Approved Professional Information for Medicines for Human Use:

CARBAMAZEPINE 200 AUSTELL

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

CARBAMAZEPINE 200 AUSTELL 200 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg carbamazepine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Pink colored capsule shaped, 13,60 mm X 5,5 mm biconvex, uncoated tablets, debossed ‘CAR’ on one side and ‘200’ on the partially scored side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CARBAMAZEPINE 200 AUSTELL is indicated for:

Epilepsy with motor and psychic manifestations:

- psychomotor or temporal-lobe epilepsy
- generalised tonic-clonic seizure
- mixed forms of seizures
- complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalisation.

Acute mania and maintenance treatment of bipolar affective disorders to prevent or attenuate recurrence.

Idiopathic trigeminal neuralgia.

Idiopathic glossopharyngeal neuralgia.

It is suitable for both monotherapy and combination therapy.

It is usually not effective in absences (petit mal) and myoclonic seizures. (See Section 4.4).

4.2 Posology and method of administration

Posology

Epilepsy

When possible CARBAMAZEPINE 200 AUSTELL should be prescribed as monotherapy.

Treatment should be initiated with low daily dosage, to be slowly increased until an optimal effect is obtained.

Determination of plasma levels may help in establishing the optimum dosage.

When CARBAMAZEPINE 200 AUSTELL is added to existing anti-epileptic therapy, this should be done gradually while maintaining, or if necessary, adapting the dosage of the other anti-epileptic(s). (See Section 4.5).

Dose for adults

Initially, 100 mg to 200 mg once or twice a day, followed by a slow increase until usually at a level of 400 mg twice or three times a day, the best response is obtained. In some instances 1600 mg in 3 to 4 divided doses may be necessary.

Special populations

Elderly

Due to interactions and different anti-epileptic medicine pharmacokinetics, the dosage of CARBAMAZEPINE 200 AUSTELL should be selected with caution in elderly patients.

Trigeminal Neuralgia

The initial dosage of 200 – 400 mg should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 – 4 times daily, in some instances it may necessitate 1600 mg daily). The dosage should then be gradually reduced to the lowest possible maintenance level. In elderly and particularly sensitive patients (see Section 4.4) an initial dosage of 100 mg twice a day is recommended.

Acute mania and maintenance treatment of (bipolar) affective disorders

Dosage range:

Approximately 400 – 1600 mg daily, the usual dosage being 400 – 600 mg daily given in 2 – 3 divided doses. In acute mania, the dosage should be increased rather quickly, whereas small dosage increments are recommended for maintenance therapy of bipolar disorders in order to ensure optimal tolerability.

Method of administration

CARBAMAZEPINE 200 AUSTELL may be taken during, after, or between meals and swallowed with adequate amount of fluid.

When the patient is transferred from another anticonvulsant medicine to CARBAMAZEPINE 200 AUSTELL, the dosage of the first should be reduced gradually.

4.3 Contraindications

- Known hypersensitivity to carbamazepine, or structurally related medicines e.g. tricyclic antidepressants, or any other component of the CARBAMAZEPINE 200 AUSTELL.
- Patients with atrioventricular block.
- Patients with a history of bone-marrow depression
- Patients with a history of porphyria (e.g. acute intermittent porphyria, variegate porphyria).

- The use of CARBAMAZEPINE 200 AUSTELL is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of MA0Is (see Section 4.5).
- Carbamazepine passes into the breast milk (about 25 - 60 % of plasma concentration). Mothers taking CARBAMAZEPINE 200 AUSTELL should not breastfeed their infants.
- Previous Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

4.4 Special warnings and precautions for use

Warnings

Agranulocytosis and aplastic anaemia have been associated with CARBAMAZEPINE 200 AUSTELL.

Decreased platelet or white blood cell counts may occur in association with the use of CARBAMAZEPINE 200 AUSTELL. Complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtain 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 medical practitioner 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 200 AUSTELL should be discontinued if the patient develops leucopenia which is sever, progressive or accompanied by clinical manifestations. e.g. fever or sore throat. CARBAMAZEPINE 200 AUSTELL should also be discontinued if any evidence of significant bone marrow depression appears.

Liver function test should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. CARBAMAZEPINE 200 AUSTELL 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 developments of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment CARBAMAZEPINE 200 AUSTELL suspended pending the outcome of the evaluation.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicines 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 CARBAMAZEPINE 200 AUSTELL. Patients with serious dermatological reactions may require hospitalisation, 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 200 AUSTELL. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, CARBAMAZEPINE 200 AUSTELL should be withdrawn at once and alternative therapy should be considered.

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 (see section 4.2). If these individuals test positive, carbamazepine should not be started. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still 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 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 %.
Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with CARBAMAZEPINE 200 AUSTELL.
The use of CARBAMAZEPINE 200 AUSTELL should be avoided in patients who are found to be positive for HLA-A*3101. Screening is generally not recommended for any current CARBAMAZEPINE 200 AUSTELL users, as the risk of SJS/TEN, AGEP, DRESS and maculopapular rash is largely confined to the first few months of
therapy, regardless of HLA-A*3101 status.

Other dermatologic reactions

Skin reactions e.g. macular or maculopapular exanthema, can also occur. However, since it may be difficult to differentiate the early signs of more serious skin reactions from mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing CARBAMAZEPINE 200 AUSTELL should the reaction worsen with continued use.
The HLA-A*3101 allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as anticonvulsant hypersensitivity syndrome or non-serious rash (maculopapular eruption). However, the HLA-B*1502 allele has not been found to predict the risk of these aforementioned skin reactions.

Hypersensitivity

CARBAMAZEPINE 200 AUSTELL 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 signs and symptoms suggestive of hypersensitivity reactions occur, CARBAMAZEPINE 200 AUSTELL 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 aromatic antiepileptic medicines (e.g. phenytoin, primidone and phenobarbitone).

CARBAMAZEPINE 200 AUSTELL should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, CARBAMAZEPINE 200 AUSTELL may exacerbate seizures. In case of exacerbation of seizures, CARBAMAZEPINE 200 AUSTELL should be discontinued.
An increase in seizure frequency may occur during switchover from an oral formulation to suppositories.

Dose reduction and withdrawal effects

Abrupt withdrawal of CARBAMAZEPINE 200 AUSTELL may precipitate seizures, therefore carbamazepine withdrawal should be gradual. If treatment with CARBAMAZEPINE 200 AUSTELL has to be withdrawn abruptly in a patient with epilepsy, the changeover to another anti-epileptic medicine should if necessary be effected under the cover of a suitable medicine.

Endocrinological effects

Breakthrough bleeding has been reported in women taking CARBAMAZEPINE 200 AUSTELL while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by CARBAMAZEPINE 200 AUSTELL and women of child-bearing potential should be advised to consider using alternative forms of birth control while taking CARBAMAZEPINE 200 AUSTELL. Patients taking CARBAMAZEPINE 200 AUSTELL 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.

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; in suspected absorption disorders; in suspected toxicity when more than one medicine is being used (see 4.5).

Precautions

CARBAMAZEPINE 200 AUSTELL 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 medicines, or interrupted courses of therapy with CARBAMAZEPINE 200 AUSTELL.

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 doing therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If hyponatraemia 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 200 AUSTELL 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 a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

Interactions

Co-administrations 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 200 AUSTELL 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 200 AUSTELL may have to be adjusted.

Carbamazepine is 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 metabolised by CYP3A4 by induction of their metabolism. (See section 4.5)

Falls

CARBAMAZEPINE 200 AUSTELL treatment has been associated with ataxia, dizziness, somnolence, hypotension, confusional state, sedation (see section 4.8) which may lead to falls and, consequently fractures or other injuries. For patients with diseases, conditions, or medication that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term CARBAMAZEPINE 200 AUSTELL treatment.

4.5 Interaction with other medicines 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 co-medications mainly metabolised 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 200 AUSTELL is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering CARBAMAZEPINE 200 AUSTELL MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see section 4.3).

Medicines 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 200 AUSTELL should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Analgesics, anti-inflammatory medicines: ibuprofen, dextropropoxyphene.

Androgens: danazol.

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

Antidepressants: fluoxetine, fluvoxamine, paroxetine, trazodone.

Antiepileptics: stiripentol, 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 medicines: diltiazem, verapamil.

Gastrointestinal medicines: possibly cimetidine, omeprazole.

Muscle relaxants: oxybutynin, dantrolene

Platelet aggregation inhibitors: ticlopidine

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

Medicines 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 200 AUSTELL 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.

Medicines that may decrease carbamazepine plasma levels:

The dose of CARBAMAZEPINE 200 AUSTELL may have to be adjusted when used concomitantly with the substances described below:

Antiepileptics: oxcarbazepine, phenobarbitone, 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: cisplastin or doxorubicin

Antituberculosis: rifampicin.

Bronchodilatators or anti-asthma medicines: theophylline, aminophylline.

Dermatological medicines: isotretinoin.

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

Effect of CARBAMAZEPINE 200 AUSTELL on plasma levels of concomitant medicines:

Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain medicines. The dosage of the following medicines may have to be adjusted to clinical requirements:

Analgesics, anti-inflammatory medicines: 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.80

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 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: praziquantel, 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 medicines: theophylline.

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

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

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

Medicines used in erectile dysfunction: tadalafil.

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus.

Thyroid medicines: levothyroxine.

Other medicines interactions: medicines containing oestrogens and/or progesterones.

Combination that require specific considerations:

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 200 AUSTELL 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, 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 High-performance liquid chromatography (HPLC) analysis due to interference.

Carbamazepine and the 10,11-epoxide metabolite may result in false positive tricyclic antidepressant concentration in fluorescence polarised immunoassay method.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Due to enzyme induction, CARBAMAZEPINE 200 AUSTELL may result in a failure of the therapeutic effect of oral contraceptive medicines containing oestrogen and/or progesterone. Women of child-bearing potential should be advised to use alternative contraceptive methods while on treatment with CARBAMAZEPINE 200 AUSTELL.

Pregnancy

Offspring of epileptic mothers 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 200 AUSTELL. Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

- Pregnant women with epilepsy should be treated with special care.
- If women receiving CARBAMAZEPINE 200 AUSTELL became pregnant or plan to become pregnant, or if the need of initiating treatment with CARBAMAZEPINE 200 AUSTELL arises during

pregnancy, the 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 200 AUSTELL should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with combination of antiepileptic medicines is greater than in those of mothers receiving the individual medicines as monotherapy. The risk of malformations following exposure to carbamazepine as polytherapy may vary depending on the specific medicines 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.
- 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 medicines 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 K_1, be given to the mother during the last weeks of pregnancy as well as to the neonate.

There have been cases of neonatal seizures and/or respiratory depression associated with maternal CARBAMAZEPINE 200 AUSTELL and other concomitant antiepileptic medicine use. Cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with

maternal CARBAMAZEPINE 200 AUSTELL use. These reactions may represent a neonatal withdrawal syndrome.

Animal studies have shown reproductive toxicity.

Breastfeeding

Carbamazepine passes into the breast milk (about 25 – 60 % of the plasma concentrations). Mothers on CARBAMAZEPINE 200 AUSTELL should not breastfeed their infants.

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 200 AUSTELL, 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

a) Summary of the safety profile

Particularly at the start of the treatment with CARBAMAZEPINE 200 AUSTELL, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur frequently, 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.

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with carbamazepine.

Frequency estimate:

Frequent

Less frequent

Not known (cannot be estimated from the available data).

System Organ Class	Frequency		
	Frequent	**Less Frequent**	**Not known**
Infections and infestations			Reactivation of Human herpes virus 6 infection.
Blood and lymphatic system disorders	Leucopenia, thrombocytopenia, eosinophilia	Leucocytosis, lymphadenopathy, agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia	Bone marrow depression.
Immune system disorders		A delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

		also be affected (e.g. liver, lungs, kidneys, pancreas, myocardium, colon). anaphylactic reaction, oedema angioedema, hypogammaglobulinaemia.	
Endocrine disorders	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.	Galactorrhoea, gynaecomastia.	
Metabolism and nutrition disorders		Folate deficiency, decreased appetite, porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).	

Psychiatric disorders		Hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state, activation of psychosis.	
Nervous system disorders	Ataxia, dizziness, somnolence, diplopia, headache.	Abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus, dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis, neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.	Sedation, memory impairment.
Eye disorders	Accommodation disorders (e.g. blurred vision).	Lenticular opacities, conjunctivitis.	
Ear and labyrinth disorders		Hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.	

Cardiac disorders		Cardiac conduction disorders, arrhythmia, atrioventricular block with syncope, bradycardia, cardiac failure congestive, coronary artery disease aggravated.	
Vascular disorders		Hypertension or hypotension, circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis.	
Respiratory, thoracic and mediastinal disorders		Pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.	
Gastrointestinal disorders	Vomiting, nausea, dry mouth, with suppositories rectal irritation may occur.	Diarrhoea, constipation, abdominal pain, pancreatitis, glossitis, stomatitis.	Colitis.
Hepatobiliary disorders		Hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice, hepatic failure, granulomatous liver disease.	

Skin and subcutaneous tissue disorders	Urticaria, which may be severe dermatitis allergic.	Dermatitis exfoliative, systemic lupus erythematous, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.	Acute Generalized Exanthematous Pustulosis (AGEP), lichenoid keratosis, onychomadesis.
Musculoskeletal and connective tissue disorders		Muscular weakness, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.	Fracture.
Renal and urinary disorders		Tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/ azotaemia), urinary retention, urinary frequency.	

Reproductive system		Sexual disturbances/erectile dysfunction spermatogenesis abnormal (with decreased sperm count and/or motility).	
General disorders and administration site conditions	Fatigue.		
Investigations	Gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant, blood alkaline phosphatase increased.	Transaminases increased, 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.	Bone density decreased.

Injury, poisoning and procedural complications			Fall (associated with CARBAMAZEPINE 200 AUSTELL 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).

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

The presenting signs and symptoms of overdosage involves 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, 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/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 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 anti-epileptic, e.g. pbenobarbitone (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, hemodialysis 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

Pharmacological Classification: A 2.5 Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent; Dibenzazepine derivative

ATC Code: N03 AF01

Carbamazepine possesses both anticonvulsant and psychotropic properties.

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is absorbed relatively slowly from the tablet. Peak plasma concentrations are attained 4 to 24 hours after a single oral dose.

Distribution

Carbamazepine is 70 - 80 % bound to plasma proteins. The concentration of carbamazepine in the saliva reflects the unbound fraction in the plasma (20 to 30 %).

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the carbamazepine-10,11-transdiol derivative and its glucuronide as the main metabolites. Cytochrome P450 is responsible for the formation of carbamazepine-10,11-epoxide from carbamazepine, while the microsomal epoxide hydrolase enzyme is responsible for the formation of the carbamazepine 10,11-transdiol derivative from carbamazepine-10,11-epoxide.

Elimination

The elimination half-life of carbamazepine is approximately 36 hours after a single oral dose, whereas after repeated administration, which leads to auto induction of hepatic enzymes, it averages only 16 to 24 hours, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme inducing anti-epileptic medicines, half-life values averaging 9 to 10 hours have been found.

Only 2 to 3 % of the dose is excreted in the urine in unchanged form. The primary metabolite is the pharmacologically active carbamazepine-10,11-epoxide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Partially Pregelatinized Maize Starch

FD & C Red 40

Crosscarmellose Sodium

Colloidal Silicon dioxide

Magnesium Stearate

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

CARBAMAZEPINE 200 AUSTELL is packed in PVDC coated rigid PVC/PE laminate and Aluminum lid foil blisters strips. The blister strips are packed into cardboard cartons in packs of 28, 56, 84 or 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Laboratories (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT