National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. Name of the medicinal product:

Carbamazepine Tablets BP 200 mg

2. Qualitative and quantitative composition

Each Uncoated Tablet contains:

Carbamazepine BP 200 mg

S. No.	Name of the Ingredient	Specification	Qty/Tablet (mg)	Functional category
Dry mixing				
1	Carbamazepine BP*	BP	200.000	Active
2	Microcrystalline Cellulose BP (PH 101)**	BP	81.500	Disintegrant
3	Sodium Starch Glycolate BP (Type A)	BP	6.500	Disintegrent
4	Sodium Lauryl Sulphate BP	BP	1.000	Lubricant
Drug Solution				
5	Povidone (K-90) BP	USP	5.000	Binder
6	Purified Water USP #	BP	90.000	Solvent
Binder:				
7	Sodium Starch Glycolate BP (Type A)	BP	4.000	Binder
8	Sodium Lauryl Sulphate BP	USP	0.500	Lubricant
Lubrication:				
9	Magnesium Stearate	BP	1.500	Lubricant
Total Core Tablet Weight:			**300.000**	

Not present in finished Product.

3. Pharmaceutical form

White color, Circular shaped, biconvex, Uncoated tablet with engraving “TEG 200” on one side and breakline on the other side.

4. Clinical particular

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

Carbamazepine is given orally, usually in two or three divided doses. Carbamazepine may be taken during, after or between meals, with a little liquid e.g. a glass of water.

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 Carbamazepine, 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 population (65 years or above): Due to the potential for drug interactions, the dosage of Carbamazepine should be selected with caution in elderly patients.

Children and adolescents: 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. Usual dosage 10-20mg/kg bodyweight daily taken in several divided doses.

Carbamazepine tablets are not recommended for very young children.

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

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

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

Maximum recommended dose

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

6-15 years of age: 1000mg/day

>15 years of age: 1200mg/day.

Wherever possible, anti-epileptic agents should be prescribed as the sole 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).

***Trigeminal neuralgia*:**

Slowly raise the initial dosage of 200-400mg daily until freedom from pain is achieved (normally at 200mg 3-4 times daily). In the majority of patients a dosage of 200mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600mg 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 1200mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Elderly population (65 years or above):

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 100mg twice daily is recommended. The initial dosage of 100mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200mg/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 400mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600mg given in divided doses is reached. The usual dosage range is 400-600mg daily, given 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 (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 contraindicated in combination with monoamine oxidase inhibitors (MAOIs)

Interaction with other medicinal products and other forms of interaction).

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 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 the 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. 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.

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 for 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. Most of the SJS/TEN cases appear in the first few months of treatment with Carbamazepine. 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.

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 Stevens-Johnson syndrome (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 HLAB* 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 general population to 26.0% among subjects of Northern 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

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 co-medications 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 may result in increased carbamazepine-10,11 epoxide plasma concentrations.

Interactions resulting in a contraindication

The use of Carbamazepine is contraindicated 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.

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 Carbamazepine should be adjusted accordingly and/or the 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), ciprofloxacine.

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).

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

Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness,

ataxia, diplopia), the dosage of Carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Quetiapine, primidone, progabide, valproic acid, valnoctamide and valpromide.

Agents that may decrease carbamazepine plasma levels:

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.

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

Other interactions: herbal preparations containing 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:

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, acenocoumarol, rivaroxaban, dabigatran, apixaban and edoxaban).

Antidepressants: bupropion, citalopram, mianserin, sertraline, trazodone, tricyclic antidepressants (e.g. imipramine,

amitriptyline, nortriptyline, clomipramine).

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, eslicarbazepine, 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.

Antihelmintics: 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.

Bronchodilatators 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.

4.5 Interaction with other medicinal products and other forms of interaction

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Antiepileptics: vigabatrin.

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

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Antituberculosis: isoniazid.

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

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Cardiovascular drugs: diltiazem, verapamil.

Gastrointestinal drugs: possibly cimetidine, omeprazole.

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

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Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

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

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Antibiotics: doxycycline, rifabutin.

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

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

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, eslicarbazepine, 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. Antihelmintics: 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.

Bronchodilatators 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.

Combinations that require specific consideration:

Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.

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.

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.

Concomitant use of carbamazepine with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma concentrations of direct acting oral anti-coagulants, which carries the risk of thrombosis. Therefore, if a concomitant use is necessary, closer monitoring of signs and symptoms of thrombosis is recommended.

Interference with serological testing

Carbamazepine may result in false positive perphenazine concentrations in HPLC analysis due to interference. Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant cncentration in fluorescence polarized immunoassay method.

4.6 Pregnancy and lactation

Pregnancy

Risk summary

Offspring of epileptic mothers with untreated epilepsy are known to be more prone to developmental disorders, including malformations. Developmental disorders and malformations, including spina bifida, and also other congenital anomalies

e.g. craniofacial defects such as clept lip/palate, cardiovascular malformations, hypospadias and anomalies involving various body systems, have been reported in association with the use of Carbamazepine. Patients should be counseled 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).

Clinical considerations

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 need 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 child-bearing 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 < 400mg 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 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 the neonate

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.

Animal studies have shown reproductive toxicity.

Breastfeeding:

Risk summary

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). 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, Carbamazepine may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with Carbamazepine.

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 the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision have been reported with 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

Summary of the safety profile

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.

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

4.9 Overdose

Signs and symptoms

The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems

Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, 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.

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 due to ADH-like effect of carbamazepine.

Laboratory findings: Hyponatraemia, possibly metabolic acidosis, possibly hyperglycaemia, 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 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 :

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. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Angiotensin II Antagonists, plain,

ATC-Code: C09CA07

Mechanism of action

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

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. 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 400mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5µg/ml.

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. 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. 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 interindividually; 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.

Special populations

Paediatric populations

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

Elderly population (65 years or above)

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.

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

Animal data

The cumulative evidence from various animal studies in mice, rats and rabbits indicates that carbamazepine has no or only minor teratogenic potential at doses relevant to man. However, the animal studies were insufficient to rule out a teratogenic effect of carbamazepine. 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. Pharmaceutical particulars

6.1 List of excipients

Microcrystalline cellulose,, Sodium Starch Glycolate (Type A), Sodium Lauryl sulphate, Povidone (K-30) and Magnesium Stearate

6.2 Incompatibilities : Not applicable.

6.3 Shelf life : 3 years

6.4 Special precautions for storage: Store in the original package below 30°C in order to protect from moisture.

6.5 Nature and contents of container

Blister pack: 10 x 10 Tablets

6.6 Special precautions for disposal and other handling No special requirements.

7. APPLICANT / MANUFACTURER

APPLICANT:

MANKIND LIFE-SCIENCES LTD
NO 2 AGGREY ROAD,
FEGGE ONITSHA,
ANAMBRA STATE, NIGERIA

MANUFACTURER:

NO 147, MADHAVARAM RED HILLS HIGH ROAD,

GRANTLYON VILLAGE, CHENNAI – 600 052, INDIA.