SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Mezacar 200 mg Tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Carbamazepine 200 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mezacar is indicated for the tretment of

- Epilepsy - generalised tonic-clonic and partial seizures. Carbamazepine Retard is indicated in newly diagnosed patients with epilepsy and in those patients who are uncontrolled or unable to tolerate their current anti-convulsant therapy.

  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 psychoses in patients unresponsive to lithium therapy.

- The paroxysmal pain of trigeminal neuralgia. Mezacar may also be used to relieve the lancinating component of other forms of deafferentation pain, for example glossopharyngeal neuralgia, peripheral diabetic neuropathy, tabetic lightning pain, superior laryngeal neuralgia, stump pain, phantom limb pain and post herpetic neuralgia.

- Management of alcohol withdrawal symptoms.

- Treatment of mania and prophylaxis of manic-depressive illness, especially in patients unresponsive to lithium.

4.2 Posology and method of administration

Posology

Carbamazepine is given orally, generally in the same total daily dose as conventional Carbamazepine dosage forms but usually in two divided doses. In a few patients when changing from other oral dosage forms of Carbamazepine to Carbamazepine Retard the total daily dose may need to be increased, particularly when it is used in polytherapy. When starting treatment with Carbamazepine Retard in monotherapy, 100-200mg once or twice daily is recommended. This may be followed by a slow increase in dosage until the best response is obtained, often 800-1200mg daily. In some instances, 1600mg or even 2000mg daily may be necessary.

Carbamazepine should not be chewed but should be swallowed with a little liquid, before, during or between meals. The divisible tablet presentation enables flexibility of dosing to be achieved.

Epilepsy:

Adults:
It is advised that with all formulations of Carbamazepine, 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.

Elderly:
Due to the potential for drug interactions, the dosage of Carbamazepine should be selected with caution in elderly patients.

Children:
It is advised that with all formulations of Carbamazepine, 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 10-20mg/kg bodyweight daily in several divided doses.
Age up to 5 years: Carbamazepine Retard Tablets are not recommended
5-10 years: 400-600mg daily
10-15 years: 600-1000mg

Wherever possible, Carbamazepine Retard should be used as the sole drug anti-epileptic agent but if used in polytherapy, the same incremental dosage pattern is advised.

When Carbamazepine is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s).

4.3 Contraindications

Known hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any other component of the formulation.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).The use of Carbamazepine is not recommended in combination with monoamine oxidase inhibitors (MAOIs).

4.4 Special warnings and precautions for use

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

Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of Carbamazepine. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline, and periodically thereafter.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult his physician immediately.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored (see Section 4.8 Undesirable Effects). However, treatment with Carbamazepine should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Carbamazepine should also be discontinued if any evidence of significant bone marrow depression appears.

Liver function tests should also be performed before commencing treatment and periodically thereafter, 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 acute liver disease.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.

Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with Carbamazepine suspended pending the outcome of the evaluation.

Mild skin reactions e.g. isolated macular or maculopapular exanthemata, are mostly transient and not hazardous, and they usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage; however, the patient should be kept under close surveillance and a worsening rash or accompanying symptoms are an indication for the immediate withdrawal of Carbamazepine.

If signs and symptoms suggestive of severe skin reactions (e.g. Stevens-Johnson syndrome, Lyell's syndrome (toxic epidermal necrolysis)) appear, Carbamazepine should be withdrawn at once.

Carbamazepine may trigger hypersensitivity reactions, including multi-organ hypersensitivity reactions, which can affect the skin, liver, haematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction.

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Carbamazepine should be withdrawn immediately.

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that 25-30 % of these patients may experience hypersensitivity reactions with oxacarbazepine.

Cross-hypersensitivity can occur between carbamazepine and phenytoin.

Carbamazepine should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, Carbamazepine may exacerbate seizures. In case of exacerbation of seizures, Carbamazepine should be discontinued.

An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.

<u>Abrupt withdrawal of Carbamazepine may precipitate seizures:</u>
If treatment with Carbamazepine has to be withdrawn abruptly, the changeover to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug (e.g. diazepam i.v., rectal; or phenytoin i.v.).

<u>Carbamazepine and oestrogen and/or progestogen preparations:</u>

Due to hepatic enzyme induction, Carbamazepine may cause failure of the therapeutic effect of oestrogen and/or progestogen containing products. This may result in failure of contraception, recurrence of symptoms or breakthrough bleeding or spotting.

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

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 (see 4.5 Interaction with other Medicaments and other forms of Interaction).

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.

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Carbamazepine has shown mild anticholinergic activity; patients with increased intraocular pressure should therefore be warned and advised regarding possible hazards.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Similarly, discontinuation of a CYP3A4 inducer may decrease the rate of metabolism of carbamazepine, leading to an increase in carbamazepine plasma levels.

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

Agents that may raise carbamazepine and/or carbamazepine-10,11-epoxide plasma levels:

Isoniazid, verapamil, diltiazem, ritonavir, dextropropoxyphene, fluoxetine, fluvoxamine, possibly cimetidine, omeprazole, acetazolamide, danazol, nicotinamide (in adults, only in high dosage), trazodone, vigabatrin, macrolide antibiotics (e.g. erythromycin, clarithromycin), azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole), loratadine, olanzapine, quetiapine, grapefruit juice, protease inhibitors for HIV treatment (e.g. ritonavir). Quetiapine, primidone and valproic acid were reported to increase concentration of the active metabolite carbamazepine-10,11- epoxide.

Since raised plasma carbamazepine and/or carbamazepine-10,11-epoxidelevels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Carbamazepine should be adjusted accordingly and/or the plasma levels monitored.

Agents that may decrease carbamazepine plasma levels:

Phenobarbitone, phenytoin and fosphenytoin, primidone or theophylline, aminophylline, rifampicin, cisplatin or doxorubicin and, although the data are partly contradictory, possibly also clonazepam or valproic acid, oxcarbazepine. Mefloquine may antagonise the anti-epileptic effect of Carbamazepine. The dose of Carbamazepine may consequently have to be adjusted.

Isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and carbamazepine-10, 11-epoxide; carbamazepine plasma concentrations should be monitored.

Serum levels of carbamazepine can be reduced by concomitant use of the herbal remedy St John's wort (Hypericum perforatum).

Effect of Carbamazepine on plasma levels of concomitant agents:

Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement: levothyroxine, clobazam, clonazepam, ethosuximide, primidone, valproic acid, alprazolam, corticosteroids, (e.g. prednisolone, dexamethasone); ciclosporin, digoxin, doxycycline; dihydropyridine derivatives, e.g. felodipine and isradipine; indinavir, saquinavir, ritonavir, haloperidol imipramine, methadone, paracetamol, tramadol, products containing oestrogens and/or progestogens (alternative contraceptive methods should be considered) see Section 4.4 “Special Warnings and Precautions for Use”, gestrinone, tibolone, toremifene, theophylline, oral anticoagulants (warfarin and acenocoumarol), lamotrigine, tiagabine, topiramate, bupropion, citalopram, trazodone, tricyclic antidepressants (e.g. imipramine, amitriptyline, nortriptyline, clomipramine), clozapine, oxcarbazapine, olanzapine, quetiapine, itraconazole, imatinib and risperidone.

Plasma phenytoin levels have been reported both to be raised and to be lowered by carbamazepine, and there have been rare reports of an increase in plasma mephenytoin.

Combinations to be taken into consideration:

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

The combination of lithium and carbamazepine may cause enhanced neurotoxicity in spite of lithium plasma concentrations being within the therapeutic range. Combined use of carbamazepine with metoclopramide or major tranquillisers, e.g. haloperidol, thioridazine, may also result in an increase in neurological side-effects.

Because it (carbamazepine) is structurally related to tricyclic anti-depressants, the use of Carbamazepine is not recommended in combination with monoamine oxidase inhibitors (MAOIs); before administering Carbamazepine, MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits.

Concomitant medication with Carbamazepine and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

Carbamazepine may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium). Their dosage should be raised and patients monitored closely for a more rapid recovery from neuromuscular blockade than expected.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
In animals (mice, rats and rabbits) oral administration of carbamazepine during organogenesis led to increased embryo mortality at a daily doses which caused maternal toxicity (above 200mg/kg b.w. daily i.e. 20 times the usual human dosage). In the rat there was also some evidence of abortion at 300mg/kg body weight daily. Near-term rat foetuses showed growth retardation, again at maternally toxic doses. There was no evidence of teratogenic potential in the three animal species tested but, in one study using mice, carbamazepine (40-240 mg/kg b.w. daily orally) caused defects (mainly dilatation of cerebral ventricles in 4.7% of exposed foetuses as compared with 1.3% in controls).

Pregnant women with epilepsy should be treated with special care.

In women of childbearing age 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.

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 potential benefits must be carefully weighed against its possible hazards, particularly in the first three months of pregnancy. Minimum effective doses should be given and monitoring of plasma levels is recommended.
During pregnancy, an effective antiepileptic treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus.

Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. The possibility that carbamazepine, like all major antiepileptic drugs, increases the risk has been reported, although conclusive evidence from controlled studies with carbamazepine monotherapy is lacking. However, there are reports on developmental disorders and malformations, including spina bifida, and also other congenital anomalies e.g. craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with Carbamazepine. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

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

In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K1, be given to the mother during the last weeks of pregnancy as well as to the 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.

Use during lactation:
Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking Carbamazepine may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).

Fertility:
There have been very rare reports of impaired male fertility and/or abnormal spermatogenesis.

4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired by dizziness and drowsiness caused by Carbamazepine, especially at the start of treatment or in connection with dose adjustments; patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

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

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

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common (> 1/10) common (> 1/100, < 1/10); uncommon (> 1/1000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports.

Blood and lymphatic system	
Very commo :	Leucopenia
Common:	Thrombocytopenia, eosinophilia.
Rare:	Leucocytosis, lymphadenopathy, folic acid deficiency.
Very rare	Agranulocytosis, aplastic anaemia, pancytopenia, pure red cell aplasia, anaemia, megaloblastic anaemia, acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda, reticulocytosis, and possibly haemolytic anaemia.
Immune system	
Rare:	A delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests, 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, angioneurotic oedema.

Endocrine disorders	
Common:	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:	Blood prolactin increased with or without clinical symptoms such as galactorrhoea, gynaecomastia, abnormal thyroid function tests; decreased l-thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol), leading to osteomalacia/osteoporosis, increased blood cholesterol, including HDL cholesterol and triglycerides.
Psychiatric disorders	
Rare:	Hallucinations (visual or auditory), depression, anorexia, restlessness, aggression, agitation, confusional state.
Very rare:	Activation of psychosis.
Nervous system	
Very common:	Dizziness, ataxia, drowsiness, 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 disturbances, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, muscle weakness, and paresis
Very rare:	Taste disturbances, neuroleptic malignant syndrome
Eye disorders	
Very rare:	lenticular opacities, conjunctivitis, intraocular pressure increased.
Ear and labyrinth disorders	
Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac disorders	
Rare:	Cardiac conduction disorders, hypertension or hypotension.
Very rare:	Bradycardia, arrhythmia, atrioventricular block with syncope, circulatory collapse, congestive heart failure, aggravation of coronary artery disease, thrombophlebitis, thrombo-embolism (e.g. pulmonary embolism).

Respiratory, thoracic and mediastinal disorders	
Very rare:	Pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.
Gastro-intestinal disorders	
Very common:	Nausea, vomiting.
Common:	Dry mouth, with suppositories rectal irritation may occur.
Uncommon:	Diarrhoea, constipation.
Rare:	Abdominal pain
Very rare:	Glossitis, stomatitis, pancreatitis.
Hepatobiliary disorders	
Very common:	Increased-gamma-GT (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, jaundice.
Very rare:	Granulomatous hepatitis. Hepatic failure.
Skin and subcutaneous tissue disorders*:*	
Very common:	Dermatitis allergic, urticaria, which may be severe.
Uncommon:	Exfoliative dermatitis and erythroderma.
Rare:	Systemic lupus erythematosus, pruritus.
Very rare:	Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhydrosis, hair loss. Very rare cases of hirsutism have been reported, but the causal relationship is not clear.
Musculoskeletal, connective tissue and bone disorders	
Very rare:	Arthralgia, muscle pain, muscle spasms.
Renal and urinary disorders	
Very rare:	Interstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/ azotaemia), urinary frequency, urinary retention, sexual disturbances/impotence.
Reproductive System	
Very rare:	Spermatogenesis abnormal (with decreased sperm count and/or motility).

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 or respiratory systems.

Central nervous system: CNS depression; disorientation, 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 and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.

Gastro-intestinal system: Vomiting, delayed gastric emptying, reduced bowel motility.

Renal function: Retention of urine, oliguria or anuria; fluid retention, water intoxication due to ADH-like effect of carbamazepine.

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

Treatment
There is no specific antidote.

Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose.

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

Special recommendations:
Hypotension: Administer dopamine or dobutamine i.v.

Disturbances of cardiac rhythm: To be handled on an individual basis.

Convulsions: Administer a benzodiazepine (e.g. diazepam) or another antiepileptic,
e.g. phenobarbitone (with caution because of increased respiratory depression) or paraldehyde.

Hyponatraemia (water intoxication): Fluid restriction and slow and careful NaCl 0.9% infusion i.v. These measures may be useful in preventing brain damage.

Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis, and peritoneal dialysis have been 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent, ATC code: N03AF01

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

The mechanism of action of carbamazepine, the active substance of Carbamazepine, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium- dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

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

The authority/EFDA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption:
Carbamazepine is almost completely absorbed but the rate of absorption from the tablets is slow and may vary amongst the various formulations and between patients. Peak concentrations of active substance in the plasma are attained within 24 hours of administration of single dose of Carbamazepine Retard tablets.

The retard formulation shows about 15% lower bioavailability than standard preparations due mainly to the considerable reduction in peak plasma levels occasioned by controlled release of the same dosage of carbamazepine. Plasma concentrations show less fluctuation but auto-induction of carbamazepine occurs as with standard carbamazepine preparations.

The bioavailability of Carbamazepine in various oral formulations has been shown to lie between 85-100%. Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Carbamazepine.

Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero- induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.

Distribution:

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels. Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Biotransformation:
Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites.
Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. 9-Hydroxy-methyl- 10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination:
The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9- 10 hours have been found.

The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

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

Characteristics in patients
The steady-state plasma concentrations of carbamazepine considered as “therapeutic range” vary considerably inter-individually; for the majority of patients a range between 4-12µg/ml corresponding to 17-50µmol/l has been reported. Concentrations of carbamazepine 10, 11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

In rats treated with carbamazepine for two years, the incidence of tumours of the liver was found to be increased. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown. Bacterial and mammalian mutagenicity studies yielded negative results.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose, Croscarmellose sodium,Hypromellose, Colloidal anhydrous silica and Magnesium stearate.

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30˚C. Protect from moisture.
Keep it out of reach of children.

6.5 Nature and contents of container

10 tablets in blister and 5 such blisters of 10 tablets in a carton along with pack insert.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Kusum Healthcare Pvt. Ltd.,
SP 289 (A), RIICO Industrial area,
Chopanki, Bhiwadi (Rajasthan), India

8. MARKETING AUTHORISATION NUMBER(S)

04612/07022/NMR/2018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 September 2019

10. DATE OF REVISION OF THE TEXT

08/2023

11. REFERENCES

SmPC published on electronic medicines compendium
https://www.medicines.org.uk/emc#gref

The MHRA published product information
https://products.mhra.gov.uk/