SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carbamazepine Essential Pharma 200 mg Chewtabs

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each chewtab contains 200 mg carbamazepine.

Excipient(s) with known effect
Each chewtab contains 607 mg sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Chewable tablet.

Pale orange, square shaped chewable tablets, with a pronounced orange odour, embossed with “T” on one side and impressed with Tegretol 200 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epilepsy - generalised tonic-clonic and partial seizures.

Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences.

The paroxysmal pain of trigeminal neuralgia.

For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

4.2 Posology and method of administration

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

The chewtabs should be chewed before swallowing, preferably with a little liquid to wash down possible remnants of the tablets.

The chewtabs are particularly suitable for children and adults who have difficulty in swallowing tablets.

Before deciding to initiate treatment, patients of Han Chinese and Thai origin should whenever possible be screened for HLA-B*1502 as this allele strongly predicts the risk of severe carbamazepine-associated Stevens-Johnson syndrome (see section 4.4).

Epilepsy
The dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures. Determination of plasma levels may help in establishing the optimum dosage. In the treatment of epilepsy, the dose of carbamazepine usually requires total plasma-carbamazepine concentrations of about 4 to 12 micrograms/mL (17 to 50 micromoles/litre) (see section 4.4).

Adults
It is advised that with all formulations of carbamazepine , a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.
Carbamazepine Essential Pharma Chewtabs should be taken in a number of divided doses although initially 100-200 mg once or twice daily is recommended. This may be followed by a slow increase until the best response is obtained, often 800-1200 mg daily. In some instances, 1600 mg or even 2000 mg daily may be necessary.

Paediatric population and adolescents
It is advised that with all formulations of carbamazepine , a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient.
Usual dosage 10-20 mg/kg bodyweight daily taken in several divided doses.

Carbamazepine Essential Pharma Chewtabs are not recommended for very young children.

1-5 years:	200 to 400 mg daily (2-4 x 100 mg chewtabs per day, where appropriate)
5-10 years:	400 to 600 mg daily (2-3 x 200 mg chewtabs per day, to be taken in divided doses).
10-15 years:	600 to 1000 mg daily (3-5 x 200 mg chewtabs per day, to be taken in several divided doses).
>15 years of age:	800 to 1200 mg daily (same as adult dose).

<u>Maximum recommended dose</u>
Up to 6 years of age: 35 mg/kg/day
6-15 years of age: 1000 mg/day
>15 years of age: 1200 mg/day.

Wherever possible, anti-epileptic agents should be prescribed as the sole anti-epileptic agent but if used in polytherapy the same incremental dosage pattern is advised.

When carbamazepine is added to existing antiepileptic therapy, this should be done gradually while maintaining or, if necessary, adapting the dosage of the other antiepileptic(s) (see section 4.5).

Trigeminal neuralgia

Slowly raise the initial dosage of 200-400 mg daily until freedom from pain is achieved (normally at 200 mg 3-4 times daily). In the majority of patients a dosage of 200 mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600 mg carbamazepine daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

Elderly population
Due to drug interactions and different antiepileptic drug pharmacokinetics, the dosage of carbamazepine should be selected with caution in elderly patients

In elderly patients, an initial dose of 100 mg twice daily is recommended. The initial dosage of 100 mg twice daily should be slowly raised daily until freedom from pain is achieved (normally at 200 mg 3 to 4 times daily). The dosage should then be gradually reduced to the lowest possible maintenance level. Maximum recommended dose is 1200 mg/day. When pain relief has been obtained, attempts should be made to gradually discontinue therapy, until another attack occurs.

For the prophylaxis of manic depressive psychosis in patients unresponsive to lithium therapy
Initial starting dose of 400 mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600 mg given in divided doses is reached. The usual dosage range is 400-600 mg daily, given in divided doses.

Renal impairment / Hepatic impairment
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

Method of administration
Oral use.

4.3 Contraindications

Hypersensitivity to carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any of the excipients listed in section 6.1.

Patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).

The use of carbamazepine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs) (see section 4.5).

4.4 Special warnings and precautions for use

Warnings
Agranulocytosis and aplastic anaemia have been associated with carbamazepine; however, due to the very low incidence of these conditions, meaningful risk estimates for carbamazepine are difficult to obtain. The overall risk in the general untreated population has

been estimated at 4.7 persons per million per year for agranulocytosis and 2.0 persons per million per year for aplastic anaemia.

Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of carbamazepine. Nonetheless, complete pre-treatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline, and periodically thereafter.

Patients and their relatives should be made aware of early toxic signs and symptoms indicative of a potential haematological problem, as well as symptoms of dermatological or hepatic reactions. If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage appear, the patient should be advised to consult the physician immediately.

If the white blood cell or platelet count is definitely low or decreased during treatment, the patient and the complete blood count should be closely monitored (see section 4.8). However, treatment with carbamazepine should be discontinued if the patient develops leucopenia which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Carbamazepine should also be discontinued if any evidence of significant bone marrow depression appears.

Liver function tests should also be performed before commencing treatment and periodically thereafter, particularly in patients with a history of liver disease and in elderly patients. The drug should be withdrawn immediately in cases of aggravated liver dysfunction or acute liver disease.

Some liver function tests in patients receiving carbamazepine may be found to be abnormal, particularly gamma glutamyl transferase. This is probably due to hepatic enzyme induction. Enzyme induction may also produce modest elevations in alkaline phosphatase. These enhancements of hepatic metabolising capacity are not an indication for the withdrawal of carbamazepine.

Severe hepatic reactions to carbamazepine occur very rarely. The development of signs and symptoms of liver dysfunction or active liver disease should be urgently evaluated and treatment with carbamazepine suspended pending the outcome of the evaluation.

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for carbamazepine.
Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Serious dermatological reactions, including toxic epidermal necrolysis (TEN: also known as Lyell’s syndrome) and Stevens Johnson syndrome (SJS) have been reported very rarely with carbamazepine. Patients with serious dermatological reactions may require hospitalization, as these conditions may be life-threatening and may be fatal. Most of the SJS/TEN cases appear in the first few months of treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations. If signs and symptoms suggestive of severe skin reactions (e.g. SJS, Lyell's syndrome/TEN) appear, carbamazepine should be withdrawn at once and alternative therapy should be considered.

Cutaneous reactions

Serious and sometimes fatal cutaneous reactions including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher.

There is growing evidence of the role of different HLA alleles in predisposing patients to immune-mediated adverse reactions (see section 4.2).

*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 unless there is no other therapeutic option. Tested patients who are found to be negative for HLA-B*1502 have a low risk of SJS, although the reactions may still very rarely occur.

There are some data that suggest an increased risk of serious carbamazepine-associated TEN/SJS in other Asian populations. Because of the prevalence of this allele in other Asian populations (e.g. above 15% in the Philippines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.

The prevalence of the HLA-B*1502 allele is negligible in e.g. European descent, African, Hispanic populations sampled, and in Japanese and Koreans (< 1%).

*HLA-A*3101 allele - European descent and Japanese populations*
There are some data that suggest HLA-A*3101 is associated with an increased risk of carbamazepine induced cutaneous adverse drug reactions including SJS, TEN, Drug rash with eosinophilia (DRESS), or less severe acute generalized exanthematous pustulosis (AGEP) and maculopapular rash (see section 4.8) in people of European descent and the Japanese.

The frequency of the HLA-A*3101 allele varies widely between ethnic populations. HLA-A*3101 allele has a prevalence of 2 to 5% in European populations and about 10% in Japanese population.

The presence of HLA-A*3101 allele may increase the risk for carbamazepine induced cutaneous reactions (mostly less severe) from 5.0% in general population to 26.0% among subjects of Northern European ancestry, whereas its absence may reduce the risk from 5.0% to 3.8%.

There are insufficient data supporting a recommendation for HLA-A*3101 screening before starting carbamazepine treatment.

If patients of European descent or Japanese origin are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed risks.

Other dermatologic reactions
Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous. They usually disappear within a few days or weeks, either during the continued course of treatment or following a decrease in dosage. 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 the drug should the reaction worsen with continued use.

The HLA-B*1502 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).

Fulminant type 1 diabetes mellitus, associated with carbamazepine-induced hypersensitivity reactions

In very rare cases, the occurrence of fulminant type 1 diabetes mellitus has been reported in association with carbamazepine use. This potentially life-threatening reaction is usually associated with delayed hypersensitivity cutaneous reactions and with concurrent infections with certain viruses (Coxsackie, EBV, CMV, HHV-6).

This disorder has been described mainly in patients of Japanese descent, where the reported incidence of DRESS-related FT1DM ranges from 0.54% to 3.45%, 50 to 350-times higher than the incidence of idiopathic FT1DM (0.01%) in Japanese population. No specific genotype has been associated with an increased risk of this disorder yet.

The disorder develops acutely and can be fatal within 24 hours if not recognized and treated. Patients with signs and symptoms of hypersensitivity cutaneous reactions associated with carbamazepine should be closely monitored for hyperglycemia and immediately treated if hyperglycemia, rapid loss of C-peptide or diabetic ketoacidosis are identified.

The monitoring should continue until the full resolution of the hypersensitivity reaction and at least 14 days after discontinuation of carbamazepine

ABCB1 (MDR) 3435C>T polymorphism and decreased carbamazepine efficacy

Pharmacogenomic data suggest that individuals with a polymorphism of the ABCB1 gene, especially at location 3435C>T, can experience reduced efficacy of carbamazepine. This polymorphism appears to be more common in Caucasian and Asian populations.

In clinical studies, the presence of the single nucleotide polymorphism at 3435C>T was associated with altered concentration-dose ratios of CBZ and increased clearance of carbamazepine and its metabolites. Additionally, data also indicates that the presence of this specific polymorphism could be related to a higher intra-individual response variability.

In such cases, the dose of carbamazepine may need to be adjusted to meet the expected effect. Patients with this specific polymorphism should be closely monitored for the therapeutic effect and carbamazepine concentration using therapeutic drug monitoring. Treatment non-responders and responders with high response variability to carbamazepine treatment, could be considered for pharmacogenomic testing.

> There is insufficient evidence available that would grant a recommendation of pharmacogenomic testing of all patients prior carbamazepine initiation for the ABCB1 3435C>T polymorphism.

Hypersensitivity

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

Carbamazepine may trigger hypersensitivity reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), reactivation of HHV6 associated with DRESS, a delayed multi-organ hypersensitivity disorder with fever, rash, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leukopenia, eosinophilia, hepato-splenomegaly, abnormal liver

function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts), that may occur in various combinations. Other organs may also be affected (e.g. lungs, kidneys, pancreas, myocardium, colon) see section 4.8.

In general, if signs and symptoms suggestive of hypersensitivity reactions occur, carbamazepine 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 (Trileptal).

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

Seizures
Carbamazepine should be used with caution in patients with mixed seizures which include absences, either typical or atypical. In all these conditions, carbamazepine may exacerbate seizures. In case of exacerbation of seizures, carbamazepine 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 may precipitate seizures therefore carbamazepine withdrawal should be gradual. If treatment with carbamazepine has to be withdrawn abruptly in a patient with epilepsy, the changeover to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug.

Women of childbearing potential
Carbamazepine may cause fetal harm when administered to a pregnant woman. Prenatal exposure to carbamazepine may increase the risks for major congenital malformations and other adverse development outcomes (see section 4.6).

Carbamazepine should not be used in women of childbearing potential unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

Women of childbearing potential should be fully informed of the potential risk to the fetus if they take carbamazepine during pregnancy.

Before the initiation of treatment with carbamazepine in a woman of childbearing potential, pregnancy testing should be considered.

Women of childbearing potential should use highly effective contraception during treatment and for at least two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives, therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods (see sections 4.5 and 4.6).

Women of childbearing potential should be counselled regarding the need to consult their physician as soon as they are planning a pregnancy to discuss switching to alternative treatments prior to conception and before contraception is discontinued (see section 4.6).

Women of childbearing potential should be counselled to contact the doctor immediately if they become pregnant or think they might be pregnant and are taking carbamazepine.

Endocrinological effects
Breakthrough bleeding has been reported in women taking carbamazepine while using hormonal contraceptives. The reliability of hormonal contraceptives may be adversely affected by carbamazepine and women of childbearing potential should be advised to consider using alternative forms of birth control while taking carbamazepine.

Patients taking carbamazepine and requiring hormonal contraception should receive a preparation containing not less than 50 µg oestrogen or use of some alternative non-hormonal method of contraception should be considered.

Monitoring of plasma levels
Although correlations between dosages and plasma levels of carbamazepine, and between plasma levels and clinical efficacy or tolerability are rather tenuous**,** monitoring of the plasma levels may be useful in the following conditions: dramatic increase in seizure frequency/verification of patient compliance; during pregnancy; when treating children or adolescents; in suspected absorption disorders; in suspected toxicity when more than one drug is being used (see section 4.5).

Precautions
Carbamazepine should be prescribed only after a critical benefit-risk appraisal and under close monitoring in patients with a history of cardiac, hepatic or renal damage, adverse haematological reactions to other drugs, or interrupted courses of therapy with carbamazepine.

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hyponatremia
Hyponatremia is known to occur with carbamazepine. In patients with pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering medicinal products (e.g. diuretics, medicinal products associated with inappropriate ADH secretion), serum sodium levels should be measured prior to initiating carbamazepine therapy. Thereafter, serum sodium levels should be measured after approximately two weeks and then at monthly intervals for the first three months during therapy, or according to clinical need. These risk factors may apply especially to elderly patients. If 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 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-administration of inhibitors of CYP3A4 or inhibitors of epoxide hydrolase with carbamazepine can induce adverse reactions (increase of carbamazepine or carbamazepine-

10,11 epoxide plasma concentrations respectively). The dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored.

Co-administration of CYP3A4 inducers with carbamazepine may decrease carbamazepine plasma concentrations and its therapeutic effect, while discontinuation of a CYP3A4 inducer may increase carbamazepine plasma concentrations. The dosage of carbamazepine may have to be adjusted.

Carbamazepine is a potent inducer of CYP3A4 and other phase I and phase II enzyme systems in the liver, and may therefore reduce plasma concentrations of co-medications mainly metabolized by CYP3A4 by induction of their metabolism. See section 4.5.

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

Falls
Carbamazepine 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 carbamazepine treatment.

Excipients
This medicine contains 304 mg sorbitol in each chewable tablet. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 3A4 (CYP 3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine 10, 11-epoxide. 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 comedications mainly metabolized by CYP3A4 by induction of their metabolism.

Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11

epoxide. Co-administration of inhibitors of human microsomal epoxide hydrolase may result in increased carbamazepine-10,11 epoxide plasma concentrations.

Interactions resulting in a contraindication
The use of carbamazepine is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering carbamazepine MAOIs should be discontinued for a minimum of 2 weeks, or longer if the clinical situation permits (see section 4.3).

Agents that may raise carbamazepine plasma levels
Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Analgesics, anti-inflammatory drugs: dextropropoxyphene.

Androgens: danazol.

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

Antidepressants: fluoxetine, fluvoxamine, paroxetine, trazodone.

Antiepileptics: vigabatrin.

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

Antipsychotics: olanzapine.

Antituberculosis: isoniazid.

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

Carbonic anhydrase inhibitors: acetazolamide.

Cardiovascular drugs: diltiazem, verapamil.

Gastrointestinal drugs: possibly cimetidine, omeprazole.

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

Agents that may raise the active metabolite carbamazepine-10,11-epoxide plasma levels
Since raised plasma carbamazepine-10,11-epoxide levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of carbamazepine should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

Neuroleptics: quetiapine
Antiepileptics: progabide, valproic acid, valnoctamide, valpromide, primidone, brivaracetam.

Agents that may decrease carbamazepine plasma levels
The dose of carbamazepine may have to be adjusted when used concomitantly with the substances described below:

Antiepileptics: oxcarbazepine, phenobarbital, phenytoin (to avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment) and fosphenytoin, primidone, and, although the data are partly contradictory, possibly also clonazepam.

Antineoplastics: cisplatin or doxorubicin.

Antituberculosis: rifampicin.

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin.

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

Effect of carbamazepine on plasma levels of concomitant agents
Carbamazepine may lower the plasma level, diminish or even abolish the activity of certain drugs. The dosage of the following drugs may have to be adjusted to clinical requirement:

Analgesics, anti-inflammatory agents: buprenorphine, methadone, paracetamol (long term administration of carbamazepine and paracetamol (acetaminophen) may be associated with hepatotoxicity), tramadol.

Antibiotics: doxycycline, rifabutin.

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

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

Antiemetics: aprepitant.

Antiepileptics: clobazam, clonazepam, ethosuximide, lamotrigine, eslicarbazepine, oxcarbazepine, primidone, tiagabine, topiramate, valproic acid, zonisamide. To avoid phenytoin intoxication and subtherapeutic concentrations of carbamazepine it is recommended to adjust the plasma concentration of phenytoin to 13 micrograms /mL before adding carbamazepine to the treatment. There have been rare reports of an increase in plasma mephenytoin levels.

Antifungals: itraconazole, voriconazole. Alternative anti-convulsants may be recommended in patients treated with voriconazole or itraconazole.

Antihelmintics: albendazole.

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus.

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

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

Anxiolytics: alprazolam.

Bronchodilatators or anti-asthma drugs: theophylline.

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

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

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

Drugs used in erectile dysfunction: tadalafil.

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus.

Thyroid agents: levothyroxine.

Other drug interactions: products containing oestrogens and/or progesterones.

Combinations that require specific consideration
Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.

Concomitant use of carbamazepine and isoniazid has been reported to increase isoniazid-induced hepatotoxicity.

The combination of lithium and carbamazepine may cause enhanced neurotoxicity in spite of lithium plasma concentrations being within the therapeutic range. Combined use of carbamazepine with metoclopramide or major tranquillisers, e.g. haloperidol, thioridazine, may also result in an increase in neurological side-effects.

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

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

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. It is therefore advisable for the patient to abstain from alcohol.

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

Interference with serological testing

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to antiepileptic medicinal products in general

Specialist medical advice regarding the potential risks to a fetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.
Sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Risks related to carbamazepine

Carbamazepine crosses the placenta in humans. Epidemiological data from pregnancy registries and cohort studies have shown that children born to mothers with epilepsy treated with carbamazepine during the first trimester of pregnancy are at an increased risk of major congenital malformations. The most common types of major congenital malformations reported in association with carbamazepine include neural tube defects including spina bifida, craniofacial defects including cleft lip/palate, cardiovascular malformations, genitourinary tract defects including hypospadias, skeletal malformations and anomalies involving various body systems. Data derived from a meta-analysis (including registries and cohort studies) has shown that 4.93% of children of epileptic women exposed to carbamazepine monotherapy during first trimester of pregnancy suffer from congenital malformations (95% CI: 3.84-6.16) compared with the background rate on the general population of around 2-3%. Malformations such as neural tube defects (spina bifida), craniofacial defects such as cleft lip/palate, cardiovascular malformations, hypospadias, hypoplasia of the fingers, and other anomalies involving various body systems, have been reported in the offspring of women who used carbamazepine during pregnancy. Specialised antenatal surveillance for these malformations is recommended.

Epidemiological study data do not indicate that carbamazepine use during pregnancy is associated with negative impact on the child in terms of measures of intelligence, developmental outcomes, or symptoms or diagnoses of autism spectrum disorders.

Carbamazepine should not be used during pregnancy unless the benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risks of taking carbamazepine during pregnancy.

Evidence 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. If based on a careful evaluation of the risks and the benefits, no alternative treatment option is suitable, and treatment with carbamazepine is continued, monotherapy and the lowest effective dose of carbamazepine should be used 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.

Neurodevelopmental disorder has been reported among children born to women with epilepsy who used carbamazepine alone or in combination with other antiepileptic drugs 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.

Some antiepileptic drugs, such as carbamazepine, have been reported to decrease serum folate levels. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation is recommended before and during pregnancy. 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.

If a woman is planning to become pregnant, all efforts should be made to switch to appropriate alternative treatment prior to conception and before contraception is discontinued. If a woman becomes pregnant while taking carbamazepine, she should be referred to a specialist to reassess carbamazepine treatment and consider alternative treatment options.

Monitoring and prevention
Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate deficiency. This deficiency may contribute to the increased incidence of birth defects in the offspring of treated epileptic women. Folic acid supplementation has therefore been recommended before and during pregnancy.

In the neonate
In order to prevent bleeding disorders in the offspring, it has also been recommended that vitamin K_1 be given to the mother during the last weeks of pregnancy as well as to the neonate.

There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal carbamazepine and other concomitant antiepileptic drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal carbamazepine use. These reactions may represent a neonatal withdrawal syndrome.

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

Women of childbearing potential
Carbamazepine should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options. The woman should be fully informed of and understand the risk of potential harm to the fetus if carbamazepine is taken during pregnancy and therefore the importance of planning any pregnancy. Pregnancy testing in women of childbearing potential should be considered prior to initiating treatment with carbamazepine.

Women of childbearing potential should use highly effective contraception during treatment and for at least two weeks after stopping treatment. Due to enzyme induction, carbamazepine may result in a failure of the therapeutic effect of hormonal contraceptives (see section 4.5), therefore, women of childbearing potential should be counselled regarding the use of other effective contraceptive methods. At least one effective method of contraception (such as an intra-uterine device) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, involving the patient in the discussion, when choosing the contraception method.

Breast-feeding
Carbamazepine passes into the breast milk **(**about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking carbamazepine may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction). There have been some reports of cholestatic hepatitis in neonates exposed to carbamazepine during antenatal and or during breast feeding. Therefore, breast-fed infants of mothers treated with carbamazepine should be carefully observed for adverse hepatobiliary effects.

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

4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision have been reported with carbamazepine, especially at the start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

4.8 Undesirable effects

Summary of the safety profile

Particularly at the start of treatment with Carbamazepine Essential Pharma, or if the initial dosage is too high, or when treating elderly patients, certain types of adverse reaction occur very commonly or commonly, e.g. CNS adverse reactions (dizziness, headache, ataxia, drowsiness, fatigue, diplopia); gastrointestinal disturbances (nausea, vomiting), as well as allergic skin reactions.

The dose-related adverse reactions usually abate within a few days, either spontaneously or after a transient dosage reduction. The occurrence of CNS adverse reactions may be a manifestation of relative overdosage or significant fluctuation in plasma levels. In such cases it is advisable to monitor the plasma levels and divide the daily dosage into smaller (i.e. 3-4) fractional doses.

Tabulated summary of adverse drug reactions compiled from clinical trials and from spontaneous reports

Adverse drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most

frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Infections and infestations	
Not known**:	reactivation of Human herpes virus 6 infection.
Blood and lymphatic system disorders	
Very common:	leucopenia.
Common:	thrombocytopenia, eosinophilia.
Rare:	leucocytosis, lymphadenopathy.
Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia.
Not known:	bone marrow depression.
Immune system disorders	
Rare:	a delayed multi-organ hypersensitivity disorder with fever, rashes, vasculitis, lymphadenopathy, pseudo lymphoma, arthralgia, leucopenia, eosinophilia, hepato-splenomegaly, abnormal liver function tests and vanishing bile duct syndrome (destruction and disappearance of the intrahepatic bile ducts) occurring in various combinations. Other organs may also be affected (e.g. liver**,** lungs, kidneys, pancreas, myocardium, colon).
Very rare:	anaphylactic reaction, oedema angioedema, hypogammaglobulinemia.
Not known**:	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).
Endocrine disorders	
Common:	oedema, fluid retention, weight increase, hyponatraemia and blood osmolarity decreased due to an antidiuretic hormone (ADH)-like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, confusional state, neurological disorders.
Very rare:	galactorrhoea, gynaecomastia.
Metabolism and nutrition disorders	
Rare:	folate deficiency, decreased appetite.
Very rare:	porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda).
Not known:	Hyperammonaemia, fulminant type 1 diabetes mellitus
Psychiatric disorders	
Rare:	hallucinations (visual or auditory), depression, aggression, agitation, restlessness, confusional state.
Very rare:	activation of psychosis.
Nervous system disorders	
Very common:	ataxia, dizziness, somnolence.

Common:	diplopia, headache.
Uncommon:	abnormal involuntary movements (e.g. tremor, asterixis, dystonia, tics), nystagmus.
Rare:	dyskinesia, eye movement disorder, speech disorders (e.g. dysarthria or slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, and paresis.
Very rare:	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
Not known**:	sedation, memory impairment.

Eye disorders	
Common:	accommodation disorders (e.g. blurred vision).
Very rare:	lenticular opacities, conjunctivitis.
Ear and labyrinth disorders	
Very rare:	hearing disorders, e.g. tinnitus, hyperacusis, hypoacusis, change in pitch perception.
Cardiac disorders	
Rare:	cardiac conduction disorders.
Very rare:	arrhythmia, atrioventricular block with syncope, bradycardia, cardiac failure congestive, coronary artery disease aggravated.
Vascular disorders	
Rare:	hypertension or hypotension.
Very rare:	circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis.
Respiratory, thoracic and mediastinal disorders	
Very rare:	pulmonary hypersensitivity characterised e.g. by fever, dyspnoea, pneumonitis or pneumonia.
Gastrointestinal disorders	
Very common:	vomiting, nausea.
Common:	dry mouth, with suppositories rectal irritation may occur.
Uncommon:	diarrhoea, constipation.
Rare:	abdominal pain.
Very rare:	pancreatitis, glossitis, stomatitis.
Not known**:	colitis.
Hepatobiliary disorders	
Rare:	hepatitis of cholestatic, parenchymal (hepatocellular) or mixed type, vanishing bile duct syndrome, jaundice.
Very rare:	hepatic failure, granulomatous liver disease.
Skin and subcutaneous tissue disorders	
Very common:	urticaria, which may be severe dermatitis allergic.
Uncommon:	dermatitis exfoliative.
Rare:	systemic lupus erythematosus, pruritus.

Very rare:	Stevens-Johnson syndrome*, toxic epidermal necrolysis, photosensitivity reaction, erythema multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.
Not known**:	Acute Generalized Exanthematous Pustulosis (AGEP)**, lichenoid keratosis, onychomadesis.
Musculoskeletal and connective tissue disorders	
Rare:	muscular weakness.
Very rare:	bone metabolism disorders (decrease in plasma calcium and blood 25-hydroxy-cholecalciferol) leading to osteomalacia/osteoporosis, arthralgia, myalgia, muscle spasms.
Not known**:	fracture.
Renal and urinary disorders	
Very rare:	tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria and blood urea/ azotaemia), urinary retention, urinary frequency.
Reproductive system and breast disorders	
Very rare:	sexual disturbances/erectile dysfunction spermatogenesis abnormal (with decreased sperm count and/or motility).
General disorders and administration site conditions	
Very common:	fatigue.
Investigations	
Very common:	gamma-glutamyl transferase increased (due to hepatic enzyme induction), usually not clinically relevant.
Common:	blood alkaline phosphatase increased.
Uncommon:	transaminases increased.
Very rare:	intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased.
Not known**:	bone density decreased.
Injury, poisoning and procedural complications	
Not known:	fall (associated with carbamazepine treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4).

* In some Asian countries also reported as rare. See also section 4.4.

**Additional adverse drug reactions from spontaneous reports (frequency not known)
The following adverse drug reactions have been derived from post-marketing experience with Carbamazepine Essential Pharma via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse

drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.
There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with carbamazepine. The mechanism by which carbamazepine affects bone metabolism has not been identified.

There is increasing evidence regarding the association of genetic markers and the occurrence of cutaneous ADRs such as SJS, TEN, DRESS, AGEP and 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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Signs and symptoms
The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, respiratory systems and the adverse drug reactions mentioned under section 4.8.

Central nervous system: CNS depression; disorientation, depressed level of consciousness, 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.

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

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

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

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

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

Management
There is no specific antidote.

Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm carbamazepine poisoning and to ascertain the size of the overdose.

Evacuation of the stomach, gastric lavage, and administration of activated charcoal. Delay in evacuating the stomach may result in delayed absorption, leading to relapse during recovery from intoxication. Supportive medical care in an intensive care unit with cardiac monitoring and careful correction of electrolyte imbalance.

Special recommendations
Charcoal haemoperfusion has been recommended. Hemodialysis is the effective treatment modality in the management of the carbamazepine overdose.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, Carboxaminde derivatives, ATC code: N03AF01.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

Mechanism of action
The mechanism of action of carbamazepine, the active substance of Carbamazepine Essential Pharma Chewtabs, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

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

5.2 Pharmacokinetic properties

Absorption
Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400 mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx. 4.5 µg/ml.

The bioavailability of carbamazepine in various oral formulations has been shown to lie between 85-100%.

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of carbamazepine.

Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.

Distribution

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma **(**20-30%**).** Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels.

Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10,11-transdiol derivative and its glucuronide as the main metabolites.

Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10,11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours **(**auto-induction of the hepatic mono-oxygenase system**)**, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.

The mean elimination half-life of the 10,11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

After administration of a single oral dose of 400 mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as

unchanged drug and about 1% as the pharmacologically active 10,11-epoxide metabolite.

Pharmacokinetic/pharmacodynamic relationship(s)
The steady-state plasma concentrations of carbamazepine considered as “therapeutic range” vary considerably inter-individually; for the majority of patients a range between 4-12 µg/ml corresponding to 17-50 µmol/l has been reported. Concentrations of carbamazepine 10,11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

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

Elderly population
There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

Patients with hepatic or renal impairment
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single and repeated dose toxicity, local tolerance, genotoxicity and carcinogenic potential. Reproductive toxicity studies in animals were insufficient to rule out a teratogenic effect of carbamazepine in humans.

Carcinogenicity
In rats treated with carbamazepine for two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence to date that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Reproductive toxicity

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

Published studies indicate that carbamazepine is a teratogen in rats and mice (craniofacial and limb malformations) with the effects in mice reported at clinically relevant exposures.

Intrauterine growth restrictions (e.g reduced crown-rump lengths), delayed skeletal ossification and reduced fetal weights have been reported in multiple studies in rodents in the open literature. In a reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

There are some reports of neurodegenerative changes in the brains of offspring exposed to carbamazepine during pregnancy from rodent studies published in the open literature. However, limitations in the study design means the toxicological significance and clinical relevance of these findings are unclear.

Fertility
In chronic toxicity studies dose related testicular atrophy and aspermatogenesis occurred in rats receiving carbamazepine. The safety margin for this effect is not known.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone
Red iron oxide (E 172)
Yellow iron oxide (E 172)
Magnesium stearate
Orange flavour 51.941/AP
Sorbitol
Stearic acid.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Carbamazepine Essential Pharma 200 mg Chewtabs come in aluminium blister packs of 56 and 100 tablets.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

7 Essential Pharma Ltd.

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8 MARKETING AUTHORISATION NUMBER(S)

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