Professional Information for BIO-CARBAMAZEPINE 200

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BIO-CARBAMAZEPINE 200 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.

White, flat, round bevelled edge tablet. One side scored. Other side engraved TARO 11.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy: Psychomotor or temporal-lobe epilepsy; grand mal; mixed forms; focal seizures.

Trigeminal neuralgia.

Idiopathic glossopharyngeal neuralgia.

4.2 Posology and method of administration

Posology

Dosage should be adjusted to the needs of the individual patient. A low initial daily dose with a gradual increase is advised. As soon as adequate control is achieved the dosage may be gradually reduced to the minimum effective level. The tablets should be taken with meals. Monitoring of plasma levels may be useful.

Epilepsy

Adults and children over 12 years: Initially 200 mg twice daily. Increase at weekly intervals by adding up to 200 mg per day until the optimum response is obtained, usually 400 mg twice or three times daily. Doses up to 1 600 mg daily have been used in adults (in divided doses).

Children: 10 to 20 mg /kg per day. Dosage should not exceed 1 000 mg daily.

Age up to 1 year:	100 – 200 mg per day
1 to 5 years:	200 – 400 mg per day
5 to 10 years:	400 – 600 mg per day
10 to 15 years:	600 – 1000 mg per day

Trigeminal neuralgia

The initial dose of 100 mg once or twice daily should be increased gradually until a satisfactory clinical response is obtained. Control of pain is achieved in most patients with 400 to 800 mg daily in 2 to 4 divided doses but in some cases up to 1 600 mg may be required.

Method of administration

Oral use.

4.3 Contraindications

- Hypersensitivity to carbamazepine, structurally related medicines, e.g. tricyclic antidepressants or any of the excipients listed in section 6.1.
- History of bone marrow depression.
- Atrioventricular block.
- BIO-CARBAMAZEPINE 200 should not be administered in conjunction with monoamine oxidase (MAO) inhibitors or less than 14 days after they have been discontinued.
- BIO-CARBAMAZEPINE 200 should not be used in patients with porphyria.

- Breastfeeding (see section 4.6).
- History of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) (see section 4.4).

4.4 Special warnings and precautions for use

Patients should be aware of early toxic signs and symptoms 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 consult a doctor immediately.

Carbamazepine should be prescribed only after a critical benefit-risk appraisal and patients with a history of cardiac, hepatic or renal damage or adverse haematological reactions to other medicines must be closely monitored. Medical supervision during treatment is essential.

Haematological effects

Aplastic anaemia and agranulocytosis have been reported and transient or persistent decreased platelet or white blood cell count may occur. Complete pre-treatment blood counts including platelets and possibly reticulocytes and serum iron should be obtained as baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts the patient should be monitored closely. Discontinuation of the medicine should be considered if any evidence of significant bone marrow depression develops.

Serious dermatological reactions

Severe dermatologic reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported. Patients with serious dermatological reactions may require hospitalisation, as these conditions may be life-threatening and may be fatal. Most of these cases appear in the first few months of treatment with BIO-CARBAMAZEPINE 200. If signs and symptoms suggestive of severe skin reactions (e.g. SJS or TEN) appear, BIO-CARBAMAZEPINE

200 should be withdrawn at once and alternative therapy should be considered (see section 4.3).

Immune-mediated adverse drug reactions

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

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

Human Leukocyte Antigen (HLA)-A*3101 may be a risk factor for the development of cutaneous adverse drug reactions such as SJS, TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP) and maculopapular rash.

Retrospective genome-wide studies in Japanese and Northern European populations reported association between severe skin reactions (SJS, TEN, DRESS, AGEP and maculopapular rash) associated with carbamazepine use and the presence of the HLA-A*3101 allele in these patients. The frequency of the HLA-A*3101 allele varies widely between ethnic populations, with a frequency between 5-15 %. A prevalence of 10 -15 % has been estimated in some ethnic groups.

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 BIO-CARBAMAZEPINE 200.

The use of BIO-CARBAMAZEPINE 200 should be avoided in patients who are found to be positive for HLA-A*3101. Screening is generally not recommended for any current BIO-CARBAMAZEPINE 200 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.

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

Retrospective studies in patients of Han Chinese ancestry found a strong correlation between SJS/TEN skin reactions associated with BIO-CARBAMAZEPINE 200 and the presence in these patients of the Human Leukocyte Antigen HLA-B*1502 allele. The prevalence of the HLA-B*1502 allele is negligible in Caucasian, African, indigenous people of the Americas, and Hispanic populations sampled.

Testing for the presence of HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with BIO-CARBAMAZEPINE 200.

The use of BIO-CARBAMAZEPINE 200 should be avoided in tested patients who are found to be positive for HLA-B*1502. HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic medicines associated with SJS/TEN. Consideration should therefore be given to avoiding use of other medicines associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally acceptable. Screening is not generally recommended in patients from populations in which the prevalence of HLA-B*1502 is low.

Screening is generally not recommended for any current BIO-CARBAMAZEPINE 200 users, as the risk of SJS/TEN is largely confined to the first few months of therapy, regardless of HLA-B*1502 status.

The identification of subjects carrying the HLA-B*1502 allele and the avoidance of BIO-CARBAMAZEPINE 200 therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with BIO-CARBAMAZEPINE 200 will not develop SJS/TEN and patients negative for HLA-B*1502 of any

ethnicity can still develop SJS/TEN. Similarly many patients positive for HLA-A*3101 and treated with BIO-CARBAMAZEPINE 200 may not develop severe cutaneous side-effects and patients negative for this allele can still develop them.

The role of other possible factors in the development of, and morbidity from, these severe cutaneous side-effects, such as other anti-epileptic medicines dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Information for the health care professionals

When testing for the presence of the HLA-B*1502 allele, high resolution "HLA-B*1502 genotyping" is recommended. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.

Similarly if testing for presence of the HLA-A*3101 allele should be performed, high-resolution "HLA-A*3101 genotyping" respectively is recommended. The test is positive if either one or two HLA-A*3101 alleles are detected and negative if no HLA-A*3101 alleles are detected.

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 less severe skin reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing BIO-CARBAMAZEPINE 200.

The HLA-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from BIO-CARBAMAZEPINE 200, 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

BIO-CARBAMAZEPINE 200 may trigger hypersensitivity reactions, including multi-organ

hypersensitivity reactions, which can affect the skin, liver (including intrahepatic bile ducts), haematopoietic organs and lymphatic system or other organs, either individually or together in the context of non-systemic reaction.

The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopapular rash. If signs and symptoms of hypersensitivity reactions occur, BIO-CARBAMAZEPINE 200 should be withdrawn immediately

Patients who have exhibited hypersensitivity reactions to BIO-CARBAMAZEPINE 200 may experience hypersensitivity reactions with oxcarbazepine.

Cross-hypersensitivity can occur between BIO-CARBAMAZEPINE 200 and aromatic antiepileptic medicines (e.g. phenytoin, primidone and phenobarbital).

Seizures

BIO-CARBAMAZEPINE 200 should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, BIO-CARBAMAZEPINE 200 may exacerbate seizures. In the event of exacerbation of seizures, BIO-CARBAMAZEPINE 200 should be discontinued.

Hepatic function

Baseline and periodic evaluations of liver function particularly in patients with a history of liver disease must be performed during treatment since liver damage may occur. BIO-CARBAMAZEPINE 200 should be discontinued immediately in cases of aggravated liver dysfunction, active liver disease, if allergic skin reactions occur, if platelet count diminishes or if any serious adverse symptoms develop.

Renal function

Baseline and periodic complete urinalysis and blood urea determinations are recommended.

Endocrinological effects

Breakthrough bleeding has been reported in patients receiving concomitant oral contraceptives and their reliability may be adversely affected. Women of childbearing age should be advised to consider using alternative forms of birth control while taking BIO-CARBAMAZEPINE 200.

Dose reduction and withdrawal effects

Abrupt withdrawal of BIO-CARBAMAZEPINE 200 may precipitate seizures. If treatment with BIO-CARBAMAZEPINE 200 is withdrawn abruptly, the change-over to other anti-epileptic medication should be started under cover of diazepam or a barbiturate.

Hyponatraemia

Hyponatraemia 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 medicines (e.g. diuretics, medicines associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating BIO-CARBAMAZEPINE 200 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 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

Patients with increased intra-ocular pressure should be closely observed as carbamazepine has

shown mild anticholinergic activity.

Psychiatric effects

Latent psychosis may be activated and in elderly patients the possibility of confusion or agitation exists.

Falls

BIO-CARBAMAZEPINE 200 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 medications that could exacerbate these effects, complete risk assessment of fall should be considered recurrently for patients on long-term BIO-CARBAMAZEPINE 200 treatment.

Other

Abnormalities of liver function and jaundice have been associated with long-term treatment.

Mild skin reactions, e.g. macular or maculopapular exanthema, are mostly transient, and they usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage; however, the patient should be kept under surveillance.

Tolerance may develop to some of the untoward effects of BIO-CARBAMAZEPINE 200. These effects can be minimised by gradual increase in dosage and adjustment to the lowest effective maintenance dosage.

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic medicines such as BIO-CARBAMAZEPINE 200 in several indications. Ameta-analysis of randomised placebo-controlled trials of antiepileptic medicines has shown an increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Therefore patients should be monitored

for signs of suicidal ideation and behaviour 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.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P4503A (CYP3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine-10,11-epoxide.

Co-administration of inhibitors of CYP3A4 may result in increased plasma concentrations, which could induce adverse reactions.

Co-administration of CYP 3A4 inducers might increase the rate of BIO-CARBAMAZEPINE 200 metabolism, thus leading to a potential decrease in carbamazepine serum level and potential decrease in the therapeutic effect.

BIO-CARBAMAZEPINE 200 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. Such inhibitors are valproic acid, valpromide, valnoctamide and progabide

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 BIO-CARBAMAZEPINE 200 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, troleandomycin, josamycin, clarithromycin) and ciprofloxacin.

Antidepressants: desipramine, fluoxetine, fluvoxamine, nefazodone, paroxetine.

Antiepileptics: stiripentol, vigabatrin.

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole).

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

Loxapine, quetiapine, primidone, progabide, valproic acid, valnoctamide, valpromide, brivaracetam.

Medicines that may decrease carbamazepine and/or carbamazepine-10,11-epoxide plasma levels

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

Antiepileptics: felbamate, methsuximide, oxcarbazepine, phenobarbital, phensuximide, phenytoin,

primidone and, although the data are partly contradictory, possibly also clonazepam.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilators or anti-asthma medicines: theophylline, aminophylline.

Dermatological medicines: isotretinoin.

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

Effect of BIO-CARBAMAZEPINE 200 on plasma levels of concomitant medicines

BIO-CARBAMAZEPINE 200 may lower the plasma level, decrease or even eliminate 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, tramadol.

Antibiotics: doxycycline, rifabutin.

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

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

The use of BIO-CARBAMAZEPINE 200 is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs). Before administering BIO-CARBAMAZEPINE 200, MAOIs should be discontinued for a minimum of 2 weeks or longer if the clinical situation permits (see section 4.3).

Antiemetics: aprepitant.

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, primidone, tiagabine, topiramate, valproic acid, zonisamide. Plasma phenytoin levels have been reported both to be increased and decreased by BIO-CARBAMAZEPINE 200 when used concomitantly, and there have been reports of an increase in plasma mephenytoin levels.

Antifungals: itraconazole, voriconazole.

Antihelmintics: praziquantel, albendazole.

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

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

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

Anxiolytics: alprazolam.

Bronchodilators 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 interactions: products containing estrogens and/or progesterones.

The level of serum folic acid should be observed during anticonvulsant therapy since BIO-CARBAMAZEPINE 200 may enhance the metabolism of folic acid.

Combinations that require specific consideration

Concomitant use of BIO-CARBAMAZEPINE 200 and levetiracetam has been reported to increase BIO-CARBAMAZEPINE 200-induced toxicity.

Concomitant use of BIO-CARBAMAZEPINE 200 and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

The combination of lithium and BIO-CARBAMAZEPINE 200 may cause enhanced neurotoxicity regardless of lithium plasma concentrations being within the therapeutic range. Combined use of BIO-CARBAMAZEPINE 200 with metoclopramide or tranquillisers, e.g. haloperidol, thioridazine,

may also result in an increase in neurological side-effects.

Concomitant medication with BIO-CARBAMAZEPINE 200 and some diuretics (hydrochlorothiazide, furosemide) may lead to symptomatic hyponatraemia.

BIO-CARBAMAZEPINE 200 may antagonise the effects of non-depolarising muscle relaxants (e.g. pancuronium). Their dosage may need to be raised, and patients should be monitored closely for more rapid recovery from neuromuscular blockade than expected.

BIO-CARBAMAZEPINE 200 may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol during treatment.

Concomitant use of BIO-CARBAMAZEPINE 200 with direct acting oral anti-coagulants (rivaroxaban, dabigatran, apixaban and edoxaban) may lead to reduced plasma concentrations of direct acting oral anti-coagulants, which carries the risk of thrombosis. Therefore, if a concomitant use is necessary, closer monitoring of signs and symptoms of thrombosis is recommended.

Interference with serological testing

Carbamazepine may result in false positive perphenazine concentrations in HPLC analysis due to interference.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of BIO-CARBAMAZEPINE 200 in pregnancy has not been demonstrated.

Patients should consult their doctor for guidance on the use of BIO-CARBAMAZEPINE 200 during

pregnancy.

Patients should be counselled regarding the possibility of an increased risk of malformations and given the opportunity of antenatal screening.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. The possibility that BIO-CARBAMAZEPINE 200 increases this risk has been reported. There are reports of developmental disorders and malformations, including spina bifida and hypospadias in association with BIO-CARBAMAZEPINE 200.

- If women receiving BIO-CARBAMAZEPINE 200 become pregnant or plan to become pregnant, or if the problem of initiating treatment with BIO-CARBAMAZEPINE 200 arises during pregnancy, the medicine's potential benefits must be carefully weighed against its possible hazards, particularly in the first 3 months of pregnancy.
- In women of childbearing age BIO-CARBAMAZEPINE 200 should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic medicines is greater than in those of mothers receiving the individual medicines as monotherapy.
- Minimum effective doses should be given and monitoring of plasma levels is recommended.
- During pregnancy, an effective antiepileptic treatment must not be interrupted, since aggravation of the illness is detrimental to both the mother and the foetus.

Folic acid deficiency is known to occur in pregnancy. Anti-epileptic medicines have been reported to aggravate folic acid 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.

To prevent bleeding disorders in the offspring, it is also recommended that vitamin K1 be given to

the mother during the last weeks of pregnancy as well as to the neonate.

Cases of neonatal seizures and/or respiratory depression associated with maternal BIO-CARBAMAZEPINE 200 and other concomitant anticonvulsant medicine use have been reported. Cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal BIO-CARBAMAZEPINE 200 use. These reactions may represent a neonatal withdrawal syndrome.

Women with manic depressive (bipolar) disorders have an increased risk to relapse during pregnancy and/or the post-partum period.

Breastfeeding

The active substance of carbamazepine passes into the breast milk. Mothers on BIO-CARBAMAZEPINE 200 should not breastfeed their infants.

Fertility

There have been reports of impaired male fertility and/or abnormal spermatogenesis.

4.7 Effects on ability to drive and use machines

Since drowsiness, dizziness, ataxia, diplopia and blurred vision may occur, patients should be cautioned about the hazards of operating machinery, driving or performing tasks where loss of concentration may lead to accidents.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequently observed side-effects, particularly at the start of therapy, are dizziness, headache, drowsiness, unsteadiness, fatigue, diplopia, gastrointestinal disturbances (nausea and vomiting), as well as allergic skin reactions.

Dose-related adverse reactions may 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.

b) Tabulated summary of adverse reactions

Blood and lymphatic system disorders

Frequent: leucopenia, thrombocytopenia, eosinophilia

Less frequent: leucocytosis, lymphadenopathy, folic acid deficiency, agranulocytosis, anaemia, aplastic anaemia, pancytopenia, megaloblastic anaemia, acute porphyria (acute intermittent porphyria and variegate porphyria), non-acute porphyria (porphyria cutanea tarda), reticulocytosis, haemolytic anaemia, pure red cell aplasia

Immune system disorders

Less frequent: a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo-lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly and abnormal liver function tests and vanishing bile duct syndrome (destruction of disappearance of the intrahepatic bile ducts), occurring in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon), aseptic meningitis, with myoclonus and peripheral eosinophilia, anaphylactic reaction, angioedema, hypogammaglobulinaemia

Endocrine disorders

Frequent: oedema, fluid retention, increased weight, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect

leading, water intoxication accompanied by lethargy, vomiting, headache, mental confusion and neurological disorders

Less frequent: galactorrhoea, gynecomastia

Metabolism and nutrition disorders

Less frequent: folate deficiency, decreased appetite

Psychiatric disorders

Less frequent: hallucinations (visual or auditory), depression, anorexia, restlessness, aggression, agitation, confusional state, activation of psychosis (particularly in elderly patients or if initial dosage is too high)

Nervous system disorders

Frequent: dizziness, ataxia, drowsiness, headache, diplopia,

Less frequent: abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus, orofacial dyskinesia, oculomotor disturbances, speech disorders (e.g. dysarthria, slurred speech, talkativeness), choreoathetosis, peripheral neuropathy, paraesthesia, paresis, taste disturbances, neuroleptic malignant syndrome

Eye disorders

Frequent: accommodation disorders (e.g. blurred vision)

Less frequent: lenticular opacities, conjunctivitis

Ear and labyrinth disorders

Less frequent: hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception

Cardiac disorders

Less frequent: cardiac conduction disorders, bradycardia, arrhythmia, atrioventricular block with syncope, congestive heart failure, aggravation of coronary artery disease

Vascular disorders

Less frequent: hypertension or hypotension, circulatory collapse, primary thrombophlebitis, recurrence of thrombophlebitis, thromboembolism (e.g. pulmonary embolism)

Respiratory, thoracic and mediastinal disorders

Less frequent: pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia

Gastrointestinal disorders

Frequent: nausea, vomiting, dryness of the mouth and pharynx

Less frequent: diarrhoea, constipation, gastric distress and abdominal pain, glossitis, stomatitis, pancreatitis

Hepato-biliary disorders

Less frequent: hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice, hepatic failure, granulomatous hepatitis

Skin and subcutaneous tissue disorder

Frequent: allergic dermatitis, urticaria which may be severe

Less frequent: exfoliative dermatitis and erythroderma, systemic lupus erythematosus, pruritus, Stevens-Johnson syndrome*, toxic epidermal necrolysis,

photosensitivity reaction, erythema multiforme and nodosum, alterations in skin pigmentation, purpura, acne, hyperhidrosis, alopecia, hirsutism

Musculoskeletal and connective tissue disorders

Less frequent: arthralgia, myalgia, muscle spasms, muscle weakness, joint pain, bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol), leading to osteomalacia/osteoporosis

Renal and urinary disorders

Less frequent: interstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and increased blood urea/uraemia), urinary frequency, urinary retention, azotaemia, microscopic deposits in the urine, glycosuria

Reproductive system and breast disorders

Less frequent: sexual dysfunction/impotence, abnormal spermatogenesis (with decreased sperm count and/or motility)

General disorders and administration site conditions

Frequent: fatigue

Investigations

Frequent: increased gamma-GT (due to hepatic enzyme induction), increased blood alkaline phosphatase

Less frequent: increased transaminases, increased intraocular pressure, increased blood cholesterol, including HDL cholesterol, and triglycerides, abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, increased blood prolactin

Post-marketing experience

The following side-effects have been derived from post-marketing experience with BIO-CARBAMAZEPINE 200 via spontaneous case reports and literature cases.

Blood and lymphatic system disorders

Bone marrow depression.

Immune system disorders

Drug rash with eosinophilia and systemic symptoms (DRESS).

Infections and infestations

Reactivation of Human herpes virus 6 infection.

Metabolism and nutritional disorders

Hyperammonaemia.

Nervous system disorders

Sedation, memory impairment.

Gastro-intestinal disorders

Colitis.

Skin and subcutaneous tissue disorders

Acute generalised exanthematous pustulosis (AGEP), lichenoid keratosis, onychomadesis.

Musculoskeletal, connective tissue and bone disorders

Fracture.

Investigations

Decreased bone density.

Injury, poisoning and procedural complications

Fall (associated with treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BIO-CARBAMAZEPINE 200 is

important. It allows continued monitoring of the benefit/risk balance of BIO-CARBAMAZEPINE 200. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Adverse Drug Reactions Reporting Form, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

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

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

Respiratory system: Respiratory depression, pulmonary oedema, irregular breathing.

Cardiovascular system: Tachycardia, hypotension, hypertension, conduction disturbances with widening of QRS complex, syncope in association with cardiac arrest.

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

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

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

Treatment

No specific antidote. Management should initially be guided by the patient's clinical condition, including admission to hospital. Measurement of the plasma level to confirm BIO-CARBAMAZEPINE 200 poisoning and to ascertain the size of the overdose.

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 intravenous dopamine or dobutamine.

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

Convulsions: administer a benzodiazepine (e.g. diazepam) or another anti-epileptic, e.g. phenobarbitone (with caution because of increased respiratory depression), or paraldehyde.

Hyponatraemia (water intoxication): fluid restriction and slow and careful NaCl 0,9 % intravenous infusion. These measures may be useful in preventing brain damage.

Charcoal haemoperfusion has been recommended. Forced diuresis, haemodialysis, and peritoneal dialysis have been reported to be not effective

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

5. PHARMACOLOGICAL PROPERTIES

Category and class: A.2.5 Anticonvulsants, including anti-epileptics

Pharmacotherapeutic group: Antiepileptics, carboxamide derivatives.

ATC code: N03A F01.

5.1 Pharmacodynamic properties

Carbamazepine has 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.

Characteristics in patients

The steady-state plasma concentrations of carbamazepine considered as in the therapeutic range, vary considerably interindividually: for the majority of patients a range between 4 – 12 µg/mL corresponding to 17 – 50 µmol/L has been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ammonium methacrylate copolymer (Eudragit RS 30D)

Croscarmellose sodium

Diethyl phthalate

Magnesium stearate

Maize starch

Microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep well closed and protect from moisture.

6.5 Nature and contents of container

BIO-CARBAMAZEPINE 200 is supplied in white, round plastic bottles in packs of 100.

6.6 Special precautions for disposal and other handling

No additional information.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

10 Melrose Street

Melrose

2196

8. REGISTRATION NUMBER

32/2.5/0144

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 July 1999

10. DATE OF REVISION OF THE TEXT

7 November 2022