Table of Contents

PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZARBIC 200 mg Film-coated tablets

ZARBIC 400 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZARBIC 200 mg Film-coated tablets:

Each film-coated tablet contains 200 mg carbamazepine.

ZARBIC 400 mg Film-coated tablets:

Each film-coated tablet contains 400 mg carbamazepine.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

ZARBIC 200 mg: White to off white film coated approximately 12.5 X 5.8 mm oval shaped biconvex tablets with “C and 2” separated by score line on both sides.

ZARBIC 400 mg: White to off white film coated approximately 17.5 X 7.0 mm oval shaped biconvex tablets,debossed with “C and 4” separated by score line on both sides.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Epilepsy with motor and psychic manifestations:

• psychomotor or temporal-lobe epilepsy

• generalized 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.

ZARBIC is suitable for both monotherapy and combination therapy.

ZARBIC 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 **ZARBIC** 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 **ZARBIC** 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 (**ZARBIC 200 mg** may be broken into two halves) 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

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.

Elderly

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

Method of administration

Oral use

ZARBIC 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 **ZARBIC** , 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 **ZARBIC** listed in section 6.1.

• 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 **ZARBIC** is contra-indicated in combination with monoamine-oxidase inhibitors (MAOIs) or within 2 weeks of discontinuation of MAOIs (see Section 4.5).

• Carbamazepine passes into the breast milk (about 25 - 60 % of plasma concentration). Mothers taking **ZARBIC** should not breastfeed their infants.

• Previous Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

4.4. Special warnings and precautions for use

Haemotologic effects

Agranulocytosis and aplastic anaemia have been associated with carbamazepine as contained in **ZARBIC** .

Transient or persistent decreased platelet or white blood cell counts may occur in association with the use of **ZARBIC**. 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 **ZARBIC** should also be discontinued if any evidence of significant bone marrow depression appears.

Hepatic function

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. **ZARBIC** should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease. If allergic skin reactions occur, if the platelet count diminishes, if tests reveal deterioration in liver function, or if any of the serious adverse symptoms develop, **ZARBIC**]should be withdrawn.

Suicide ideation and behaviour:

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:

Serious dermatological reactions, including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome) and Stevens Johnson syndrome (SJS) have been reported with carbamazepine as in **ZARBIC** . 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. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, **ZARBIC** should be withdrawn at once and alternative therapy should be considered (see section 4.3).

Immune-mediated ADRs

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

Association with HLA-A*3101

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 generalized 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 **ZARBIC** .

The use of **ZARBIC** should be avoided in patients who are found to be positive for HLA-A*3101.

Screening is generally not recommended for any current **ZARBIC** 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*

Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between SJS/TEN skin reactions associated with **ZARBIC** and the presence in these patients of the Human Leukocyte Antigen HLA-B*1502 allele. The frequency of HLA-B*1502 allele ranges from 2 to 12 % in Han Chinese populations and is about 8 % in Thai populations. Higher reporting rates of SJS (rare rather than very rare) are reported in some countries in Asia (e.g. Taiwan, Malaysia and the Philippines) in which there is a higher frequency of the HLA-B*1502 allele in the

population (e.g. above 15 % in the Philippines and some Malaysian populations).

Allele frequencies up to about 2 % and 6 % have been reported in Korea and India, respectively.

The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous people of the Americas, Hispanic populations sampled and in Japanese (< 1 %).

The allele frequencies listed here, represent the percentage of chromosomes in the specified population that carry the allele of interest, meaning that the percentage of patients who carry a

copy of the allele on at least one of their two chromosomes (i.e. the “carrier frequency”) is nearly twice as high as the allele frequency. Therefore, the percentage of patients who may be at risk is nearly twice the allele frequency.

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 ZARBIC

The use of **ZARBIC** should be avoided in tested patients who are found to be positive for HLAB*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 **ZARBIC** 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 [PRODOCUT NAME] 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 **ZARBIC** 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 **ZARBIC** 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 Healthcare 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 mild transient reactions, the patient should be kept under close surveillance with consideration given to immediately withdrawing **ZARBIC** should the reaction worsen with continued use. The HLA-A*3101 allele has 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

Class I (immediate) hypersensitivity reactions including rash, pruritus, urticaria, angioedema and reports of anaphylaxis have been reported with **ZARBIC** . If a patient develops these reactions after treatment with **ZARBIC** , the medicine must be discontinued, and an alternative treatment started.

ZARBIC may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudolymphoma, 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, **ZARBIC** 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).

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

Dose reduction and withdrawal effects

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

Abrupt withdrawal of **ZARBIC** may precipitate seizures, therefore carbamazepine withdrawal should be gradual over 6 month period . If treatment with **ZARBIC** 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 as in **ZARBIC** while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by **ZARBIC** and women of child-bearing potential should be advised to consider using

alternative forms of birth control while taking **ZARBIC** .

Patients taking **ZARBIC** and requiring hormonal contraception should receive a preparation containing not less than 50µg oestrogen or use of some alternative nonhormonal 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 section 4.5).

Renal function

ZARBIC 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 **ZARBIC** . 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 medicines (e.g. diuretics, medicines 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

ZARBIC 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 **ZARBIC** 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 **ZARBIC** 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

ZARBIC 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 **ZARBIC** 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. Such inhibitors are valproic acid, valpromide, valnoctamide and progabide.

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 **ZARBIC** is contraindicated in combination with monoamineoxidase inhibitors (MAOIs); before administering **ZARBIC** 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 **ZARBIC** should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the medicines described below:

Analgesics, anti-inflammatory medicines: ibuprofen, dextropropoxyphene.

Androgens: danazol.

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

Antidepressants: fluoxetine, fluvoxamine, paroxetine, trazodone, desipramine, nefazodone and viloxazine.

Antiepileptics: stiripentol, vigabatrin.

Antifungals: azoles (e.g. itraconazole, ketoconazole, fluconazole, voriconazole). Alternative anticonvulsants 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 **ZARBIC** should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the medicines described below: Quetiapine, primidone, progabide, valproic acid, valnoctamide, loxapine, brivaracetam and valpromide.

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

The dose of **ZARBIC** may have to be adjusted when used concomitantly with the medicines 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, , felbamate, methsuximide, 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 ZARBIC 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.

Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, eslicarbazepine, oxcarbazepine, felbamate, 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 maybe recommended in patients treated with voriconazole or itraconazole.

Antihelmintics: praziquantel, albendazole.

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

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

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

Anxiolytics: alprazolam, midazolam.

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.

The level of serum folic acid should be observed during anticonvulsant therapy since **ZARBIC** may enhance the metabolism of folic acid.

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.

Combined use of **ZARBIC** and lithium, or metoclopramide on the one hand, and **ZARBIC** and neuroleptics (haloperidol, thioridazine) on the other, may lead to increased neurological adverse reactions (with the latter combination even in the presence of ‘therapeutic plasma levels’).

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

ZARBIC 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.

ZARBIC may reduce the patient's alcohol tolerance; it is therefore advisable to abstain from alcohol during treatment. 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 anticoagulants, 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

Women of childbearing potential receiving **ZARBIC** should be advised to use an appropriate method of contraception and for 2 weeks after the last dose. Due to enzyme induction, **ZARBIC** may result in a failure of the therapeutic

effect of oral contraceptive medicines containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use alternative contraceptive methods while on treatment with **ZARBIC**.

Pregnancy

Safety of **ZARBIC** in pregnancy has not been demonstrated.

Offspring of epileptic mothers are known to be more prone to developmental disorders, including malformations. Developmental disorders and malformations, including spina bifida, and hypospadias have been reported in association with the use of **ZARBIC**.
Neurodevelopmental disorders have been reported among children born to women with epilepsy treated with carbamazepine alone or in combination with other antiepileptic medicines during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to carbamazepine during pregnancy are contradictory and a risk cannot be excluded.
- 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 **ZARBIC** became pregnant or plan to become pregnant, or if the need of initiating treatment with **ZARBIC** 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 **ZARBIC** 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 foetus.

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 K1, 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 as contained in **ZARBIC** and other concomitant antiepileptic medicine use. 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.

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

Breastfeeding

Carbamazepine passes into the breast milk (about 25 – 60 % of the plasma concentrations). Mothers on **ZARBIC** 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 **ZARBIC** , 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 **ZARBIC** , 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.

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:

System Organ Class	**Frequent**	**Less Frequent**	**Not known**
Infections and			Reactivation of Human herpes

infestations			virus 6 infection.
Blood and lymphatic system disorders	Leukopenia, thrombocytopenia, eosinophilia	Leukocytosis, 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, leukopenia, 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 also be	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

		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, dysrhythmia, 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	Diarrhoea, constipation, abdominal pain,	Colitis.

		pancreatitis, glossitis, stomatitis.	
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)	Fracture.

		leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.	
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	Transaminases increased, intraocular pressure increased, blood cholesterol increased, high	Bone density decreased.

	induction), usually not clinically relevant, blood alkaline phosphatase increased.	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.	
Injury, poisoning and procedural complications			Fall (associated with **ZARBIC** treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4).

* In some Asian countries also reported as rare. See also section 4.4.
**Additional adverse drug reactions from spontaneous reports (frequency not known).

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 providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9. Overdose

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

Central nervous system: CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, hallucination, coma; blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyper-reflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, hypothermia, mydriasis.

Respiratory system: Respiratory depression, pulmonary oedema.

Cardiovascular system: Tachycardia, hypotension and at times hypertension, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.

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

Musculoskeletal system: There have been some cases which reported rhabdomyolysis in association with carbamazepine toxicity.

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

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

Management/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.

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. Haemodialysis is the effective treatment modality in the management of **ZARBIC** overdose.

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

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.

Mechanism of action

The mechanism of action of carbamazepine has only been partially elucidated.

Carbamazepine stabilizes hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarized neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

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

5.2. Pharmacokinetic properties

Absorption

Carbamazepine is absorbed relatively slowly from the tablet. Peak plasma concentrations are attained 4 to 24 hours after a single oral dose. The CR 200 tablets yield a mean peak plasma concentration of the carbamazepine within 24 hours.

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

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.

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

Intragranular Ingredients

Cellulose Microcrystalline

Magnesium stearate

Silica Colloidal Anhydrous

Granulating Fluids

Ethyl Cellulose

Extra granular materials

Cellulose Microcrystalline

Croscarmellose Sodium

Silica Colloidal Anhydrous

Talc

Magnesium Stearate

6.1. Incompatibilities

Not applicable.

6.2. Shelf life

24 months.

6.3. Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

6.4. Nature and contents of container

ZARBIC capsules are available in the following containers:

Blister strips (PVC/foil) containing, 30 capsules.

Not all pack sizes may be marketed These blisters shall be packed in a pre-printed carton with a packaging leaflet.

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (PTY) LTD

WOODHILL OFFICE PARK, BUILDING 1, FIRST FLOOR

53 PHILLIP ENGELBRECHT AVENUE

MEYERSDAL, EXT. 12, 1448

JOHANNESBURG

SOUTH AFRICA

8. REGISTRATION NUMBER

ZARBIC 200 mg: 59/2.5/0418

ZARBIC 400 mg : 59/2.5/0419

9. DATE OF FIRST AUTHORISATION

14 JULY 2026