticoagulants (e.g. warfarin and acenocoumarol).

Antidepressants: bupropion, citalopram, mianserin, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine).

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to

13 micrograms /mL before adding carbamazepine to the treatment. There have been rare reports of an increase in plasma mephenytoin levels.

Antifungals: itraconazole, voriconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.

Anthelmintics: albendazole.

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

Antipsychotics: clozapine, haloperidol and bromperidol, olanzapine, quetiapine, risperidone, aripiprazole, paliperidone.

Antivirals: protease inhibitors for HIV treatment (e.g. indinavir, ritonavir, saquinavir).

Anxiolytics: alprazolam.

Bronchodilators or anti-asthma drugs: theophylline.

Contraceptives: hormonal contraceptives (alternative contraceptive methods should be considered).

Cardiovascular drugs: calcium channel blockers (dihydropyridine group) e.g. felodipine, digoxin, simvastatin, atorvastatin, lovastatin, cerivastatin, ivabradine.

Corticosteroids: corticosteroids (e.g. prednisolone, dexamethasone).

Drugs used in erectile dysfunction: tadalafil.

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus.

Thyroid agents: levothyroxine.

Other drug interactions: products containing oestrogens and/or progesterones.

Agents that may decrease the plasma levels of carbamazepine:

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

Antiepileptics: oxcarbazepine, phenobarbital, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment) and fosphenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

Other interactions: herbal preparations containing St John's wort (*Hypericum perforatum*).

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

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

Agents that may raise carbamazepine plasma levels

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

Analgesics, anti-inflammatory drugs: dextropropoxyphene.

Androgens: danazol.

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

Antidepressants: fluoxetine, fluvoxamine, paroxetine, trazodone.

Antiepileptics: vigabatrin.

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

Antihistamines: loratadine.

Antipsychotics: olanzapine.

Antituberculosis: isoniazid.

Antivirals: protease inhibitors for HIV treatment (e.g. ritonavir).

Carbonic anhydrase inhibitors: acetazolamide.

Cardiovascular drugs: diltiazem, verapamil.

Gastrointestinal drugs: possibly cimetidine, omeprazole.

Other interactions: grapefruit juice, nicotinamide (only in high dosage).

Combinations that require specific consideration:

Increased carbamazepine-induced toxicity has been reported upon the concomitant use of carbamazepine and levetiracetam.

Co-administration with isoniazid may lead to increased isoniazid induced hepatotoxicity.

Co-administration with some diuretics (hydrochlorothiazide or furosemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonise the effects of non-depolarising muscle relaxants such as pancuronium: the dosage may need to be raised and the patient monitored closely for an unexpectedly rapid recovery from neuromuscular blockade.

The combination of lithium and carbamazepine may cause enhanced neurotoxicity in spite of lithium plasma concentrations being within the therapeutic range. Co-administration with major tranquilisers

(eg haloperidol, thioridazine) or metoclopramide may also cause an increase in neurological side effects.

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol.

4.6 Pregnancy and Lactation

Pregnancy

The offspring of mothers with untreated epilepsy are known to be more prone to developmental disorders such as malformations. Developmental disorders and malformations, including spina bifida and also congenital anomalies e.g. craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias and anomalies involving various body systems, have also been reported in association with maternal carbamazepine use. Patients should therefore be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening. Based on data in a North American pregnancy registry, the rate of major congenital malformations, defined as a structural abnormality with surgical, medical, or cosmetic importance, diagnosed within 12 weeks of birth was 3.0% (95% CI 2.1 to 4.2%) among mothers exposed to carbamazepine monotherapy in the first trimester and 1.1% (95% CI 0.35 to 2.5%) among pregnant women not taking any antiepileptic drug (relative risk 2.7, 95% CI 1.1 to 7.0).

Taking these data into consideration:

- Pregnant women with epilepsy should be treated with special care.
- If women receiving carbamazepine become pregnant or plan to become pregnant, or if the problem of initiating treatment with carbamazepine arises during pregnancy, the drug's expected benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing potential carbamazepine should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific drugs used and may be higher in polytherapy combinations that include valproate.
- Minimum effective doses should be given and monitoring of plasma levels is recommended. The plasma concentration could be maintained in the lower side of the therapeutic range 4 to 12 micrograms/mL provided seizure control is maintained. There is evidence to suggest that the risk of malformation with carbamazepine may be dose-dependent i.e. at a dose < 400 mg per day, the rates of malformation were lower than with higher doses of carbamazepine.

- Patients should be counseled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.
- During pregnancy, an effective antiepileptic treatment should not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

Monitoring and prevention

Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate folic acid deficiency during pregnancy, which may contribute to the increased incidence of birth defects in the offspring of treated epileptic mothers. Folic acid supplementation is therefore recommended before and during pregnancy.

In the neonate

It is recommended that vitamin K1 be given to the mother during the last few weeks of pregnancy, in order to avoid bleeding disorders in the offspring. Vitamin K1 should also be given to the neonate.

There have been a few cases of neonatal seizures and /or respiratory depression associated with maternal carbamazepine and other concomitant antiepileptic drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal carbamazepine use. These reactions may represent a neonatal withdrawal syndrome.

Breast-feeding:

Carbamazepine passes into breast milk (about 25-60% of the plasma concentration). Thus, the benefits of breast-feeding should be weighed against the risks to the infant. Infants of breast-feeding mothers should be monitored for possible adverse reactions (e.g. allergic skin reactions, excessive somnolence). There have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during antenatal and or during breast feeding. Therefore breast-fed infants of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects.

Females and males of reproductive potential

Contraception

Due to enzyme induction, Tegretol may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should use effective contraception during treatment with Tegretol and for a period of 28 days after discontinuation of treatment. According to national recommendations (FSRH Clinical Guidance: Drug Interactions with Hormonal Contraception), women taking carbamazepine should preferably change to a contraceptive method unaffected by enzyme inducing drugs (i.e. copper IUDs and the levonorgestrel-releasing IUD or depot progestogen-only injections).

Fertility

Reports of impaired male fertility and/or abnormal spermatogenesis are very rare.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Particularly at the start of treatment with Tegretol, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia), gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.

The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses.

Tabulated summary of adverse drug reactions compiled from clinical trials and from spontaneous reports

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

<i>Blood and lymphatic system disorders</i>	
<i>Very common:</i>	leucopenia.
<i>Common:</i>	thrombocytopenia, eosinophilia.
<i>Rare</i>	leucocytosis, lymphadenopathy.

<i>Very Rare</i>	agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia.
<i>Not Known</i>	bone marrow depression.
<i>Immune system disorders</i>	
<i>Rare:</i>	a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon).
<i>Very Rare:</i>	anaphylactic reaction, oedema angioedema, hypogammaglobulinaemia.
<i>Not known**:</i>	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).
Infections and infestations	
<i>Not known**:</i>	reactivation of Human herpes virus 6 infection.
<i>Endocrine disorders</i>	
<i>Common:</i>	Oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders.
Very Rare:	galactorrhoea, gynaecomastia.
<i>Metabolism and nutrition disorders</i>	
<i>Rare:</i>	folate deficiency, decreased appetite.
<i>Very rare:</i>	porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).
<i>Psychiatric disorders</i>	
<i>Rare:</i>	hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state.
<i>Very rare:</i>	activation of psychosis.
<i>Nervous system disorders</i>	
<i>Very common:</i>	ataxia, dizziness, somnolence.
<i>Common:</i>	diplopia, headache.
<i>Uncommon:</i>	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus.

<i>Rare:</i>	dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis.
<i>Very Rare:</i>	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
<i>Not known**:</i>	sedation, memory impairment.
<i>Eye disorders</i>	
<i>Common:</i>	accommodation disorders (e.g. blurred vision)
<i>Very rare:</i>	lenticular opacities, conjunctivitis.
<i>Ear and labyrinth disorders</i>	
<i>Very rare:</i>	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
<i>Cardiac disorders</i>	
<i>Rare:</i>	cardiac conduction disorders.
<i>Very rare:</i>	arrhythmia, atrioventricular block with syncope, bradycardia, cardiac failure congestive, coronary artery disease aggravated.
<i>Vascular disorders</i>	
<i>Rare:</i>	hypertension or hypotension.
<i>Very rare:</i>	circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis.
<i>Respiratory, thoracic and mediastinal disorders</i>	
<i>Very rare:</i>	pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.
<i>Gastro-intestinal disorders</i>	
<i>Very common:</i>	vomiting, nausea.
<i>Common:</i>	dry mouth, with suppositories rectal irritation may occur
<i>Uncommon:</i>	diarrhoea, constipation.
<i>Rare:</i>	abdominal pain.
<i>Very Rare:</i>	Pancreatitis, glossitis, stomatitis.
<i>Not known**:</i>	colitis.
<i>Hepatobiliary disorders</i>	
<i>Rare:</i>	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice.
<i>Very Rare:</i>	hepatic failure, granulomatous liver disease.
<i>Skin and subcutaneous tissue disorders:</i>	
<i>Very common:</i>	
<i>Common:</i>	urticaria, which may be severe dermatitis allergic.
<i>Uncommon:</i>	dermatitis exfoliative.
<i>Rare:</i>	systemic lupus erythematosus, pruritus.
<i>Very Rare:</i>	Stevens-Johnson syndrome*, toxic epidermal

	necrosis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhidrosis, alopecia, hirsutism.
<i>Not known**:</i>	Acute Generalized Exanthematous Pustulosis (AGEP)**, lichenoid keratosis, onychomadesis
<i>Musculoskeletal, connective tissue and bone disorders</i>	
<i>Rare:</i>	muscular weakness.
<i>Very Rare:</i>	bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.
<i>Not known**:</i>	fracture.
<i>Renal and urinary disorders</i>	
<i>Very Rare:</i>	tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/ azotaemia), urinary retention, urinary frequency.
<i>Reproductive System</i>	
<i>Very Rare:</i>	sexual disturbances/erectile dysfunction spermatogenesis abnormal (with decreased sperm count and/or motility).
<i>General disorders and administration site conditions</i>	
<i>Very common:</i>	fatigue.
<i>Investigations</i>	
<i>Very common:</i>	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant.
<i>Common:</i>	blood alkaline phosphatase increased.
<i>Uncommon:</i>	transaminases increased.
<i>Very Rare:</i>	intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxine (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased,
<i>Not known**:</i>	bone density decreased.
<i>Injury, poisoning and procedural complications</i>	
<i>Not known**:</i>	Fall (associated with Tegetol treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4

warning and precautions).

* In some Asian countries also reported as rare. See also section 4.4 Special warnings and precautions for use.

**Additional adverse drug reactions from spontaneous reports (frequency not known).

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and maculopapular rash. In Japanese and European patients, these reactions have been reported to be associated with the use of carbamazepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections 4.2 and 4.4 for further information).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at <https://primaryreporting.who-umc.org/ET> or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Overdose

Signs and symptoms:

The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under section 4.8.

Central nervous system: CNS depression, disorientation, depressed level of consciousness, agitation, somnolence, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system: respiratory depression and pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex, syncope in association with cardiac arrest.

Gastrointestinal system: delayed gastric emptying, reduced bowel motility, vomiting.

Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.

Renal function: retention of urine, oliguria or anuria, fluid retention, water intoxication caused by

carbamazepine's ADH-like effect.

Laboratory findings: hyponatraemia, increased muscle creatine phosphokinase, possibly metabolic acidosis, possibly hyperglycaemia.

Management:

There is no specific antidote.

The patients' clinical condition should initially guide the management: admission to hospital, confirmation of carbamazepine poisoning and assessment of the size of the overdose by measurement of the plasma level of the drug.

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

Special recommendations:

Charcoal haemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.

Relapse and aggravation of symptomatology on the 2nd and 3rd day after overdose, due to delayed absorption, should be anticipated

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties

Therapeutic class: Anti-epileptic, neurotropic and psychotropic agent; (ATC Code: N03 AF01).
Dibenzazepine derivative.

Carbamazepine is an anti-epileptic agent used to control generalised tonic-clonic (grand mal) and partial (simple and complex) seizures with or without secondary generalisation, including combinations of these types of seizures. Its mode of action in epilepsy is not fully understood but some of its actions resemble those of phenytoin.

Mechanism of action

The mechanism of carbamazepine action has only been partially solved. Its main mechanism of action may involve the inhibition of repetitive firing of sodium-dependent action potentials via use- and voltage-dependent blockage of sodium channels in depolarized neurons. In addition, carbamazepine also stabilizes hyperexcited nerve membranes, inhibits repetitive neuronal discharge and reduces synaptic propagation of electrical impulses.

Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be

responsible for the antimanic properties of carbamazepine.

5.2 Pharmacokinetic Properties

Absorption

Carbamazepine is slowly, but almost completely absorbed from the gastro-intestinal tract. Following single oral doses of carbamazepine tablets, mean peak plasma concentrations of the unmetabolised substance are found within 12 hours. The mean peak concentration of unmetabolised carbamazepine in the plasma after a single oral dose of 400 mg carbamazepine (tablets) is approximately 4.5 µg/ml. The rate and extent of absorption is not significantly influenced by the ingestion of food.

Within about 1-2 weeks, steady state plasma concentrations of carbamazepine are attained, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, pre-treatment status, dose and duration of treatment.

The bioavailability in different preparations of carbamazepine may vary; the bioavailability of carbamazepine in various oral formulations has been shown to lie between 85-100%. To avoid reduced effect or the risk of breakthrough seizures or excessive side effects, the formulation should not be altered.

Distribution

Carbamazepine is widely distributed throughout the body and approximately 70-80% of carbamazepine is bound to plasma proteins. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). In addition, carbamazepine crosses the placental barrier. In breast milk, concentrations of carbamazepine equivalent to 25-60% of the corresponding plasma levels were found.

The apparent volume of distribution, assuming complete absorption of carbamazepine, ranges from 0.8 to 1.9 L/kg.

Biotransformation

Carbamazepine is extensively metabolised in the liver and one of its primary metabolites, carbamazepine-10, 11-epoxide has been reported to have about one-third of the anti-epileptic activity of carbamazepine.

Cytochrome P450 3A4 is the major isoform responsible for the formation of carbamazepine-10, 11-epoxide. The further metabolism of carbamazepine-10, 11-epoxide by human microsomal epoxide hydrolase results in the formation of the 10, 11-transdiol derivative. A minor metabolite related to this pathway is 9-hydroxy-methyl-10-carbomoyl acridan. After a single dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

The biotransformation of carbamazepine also leads to various monohydroxylated compounds as well

as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination

Following a single oral dose of carbamazepine, the elimination half-life of unmetabolised carbamazepine averages approximately 36 hours. In comparison, it averages only 16-24 hours after repeated administration, due to the auto-induction of the hepatic mono-oxygenase system, although this is dependent on the duration of the medication. Moreover, the metabolism of carbamazepine is readily induced by drugs, such as phenytoin and phenobarbitone, which induce hepatic microsomal enzymes. In patients receiving concomitant treatment with enzyme-inducing drugs, half-lives of 9-10 hours have been found.

Following single oral doses of the pharmacologically active metabolite carbamazepine 10, 11-epoxide, the elimination half-life is approximately 6 hours.

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

5.3 Preclinical Safety Data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential. Reproductive toxicity studies in animals were insufficient to rule out a teratogenic effect of carbamazepine in humans.

Carcinogenicity

In rats treated with carbamazepine for two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence to date that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Reproductive toxicity

In animals studies in mice, rats and rabbits oral administration of carbamazepine during organogenesis led to increased embryo-foetal mortality and foetal growth retardation at daily doses which were associated with maternal toxicity (above 200 mg/kg/day). Carbamazepine was teratogenic in a number of studies, particularly in mice, however showed no or only minor teratogenic potential at doses relevant to humans. In a reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

Fertility

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

6.0 Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose, Lactose Monohydrate, Maize starch, Polacrillin Potassium (Kyron – T 314), Sodium Starch Glycolate (Type A), Colloidal Anhydrous Silica, Povidone K-30 BP, Purified Talc, Magnesium Stearate, Isopropyl Alcohol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacture.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C in a dry place. Protect from light.

Keep out of reach of children.

6.5 Nature and contents of container

10 Tablets packed in Printed Blister Aluminium foil and Clear PVC film and such 10 blister packed in a unit carton along with package insert.

Blister Pack (Blister Aluminium foil with Clear PVC film)

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

MEDICAMEN Biotech Limited

SP-1192 A&B, PHASE - IV,

Industrial Area,

Bhiwadi - 301 019

Distt. Alwar,

Rajasthan, India.

8. NUMBER(S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

Certificate No: 08509/09871/NMR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Mar 23, 2023

10. DATE OF REVISION OF THE TEXT

July 2023