Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Carbamazepine Essential Pharma 125 mg Suppositories

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository contains 125 mg carbamazepine

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suppository

White to off-white, torpedo shaped suppositories with a fatty odour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an anticonvulsant in the management of epilepsy (generalised tonic-clonic and partial seizures).

Carbamazepine Essential Pharma suppositories are for short-term use as replacement therapy in patients where oral treatment is temporarily not possible.

4.2 Posology and method of administration

Posology

Carbamazepine Essential Pharma is available in suppositories, for short term use. They are intended as replacement therapy (maximum period recommended: 7 days) in patients for whom oral treatment is temporarily not possible, for example in post-operative patients.

When switching from oral formulations of carbamazepine to suppositories the dosage should be increased by approximately 25% (the 125 mg and 250 mg suppositories correspond to the 100 mg and 200 mg tablets respectively).

The final dose adjustment should always depend on the clinical response in the individual patient. Carbamazepine Essential Pharma suppositories, in appropriate doses, have been shown to provide plasma levels which are well within the therapeutic range.

The pharmacokinetic properties of the suppositories are such that the maximum daily dose is limited to 1000 mg (250 mg four times daily at 6 hourly intervals).

Use in the elderly
Due to the potential for drug interactions, the dosage of Carbamazepine Essential Pharma should be selected with caution in elderly patients.

Paediatric population
Carbamazepine Essential Pharma suppositories are not recommended for very young children.

Special populations

Renal impairment / Hepatic impairment
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.
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 SJS (See information on genetic testings and cutaneous reactions in section 4.4).

Method of administration:
Rectal use.

4.3 Contraindications

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

Patients with atrioventricular block.

Patients with a history of bone-marrow depression.

Patients with a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).

The use of Carbamazepine Essential Pharma is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs) (see section 4.5).

Herbal preparations containing St .John's wort (Hypericum perforatum) must not be used while taking Carbamazepine Essential Pharma due to the risk of decreased plasma concentrations and reduced clinical effects of Carbamazepine Essential Pharma (see section 4.5).

4.4 Special warnings and precautions for use

Carbamazepine Essential Pharma should be given only under medical supervision. Carbamazepine Essential Pharma 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 Essential Pharma.

Haematological effects
Agranulocytosis and aplastic anaemia have been associated with Carbamazepine Essential Pharma; however, due to the very low incidence of these diseases, meaningful risk estimates for Carbamazepine Essential Pharma 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 Essential Pharma. Nonetheless, complete pre-treatment blood counts, including platelets (and possibly reticulocytes and serum iron), should be obtained as a baseline, and periodically thereafter.

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 Essential Pharma should be discontinued if the patient develops leucopenia, which is severe, progressive or accompanied by clinical manifestations, e.g. fever or sore throat. Carbamazepine Essential Pharma should be discontinued if any evidence of significant bone marrow depression appears.

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 his physician immediately.

Cutaneous reactions
Serious and sometimes fatal cutaneous reactions, including toxic epidermal necrolysis (TEN; also known as Lyell's syndrome) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Carbamazepine Essential Pharma. Patients

should be advised of the signs and symptoms and monitored closely for skin reactions. These reactions are estimated to occur in 1-6 per 10000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. 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 Essential Pharma.If signs and symptoms of SJS, Lyell's syndrome/TEN (e.g. progressive skin rash often with blisters or mucosal lesions) appear, Carbamazepine Essential Pharma should be withdrawn at once and alternative therapy should be considered. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis. If the patient has developed SJS or TEN with the use of Carbamazepine Essential Pharma, Carbamazepine Essential Pharma must not be re-started in this patient at any time.

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

*Association with HLA-B*1502 allele*
Retrospective studies in patients of Han Chinese and Thai origin found a strong correlation between the risk of developing SJS/TEN skin reactions associated with carbamazepine 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.
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 Philipines and Malaysia), testing genetically at risk populations for the presence of HLA-B*1502 may be considered.
The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous peoples 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.

Whenever possible, screening for the presence of HLA-B*1502 allele should be carried out in patients with ancestry in genetically at-risk populations, prior to initiating treatment with carbamazepine (see section 4.2). (If testing for the presence of the HLA-B*1502 allele should be performed, 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). 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.
HLA-B*1502 may be a risk factor for the development of SJS/TEN in Chinese patients taking other anti-epileptic drugs (AED) associated with SJS/TEN. Consideration should therefore be given to avoiding use of other drugs 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 Carbamazepine Essential Pharma 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 carbamazepine therapy in these subjects has been shown to decrease the incidence of carbamazepine-induced SJS/TEN.

*Association with HLA-A*3101 allele*
There are some data that suggest Human Leukocyte Antigen *(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 and its frequency is about 2 to 5% in European populations and about 10% in the Japanese population.

The frequency of this allele is estimated to be less than 5% in the majority of Australian, Asian, African and North American populations with some exceptions within 5-12%. Prevalence above 15% has been estimated in some ethnic groups in South America (Argentina and Brazil), North America (US Navajo and Sioux, and Mexico Sonora Seri) and Southern India (Tamil Nadu) and between 10%-15% in other native ethnicities in these same regions and about 10% in Japanese populations.

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.

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

Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with Carbamazepine Essential Pharma. (If testing for the presence of the HLA-A*3101 allele is performed, high-resolution "HLA-A*3101 genotyping" 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).
The use of Carbamazepine Essential Pharma should be avoided in patients who are found to be positive for HLA-A*3101, unless the benefits clearly outweigh the risks. Screening is generally not recommended for any current Carbamazepine Essential Pharma 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.

Limitation of genetic screening
Genetic screening results must never substitute for appropriate clinical vigilance and patient management. Many Asian patients positive for HLA-B*1502 and treated with Carbamazepine Essential Pharma 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 Carbamazepine Essential Pharma will not develop SJS, TEN, DRESS, AGEP or maculopapular rash and patients negative for HLA-A*3101 of any ethnicity can still develop these severe cutaneous adverse reactions. The role of other possible factors in the development of, and morbidity from, these severe cutaneous adverse reactions such as AED dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

Other dermatologic reactions
Mild skin reactions e.g. isolated macular or maculopapular exanthema, can also occur and are mostly transient and not hazardous, and 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-A*3101 allele has been found to be associated with less severe adverse cutaneous reactions from carbamazepine and may predict the risk of these 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 carbamazepine. If a patient develops these reactions after treatment with carbamazepine, the medicinal product must be discontinued, and an alternative treatment started.

Carbamazepine Essential Pharma may trigger hypersensitivity reactions including Drug Rash with Eosinophilia and Systemic Symptoms (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, (including 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).
The HLA-A*3101 allele has been found to be associated with the occurrence of hypersensitivity syndrome, including maculopapular rash.
Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25 to 30% of these patients may experience hypersensitivity reactions with oxcarbazepine (Trileptal®). Cross-hypersensitivity can occur between carbamazepine and aromatic antiepileptic drugs (e.g. phenytoin, primidone and phenobarbital).
In general, if signs and symptoms suggestive of hypersensitivity reactions occur, Carbamazepine Essential Pharma should be withdrawn immediately.

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

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

An increase in seizure frequency may occur during the switch from an oral formulation to suppositories.

Abrupt withdrawal of Carbamazepine Essential Pharma may precipitate seizures.

Hepatic function
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 of 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 Essential Pharma suspended pending the outcome of the evaluation.

Renal function
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 Essential Pharma has shown mild anticholinergic activity; patients with glaucoma and urinary retention should therefore be warned and advised regarding possible hazards.

Psychiatric effects
The possibility of activation of a latent psychosis, and in elderly patients the possibility of agitation or confusion, especially when high doses of Carbamazepine Essential Pharma are administered should be borne in mind.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with antiepileptic 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.

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 effective contraception during treatment and for 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 her physician as soon as she is planning 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 her doctor immediately if she becomes pregnant or thinks she may be pregnant and is taking carbamazepine.

Endocrinology
The induction of hepatic enzymes by carbamazepine may reduce the activity of the hormones contained in the combined oralcontraceptive pill. This may appear clinically as breakthrough bleeding or spotting.Breakthrough bleeding has been reported in women taking Carbamazepine Essential Pharma while using hormonal contraceptives; the reliability of oral contraceptives may be adversely affected by Carbamazepine Essential Pharma and women of childbearing potential should be advised to consider using alternative forms of birth control while taking Carbamazepine Essential Pharma.

Monitoring plasma levels
Although correlations between dosage 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 situations: dramatic increase in seizure frequency; during pregnancy; when treating children or adolescents; in suspected absorption disorders; for verification of compliance; in suspected toxicity where more than one drug is being used (see section 4.5).

Dose reduction and withdrawal
Abrupt withdrawal of Carbamazepine Essential Pharma may precipitate seizures therefore carbamazepine should be withdrawn gradually over a 6-month period. If treatment with Carbamazepine Essential Pharma has to be withdrawn abruptly, the switch to another anti-epileptic drug should if necessary be effected under the cover of a suitable drug.

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

Pregnancy and females of reproductive potential:
Carbamazepine may be associated with foetal harm when administered to a pregnant woman (see section 4.6). Carbamazepine Essential Pharma should be used during pregnancy only if the potential benefit justifies the potential risks.
Adequate counselling should be made available to all pregnant women and women of childbearing potential, regarding the risks associated with pregnancy due to potential teratogenic risk to the foetus (see section 4.6).
Women of childbearing potential should use effective contraception during treatment with Carbamazepine Essential Pharma and for 2 weeks after the last dose (see sub-sections "Endocrinology" and "Interactions"); (see section 4.6).

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 Essential Pharma 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 Essential Pharma 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 Essential Pharma with hormonal contraceptives may render this type of contraceptive ineffective (see sections 4.5 and 4.6). Alternative non-hormonal forms of contraception are recommended when using Carbamazepine Essential Pharma.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P4503A4 (CYP3A4) is the main enzyme catalysing formation of the active metabolite carbamazepine 10, 11 epoxide. Co-administration of inhibitors of CYP3A4 may result in increased carbamazepine plasma concentrations, which could induce adverse reactions. Coadministration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading topotential decreases in the carbamazepine serum level and potential decrease in the 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 Essential Pharma is contraindicated in combination with monoamine-oxidase inhibitors (MAOIs); before administering Carbamazepine Essential Pharma 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 carbamazepineplasma levels:
Since raised plasma carbamazepine levels may result in adverse reactions (e.g. dizziness, drowsiness, ataxia, diplopia), the dosage of Carbamazepine Essential Pharma should be adjusted accordingly and /or the plasma levels monitored when used concomitantly with the substances described below:

Analgesics: anti-inflammatory drugs: dextropropoxyphene, ibuprofen.

Androgens: danazol.

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

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

Antiepileptics: stiripentol, vigabatrin.

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

Antihistamines: terfenadine.

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.

Muscle relaxants: oxybutynin, dantrolene.

Platelet aggregation inhibitors: ticlopidine.

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 Essential Pharma should be adjusted accordingly and/or the plasma levels monitored when used concomitantly with the substances described below:

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

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

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

Antimalarials: mefloquine, may antagonise the anticonvulsant effect of carbamazepine

Antituberculosis: rifampicin.

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline.

Dermatological drugs: isotretinoin has been reported to alter the bioavailability and/or clearance of carbamazepine and carbamazepine 10,11 epoxide. Carbamazepine levels should be monitored.

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

Effect of Carbamazepine on plasma levels of concomitant agents:
Plasma or whole blood concentrations of carbamazepine can be reduced by concomitant use of the herbal preparation St John's wort (Hypericum perforatum). This is due to induction of drug metabolising enzymes by St John's wort. Herbal preparations containing St John's wort should therefore not be combined with Carbamazepine Essential Pharma. The inducing effect may persist for at least 2 weeks after cessation of treatment with St. John's wort. If a patient is already taking St John's wort check carbamazepine blood levels and stop St John's wort. Carbamazepine levels may increase on stopping St John's wort. The dose of carbamazepine may need adjusting.

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

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

Antibiotics: doxycycline, rifabutin.

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

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

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, 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: 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 drugs: theophylline.

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

Cardiovascular drugs: digoxin, calcium channel blockers (dihydropyridine group) e.g. felodipine, 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 (gestrinone, tribolone, toremifene)

Plasma phenytoin levels have been reported both to be raised and to be lowered by carbamazepine, and plasma mephenytoin levels have been reported in rare instances to increase.

Combinations that require specific consideration
Co-administration of carbamazepine and paracetamol may reduce the bioavailability paracetamol / acetaminophen.

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 hepatotoxicity.

Combined use of carbamazepine and lithium or metoclopramide on the one hand, and carbamazepine 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 Carbamazepine Essential Pharma 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 Essential Pharma crosses the placenta in humans. Prenatal exposure to carbamazepine may increase the risks for congenital malformations and other adverse developmental outcomes. In humans, carbamazepine exposure during pregnancy is associated with a frequency of major malformations 2 to 3 times higher than that of the general population, which has a frequency of 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. Neurodevelopmental disorder has been reported among children born to women with epilepsy who used carbamazepine alone or in combination with other AEDs 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.

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. 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.

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 folic acid deficiency. 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 the neonate

It has been recommended that vitamin K1 should be given to the neonate in order to prevent bleeding disorders.
There have been a few cases of neonatal seizures and/or respiratory depression associated with maternal Carbamazepine Essential Pharma and other concomitant anticonvulsant drug use. A few cases of neonatal vomiting, diarrhoea and/or decreased feeding have also been reported in association with maternal Carbamazepine Essential Pharma use. These reactions may represent a neonatal withdrawal syndrome.

Women of child-bearing 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 effective contraception during treatment and for 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
Although carbamazepine passes into the breast milk in concentrations of about 25-60% of the plasma level, this is not believed to present a significant hazard to the infant, which is likely to receive at most 10% of an appropriate therapeutic dose of carbamazepine for an infant with epilepsy. As with all drugs, the benefits of breast-feeding should be weighed against the remote possibility of an adverse effect occurring in the infant. Mothers taking Carbamazepine Essential Pharma 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 patients` ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness ataxia, diplopia, impaired accommodation and blurred vision reported with Carbamazepine Essential Pharma, especially in the early stages of treatment. Patients should therefore exercise 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) and 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.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with Carbamazepine Essential Pharma. The mechanism by which Carbamazepine Essential Pharma affects bone metabolism has not been identified.

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

Adverse drug reactions (Table 1) 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).

Table 1

Blood and lymphatic system disorders		
	Very common:	leukopenia.
	Common:	thrombocytopenia, eosinophilia.
	Rare:	leukocytosis, lymphadenopathy.
	Very rare:	agranulocytosis, aplastic anaemia, pancytopenia, aplasia pure red cell, anaemia, anaemia megaloblastic, reticulocytosis, haemolytic anaemia.
Immune system disorders		
	Rare:	a delayed multiorgan hypersensitivity disorder (of serum sickness type) 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 affected (e.g. lungs, kidneys, pancreas, myocardium, colon). Treatment must be discontinued immediately if such hypersensitivity reactions occur.
	Very rare:	anaphylactic reaction, angioedema, hypogammaglobulinaemia.
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, gynecomastia.
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	hyperammoneamia
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, slurred speech), choreoathetosis, neuropathy peripheral, paraesthesia, paresis.
	Very rare:	neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia, dysgeusia.
Eye disorders		
	Common: Very rare:	Accommodation disorders (e.g. blurred vision). 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: Very rare:	hypertension or hypotension circulatory collapse, embolism (e.g. pulmonary embolism), thrombophlebitis
Respiratory, thoracic and mediastinal disorders	Very rare:	pulmonary hypersensitivity characterized 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.
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:	Severe cutaneous adverse rections (SCARs) e.g. Stevens-Johnson syndrome (SJS)*, toxic epidermal necrolysis (TEN) (see Section 4.4), photosensitivity reaction, erythema

		multiforme, erythema nodosum, pigmentation disorder, purpura, acne, hyperhydrosis, alopecia, hirsutism.
Musculoskeletal, connective tissue and bone 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.
Renal and urinary disorders		
	Very rare:	tubulointerstitial nephritis, renal failure, renal impairment (e.g. albuminuria, haematuria, oliguria, and blood urea increased/azotemia), urinary retention, urinary frequency.
Reproductive system		
	Very rare:	sexual dysfunction/ erectile dysfunction, spermatogenesis abnormal (with decreased sperm count and/or motility).
General disorders and administration site conditions	Very common:	fatigue.
Investigations	Very common: Common: Uncommon: Very rare:	gamma-glutamyltransferase increased (due to hepatic enzyme induction), usually not clinically relevant. blood alkaline phosphatase increased. transaminases increased. intraocular pressure increased, blood cholesterol increased, high density lipoprotein increased, blood triglycerides increased. Thyroid function test abnormal: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased.

* 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.

Infections and infestations
Reactivation of Human herpesvirus 6 infection.

Blood and lymphatic system disorders
Bone marrow failure.

Nervous system disorders
Sedation, memory impairment.

Gastrointestinal disorders
Colitis.

Immune system disorders
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS).

Skin and subcutaneous tissue disorders
Acute Generalized Exanthematous Pustulosis (AGEP), lichenoid keratosis, onychomadesis.

Musculoskeletal and connective tissue disorders
Fracture.

Investigations
Bone density decreased.

Injury, poisoning and procedural complications
Fall (associated with carbamazepine treatment induced ataxia, dizziness, somnolence, hypotension, confusional state, sedation) (see section 4.4).

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 carbazemepine and the presence of the HLA-A*3101 allele. Another marker, HLA-B*1502 has been shown to be strongly associated with SJS and TEN among individuals of Han Chinese, Thai and some other Asian ancestry (see sections 4.2 and 4.4 for further information).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the 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 HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

Signs and symptoms
The presenting signs and symptoms of overdosage usually 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, changes in blood pressure (hypotension and at times hypertension), cardiac arrhythmias, conduction disturbance with widening of QRS complex; syncope, in association with cardiac arrest.

Gastrointestinal 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 creatinine phosphokinase.

Treatment
There is no specific antidote.

Management should initially be guided by the patient's clinical condition. Possible 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, if required.

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 derivative, ATC code: N03AF01

As an antiepilepticagent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalization; generalized 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, 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
As measured by AUC calculations the total bioavailability of carbamazepine from Carbamazepine Essential Pharma suppositories is approximately 25 % less than from oral concentrations. No change of fluctuation index, but slight decrease of Cmax and Cmin compared to tablets was found at steady state . For doses up to 300 mg carbamazepine approximately 75% of the total amount absorbed reaches the general blood circulation within 6 hours after application . The result has led to the recommendation that the maximal daily dose be limited to 250 mg q.i.d. (1000 mg per day), the equivalent to 800 mg per day orally.

The steady-state plasma concentrations of carbamazepine considered as 'therapeutic range' vary considerably interindividually: for the majority of patients a range between 4 to 12 micrograms/mL corresponding to 17 to 50 micromol/L has been reported. Concentrations of carbamazepine-10,11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels .

Distribution
Carbamazepine is bound to serum proteins to the extent of 70 to 80% . The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in the plasma (20 to 30%). Concentrations in breast milk were found to be equivalent to 25 to 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 metabolized 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 the pharmacologically active 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 to 24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other liver-enzyme inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9 to 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.

Special populations

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

Elderly population
There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults but its metabolism may be affected by hepatic dysfunction.

Patients with hepatic or renal impairment
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function. In advanced hepatic disease carbamazepine metabolism may be impaired

5.3 Preclinical safety data

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

Rectal local toxicity
The local tolerability of carbamazepine suppositories administered by the rectal route to rabbits once daily for 2 weeks was not different to control animals receiving vehicle only.

Carcinogenicity
In rats treated with carbamazepine for 2 years, there was an increased incidence of hepatocellular tumors in females and benign testicular tumors in males.
However, there is no evidence that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Genotoxicity
Carbamazepine was not found to be genotoxic in various standard bacterial and mammalian mutagenicity studies.

Reproductive toxicity
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. In a reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hypromellose
Hard fat

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Packs of 5 suppositories sealed in polyethylene laminated aluminium foil.

6.6 Special precautions for disposal and other handling

No special requirements

7 MARKETING AUTHORISATION HOLDER

Essential Pharma (M) Limited
Vision Exchange Building
Triq it-Territorjals, Zone 1
Central Business District
Birkirkara, CBD 1070
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