SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the finished pharmaceutical product

PUREZEPINE [Carbamazepine Tablets BP 200mg]

2. Qualitative and quantitative composition

Each uncoated tablet contains:
Carbamazepine BP 200mg
Excipients q.s

3. Pharmaceutical form

Tablet

4. Clinical particulars

Therapeutic indication

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.

4.1 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. (see information on genetic testings and cutaneous reactions in section 4.4)

Epilepsy:

It is advised that a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient to achieve adequate control of seizures. If possible a sole anti-epileptic agent should be used but if polytherapy is necessary, the same incremental dosage pattern should be followed.

If adding carbamazepine to existing antiepileptic treatment, the dose should be increased gradually, and if needed, the dose of the existing antiepileptics adjusted

Monitoring of the plasma level of carbamazepine will ensure that the optimum dose is prescribed. 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) (see warnings and precautions).

Adults:

Carbamazepine should be taken in a number of divided doses. Initially: 100 – 200 mg once or twice a day, followed by a slow increase until the best response is obtained, often 800 – 1200 mg daily in divided doses. In some cases, 1600 mg or even 2000 mg daily in divided doses 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 (see sections 4.4. and 5.2).

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.

Method of administration

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

4.2 Contraindications

Hypersensitivity to carbamazepine, or structurally related drugs,

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 contraindicated in combination with monoamine oxidase inhibitors (MAOIs)

4.3 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.

Decreased platelet or white blood cell counts occur occasionally to frequently in association with 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 their 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). 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 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.

Most of the SJS/TEN cases appear in the first few months of treatment with Carbagen. 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 (see section 4.2).

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 reaction Steven-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 (see section 4.2). 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 (see section 4.8) 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 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

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, 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.

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) (see section 4.8).

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

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

Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).

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 (see section 4.5).

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 (see section 4.8).

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 (see section 4.5).

Female patients of childbearing potential should be warned that the concurrent use of carbamazepine with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.5 and 4.6). Alternative non-hormonal forms of contraception are recommended when using carbamazepine.

Falls

Carbamazepine treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 4.8 Undesirable effects) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term carbamazepine treatment.

4.4 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. 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 hydralase 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, 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.

***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.

Bronchodilatators 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), 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).

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.

Concomitant use of carbamazepine with direct action oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma concentration if 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 concentration in fluorescence polarized immunoassay method.

4.5 Fertility, pregnancy and lactation

Pregnancy:

Risk summary

The offspring of epileptic 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 clept 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).

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 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 K_1 be given to the mother during the last few weeks of pregnancy, in order to avoid bleeding disorders in the offspring. Vitamin K_1 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.

Animal studies have shown reproductive toxicity (see section 5.3).

Breast-feeding:

Risk summary

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, 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:

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

4.6 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.

4.7 Undesirable effects

Summary of safety profile

Provided a gradually increasing dosage scheme is followed, carbamazepine is generally well tolerated but side effects may occur particularly at the start of the treatment or if the initial dose 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 disappear spontaneously after a few days or following a temporary reduction in dosage. 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).

Blood and lymphatic system disorders	
Very common:	Leucopenia.
Common:	Thrombocytopenia, eosinophilia.
Rare:	Leucocytosis, lymphadenopathy.
Very rare:	Agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia.
*Not known**:*	Bone marrow depression.
Immune system disorders	
Rare:	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 intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, liver, colon)
Very rare:	Anaphylactic reaction, oedema angioedema, hypogammaglobulinaemia.
*Not known**:*	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).
Infections and infestations	
*Not known**:*	Reactivation of Human herpes virus 6 infection.
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:	Gynaecomastia, galactorrhoea.
Metabolism and nutrition disorders	
Rare:	Folate deficiency, decreased appetite.
Very rare:	Porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).
Psychiatric disorders	
Rare:	Depression, visual or auditory hallucinations, restlessness, aggressive behaviour, confusional state, agitation.
Very rare:	Activation of psychosis.
Nervous system disorders	
Very common:	Dizziness, ataxia, somnolence.
Common:	Diplopia, headache.
Uncommon:	Nystagmus, abnormal involuntary movements (e.g. tremor asterixis, tics, dystonia).
Rare:	Paraesthesia, peripheral neuropathy, speech disorders (e.g. dysarthria or slurred speech), eye movement disorders, dyskinesia, choreoathetosis and paresis.
Very rare:	Neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
*Not known**:*	Sedation, memory impairment.
Eye disorders	
Common:	Accommodation disorders (e.g. blurred vision).
Very rare:	Lenticular opacities, conjunctivitis.
Ear and labyrinth disorders	
Very rare:	Hearing disorders, e.g. change in pitch perception, tinnitus, hyperacusis and hypoacusis.
Cardiac disorders	

Rare:	Cardiac conduction disorders.
Very rare:	Arrhythmias, bradycardia, atrioventricular block with syncope, congestive cardiac failure, aggravation of coronary artery disease.
Vascular disorders	
Rare:	Hypertension or hypotension.
Very rare:	Circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis.
Respiratory, thoracic and mediastinal disorders	
Very rare:	Pulmonary hypersensitivity characterised e.g. by dyspnoea, pneumonia, pneumonitis, fever.
Gastro-intestinal disorders	
Very common:	Vomiting, nausea.
Common:	Dry mouth, with suppositories rectal irritation may occur.
Uncommon:	Diarrhoea, constipation.
Rare:	Abdominal pain.
Very rare:	Glossitis, pancreatitis, stomatitis.
*Not known**:*	Colitis.
Hepatobiliary disorders	
Rare:	Jaundice, hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome.
Very rare:	Granulomatous liver disease, hepatic failure.
Skin and subcutaneous tissue disorders	
Very common:	Urticaria, which may be severe dermatitus allergic..
Uncommon:	Dermatitis exfoliative.
Rare:	Pruritus, systemic lupus erythematosus.
Very rare:	Stevens-Johnson syndrome* (SJS), toxic epidermal necrolysis (TEN), photosensitivity reaction, erythema multiforme and nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.
*Not known**:*	Acute Generalized Exanthematous Pustulosis (AGEP)**, lichenoid keratosis, onychomadesis.
Musculoskeletal, connective tissue and bone disorders	
Rare:	Muscular weakness.
Very rare:	Bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxycholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.
*Not known**:*	Fracture.
Renal and urinary disorders	
Very rare:	Tubulointerstitial nephritis, renal failure, renal impairment (e.g.

	albuminuria, haematuria, oliguria and blood urea/azotaemia), urinary retention, urinary frequency.
Reproductive System	
Very rare:	Sexual disturbances/erectile dysfunction, abnormal spermatogenesis (with decreased sperm count and/or motility).
General disorders and administration site conditions	
Very common:	Fatigue.
Investigations	
Very common:	Gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant.
Common:	Blood alkaline phosphatase increased.
Uncommon:	Transaminases increased.
Very rare:	Intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased.
*Not known**:*	Bone density decreased.
Injury, poisoning and procedural complications	
*Not known**:*	Fall (associated with carbamazepine 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.

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

The following adverse drug reactions have been derived from post-marketing experience with carbamazepine via spontaneous case reports and literature cases. Because these reactions are reported voluntary from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ class in MedRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

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 aculopapular 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).

4.8 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.

Gastro-intestinal 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.

Treatment:

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 the signs and symptoms of overdose may occur on the second or third day due to delayed absorption.

5. 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 depolarised neurons. In addition, carbamazepine also stabilises 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

Not Applicable

6. Pharmaceutical particulars

6.1 List of excipients

Maize starch BP
Microcrystalline Cellulose BP
Lactose BP
PVP-K30 BP
Sodium Methyl Paraben BP
Sodium Propyl Paraben BP
Isopropyl Alcohol BP
Talcum BP
Magnesium Stearate BP
Crospovidone BP
Croscarmellose Sodium BP
Aerosil BP

6.2 Incompatibilities

None Stated

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

10 x 10 Alu/Pvc tablets, Such 10 Blister packed in carton along with insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. REGISTRANT

M/S. Pure Generic Ltd

Nigeria

8. MANUFACTURER

Merit Organics Ltd
Plot No 2104/2/A, G.I.D.C , Sarigam , Bhilad,
Dist- Valsad-396155, Gujarat , INDIA

9. DATE OF REVISION OF THE TEXT

Applicable once the registration is obtained.