CARBAMAZEPINE CR TABLETS USP 200MG/400MG
TAJ PHARMA

1. NAME OF THE MEDICINAL PRODUCT

Carbamazepine CR Tablets USP 200mg Taj Pharma

Carbamazepine CR Tablets USP 400mg Taj Pharma

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

a) Each Controlled-release tablet contains:

Carbamazepine USP	200mg
Excipients	q.s.

b) Each Controlled-release tablet contains:

Carbamazepine USP	400mg
Excipients	q.s.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Controlled-release tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Epilepsy
  - generalised tonic-clonic
  - partial seizures
- For the paroxysmal pain of trigeminal neuralgia.
- For the prophylaxis of manic or hypomanic phases of manic-depressive psychosis in patients unresponsive or with contraindications to lithium therapy.

4.2 Posology and method of administration

Posology

Doses should be based on seizure control and the development of clinical intolerance. Plasma levels are indicative whether a patient is within or outside the therapeutic range in order to explain a lack of seizure control or development of intolerance. This may be particularly useful, if combination therapy is used. Therapeutic plasma levels of carbamazepine are typically between 4 - 12 µg/l corresponding to a dosage of 400 - 1200mg/400mg per day.

A maximum daily dose of 1600 - 2000 mg may be required in adults.

When patients are transferred from an immediate-release carbamazepine product, the same total daily dose will generally be suitable. In a few patients, it may be necessary to increase the total daily dose, particularly when it is used with other antiepileptics.

In patients with severe cardio-vascular disease, liver disease or renal damage and in older people a reduced dose may be sufficient.

Furthermore the dose required by some patients may differ substantially from the recommendation for initial and maintenance dose below, due to increased metabolism caused by auto-induction of hepatic enzymes or drug interactions during combination therapy.

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 (SJS) (see information on genetic testings and cutaneous reactions in section 4.4).

Dosage recommendations:

Epilepsy:

Treatment is started with a low dose set individually according to the type and severity of symptoms. The dose is then slowly increased to the optimal maintenance dose to suit the patient.

It is recommended that a carbamazepine monotherapy treatment is used whenever possible. When treatment is changed from another drug to carbamazepine the dose of the other antiepileptic drug should be reduced slowly.

If a change of therapy to a different antiepileptic drug is required, the change may not be done in one sudden step, but must be done gradually in small increments.

Carbamazepine therapy is discontinued by slow dose reduction.

	Initial dose	**Maintenance dose**
Adults	100 – 200mg/400mg once or twice daily	400 – 600 mg morning and night
Children 5-10 years*	200mg/400mg at night (or 100 mg morning and night)	100 – 200mg/400mg morning and 200 – 400 mg at night
Children 10-15 years	200mg/400mg at night (or 100 mg morning and night)	100 – 400 mg morning and 400 – 600 mg at night

Carbamazepine Controlled-release tablets can be broken in half to treat children/adults with divided doses where necessary.

* Carbamazepine Controlled-release tablets are not generally suitable for children under the age of 5 years. A conventional tablet or syrup presentation of carbamazepine may be given.

Antiepileptic therapy is a long-term treatment.

In general, a dose reduction or withdrawal of antiepileptic medication may be considered, when patients are seizure-free for at least two or three years. Instead of age dependant dose adjustment, children may outgrow the dose per kg body weight.

Prevention of paroxysmal pain of trigeminal neuralgia:

The recommended initial daily dose is 100 - 400 mg/day carbamazepine. The lower initial dose may be sufficient for older or sensitive patients. The dose is increased until the patient is free of pain, generally with a dose of 600 - 800 mg/day taken in 1 - 2 doses with a maximum dose of 1600 mg. The dose may be gradually reduced if the patient is pain-free thereafter, and may possibly be stopped after a few weeks of treatment, if there is no recurrence of pain.

Prophylaxis of manic-depressive psychosis

An initial dose of 100 - 400 mg daily in divided doses, increased gradually until symptoms are controlled, or a maximum of 800 mg, in exceptional cases maximum 1600 mg, in divided doses is reached. The recommended maintenance dose is 400 - 600 mg daily, given in divided doses.

Prophylaxis of manic-depressive psychosis is a long-term treatment.

In order to prevent a drug interaction, it is necessary to keep the plasma level of carbamazepine below 8 µg/ml and lithium at a low therapeutic dosage (0.3 - 0.8 mval/L),

if in exceptional cases carbamazepine is used in combination with lithium for the prophylaxis of manic depressive psychosis, which cannot be controlled with lithium treatment alone. Neuroleptic treatment must not be done concurrently and must have been discontinued at least 8 weeks beforehand.

The impairment of the ability to react quickly appears in particular with combination therapy with lithium (see section 4.7).

Method of administration

The tablet can be divided into equal halves and the daily dose is normally taken in two divided doses, during or after a meal with a drink of water. The Controlled-release tablets should be swallowed whole and not chewed or crushed.

Patients who have difficulties in swallowing, may take the Controlled-release tablets in water following their disintegration into their granules. The Controlled-release characteristics of the tablets are maintained for a short period of time after their suspension. Therefore the suspension should be taken immediately.

4.3 Contraindications

Carbamazepine may not be taken with:

- known bone marrow depression.

- atrio ventricular conduction abnormalities.

- hypersensitivity to the active substance or structurally related drugs (for example tricyclic antidepressants) or to any of the excipients listed in section 6.1.

- history of hepatic porphyrias (*e.g.* acute intermittent porphyria, variegate porphyria, porphyria cutanea tarda).

- concomitant treatment with monoamine oxidase inhibitors (MAOIs) (see section 4.5)

- concomitant treatment with voriconazole (see section 4.5).

- herbal preparations containing St. John's wort (*Hypericum perforatum*) (see section 4.5).

4.4 Special warnings and precautions for use

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 antiepileptic 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 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 1-6 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 the severe cutaneous reactions known as Stevens-Johnson syndrome (SJS) when treated with carbamazepine. The prevalence of HLA-B*1502 carrier is about 10% of 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 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 generalised 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 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.

Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (*e.g.* progressive skin rash often with blisters or mucosal lesions) are present, carbamazapine treatment should be discontinued.

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 carbamazapine, carbamazapine

must not be re-started in this patient at any time.

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 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 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 dermatological reactions

Mild skin reactions *e.g.* isolated macular or macropapular exanthemata, 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 to 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.

Carbamazepine may only be used after careful risk/benefit evaluation and with special care during the following conditions:

- haematological disturbances

- disturbed sodium metabolism

- severe cardiac, liver and kidney dysfunction

- pregnancy and lactation

- myotonic dystrophy, as cardiac conduction abnormalities are likely in these patients

Haematological events

The occurrence of agranulocytosis and aplastic anaemia has been associated with carbamazepine; however, due to the very low frequency it is difficult to estimate the risk. In the untreated population, the probability of occurrence is 4.7 cases/million/year for agranulocytosis and 2 cases/million/year for aplastic anaemia.

Blood counts, platelet count and serum biochemistry including iron and electrolytes should be checked before commencing treatment with carbamazepine. Blood counts should be performed on a monthly basis for the first five months. Thereafter 2-4 times a year.

Clinical monitoring is of primary importance during the entire treatment period. Carbamazepine must be discontinued, if severe leucopenia or thrombocytopenia appear.

A temporary or lasting lowering of the number of leukocytes or thrombocytes is often seen during carbamazepine treatment, but is usually transient and does not indicate

the onset of agranulocytosis or aplastic anaemia. However, carbamazepine must be discontinued if severe leucopenia (mainly neutropenia) or thrombocytopenia accompanied by clinical manifestations *e.g.* fever or sore throat or significant depression of the bone marrow appear.

If reactions such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric haemorrhage, nausea, yellowing of the skin, and liver enlargement appears, the patient should be advised to consult his physician immediately.

In patients with severe cardio-vascular disease, liver disease or renal damage and in older people a special observation is necessary. Doses should be adapted to each case.

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 absences. In case of exacerbation of absences, carbamazepine should be discontinued.

As with other antiepileptic drugs some patients may experience an increase in seizure frequency or the onset of new types of seizures. These phenomena may also be the consequence of an overdosage, a decrease in plasma concentrations of concomitant antiepileptic treatment, or a paradoxical effect.

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 older patients. Patients must be instructed to contact the doctor immediately should symptoms of hepatitis occur such as fatigue, loss of appetite, nausea, yellowing of the skin or enlarged liver. Treatment with carbamazepine should be suspended, if signs and symptoms of liver dysfunction develop.

Renal function

Baseline and periodic complete urinalysis and BUN determinations are recommended.

Hypersensitivity reactions

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, which can affect the skin, liver (including intrahepatic bile ducts), haematopoietic organs and lymphatic system or other organs, either individually or together in the context of a systemic reaction (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 25-30% of the patients experience hypersensitivity reactions to oxcarbazepine. Cross-hypersensitivity can occur between carbamazepine and phenytoin.

Treatment should be discontinued immediately, if severe hypersensitivity reactions occur.

Hyponatraemia

Hyponatraemia can occur when taking carbamazepine. In patients with pre-existing kidney disorders associated with low serum sodium concentrations, or in patients who are

being concomitantly treated with medicines that lower serum sodium concentration *e.g.* diuretics, the serum sodium concentration should be determined before treatment. The serum sodium concentration should be monitored after two weeks and then monthly for three months or according to the clinical necessity. Older patients are particularly susceptible to these risk factors and if hyponatraemia is diagnosed, water restriction is an important countermeasure.

Hypothyroidism

Carbamazepine can reduce serum thyroid hormone concentrations through enzyme induction, requiring an increased dose of hormone replacement therapy (HRT) in patients with hypothyroidism. Monitoring the thyroid function is recommended in order to adjust the HRT dose.

Due to the possibility of photosensitivity, patients should avoid excessive exposure to sunlight during carbamazepine therapy.

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 may precipitate seizures. Patients should be gradually weaned off carbamazepine over a period of a few months. If treatment with carbamazepine has to be withdrawn abruptly, the switch to another antiepileptic drug should if necessary be effected under the cover of a suitable drug *e.g. i.v.* or rectal benzodiazepines, or *i.v.* phenytoin.

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 (see section 4.6).

Precautions:

Patients with glaucoma and urinary retention should be informed about possible hazards associated with carbamazepine's mild anticholinergic activity. The intra-ocular pressure and kidney function of these patients should be checked regularly.

High doses of carbamazepine could result in activation of latent psychosis and possibly agitation or confusion in older patients.

Alcohol ingestion is not recommended, carbamazepine may increase its effects.

4.5 Interaction with other medicinal products and other forms of interaction

Cytochrome P450 inducers and inhibitors

Cytochrome P450 3A4 (CYP3A4) is the main enzyme catalysing formulation 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. Co-administration of CYP3A4 inducers might increase the rate of carbamazepine metabolism, thus leading to a potential

decrease in 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 strong inducer of CYP3A4 and other phase I and II enzyme systems in the liver. Concomitant use of carbamazepine may increase the metabolism and thus decrease the plasma concentrations of several drugs that are eliminated by metabolism.

It should be noted especially that rifampicin is known to also be a very strong inducer of CYP 450 and reduces carbamazepine levels.

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.

Monoamine oxidase inhibitors

Because it is structurally related to tricyclic antidepressants, it is not recommended to give carbamazepine in combination with monoamine oxidase inhibitors (MAOIs). MAOIs should be discontinued at least 2 weeks before carbamazepine therapy is started if the clinical situation permits (see section 4.3).

Drugs that may decrease carbamazepine plasma levels

The plasma level of carbamazepine may be decreased by other enzyme inducers such as:

Antiepileptics: phenobarbital, phenytoin, primidone, felbamate (~25%), methosuximide, oxcarbazepine, fosphenytoin, progabide, valpromide, valproic acid, phensuximide, and clonazepam

Antimalarials: mefloquine

Bronchodilatators or anti-asthma drugs: theophylline, aminophylline

Antituberculosis: rifampicin,

Antineoplastics: cisplatin or doxorubicin

Cardiovascular drugs: digoxin

Dermatological drugs: isotretinoin

Due to potential interactions during combination therapy of epilepsy, plasma levels should be regularly monitored, and dosage adjusted accordingly as required. Blood assays of their respective plasma levels may vary from one patient to another, and moreover are usually bi-directional.

Serum levels 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, which may persist for at least 2 weeks after cessation of treatment with St. John's wort. For patients taking St. John's wort, serum levels of carbamazepine should be monitored and St. John's wort stopped. Carbamazepine levels may increase on stopping St. John's wort. The dose of carbamazepine may need adjusting.

Drugs that increase the active metabolite carbamazepine-10,11-epoxide plasma levels

The plasma level of the active carbamazepine-10,11-epoxide metabolite may be increased by quetiapine, progabide, loxapine, valnoctamide, valpromide, valproic acid, felbamate (~50%), primidone, clonazepam and digoxin.

Drugs that may increase carbamazepine plasma levels

Raised plasma levels of carbamazepine may lead to the symptoms listed under section 4.8 *e.g.* dizziness, tiredness, unsteady gait, double vision. The carbamazepine plasma level should be checked and the dosage reduced, if necessary, when used concomitantly with:

Analgesic, anti-inflammatory drugs: dextropropoxyphene, propoxyphene, ibuprofen

Androgens: danazol

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

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

Antiepileptics: felbamate, lamotrigine, phenobarbital, primidone, stiripentol, vigabatrin

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

Antihistamines: loratadine, 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

Neuroleptics: loxapine, olanzapine, quetiapine

Platelet aggregation inhibitors: ticlopidine

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

Effect of carbamazepine on plasma levels of other drugs taken concomitantly

Carbamazepine may decrease, diminish or even abolish the activity of certain drugs. Concurrent use of carbamazepine with the following drug substances may require dose adjustment to ensure the required clinical response, especially when starting or discontinuing carbamazepine –

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

Antibiotics: doxycycline, rifabutin

Anticoagulants: oral anticoagulants (*e.g.* warfarin, phenprocoumon, dicoumarol and acenocoumarol)

Antidepressants: bupropion, citalopram, mianserin, sertraline, nefazodone, trazodone

Tricyclic antidepressants: imipramine, amitriptyline, nortriptyline, clomipramine

Antiemetics: aprepitant

Antiepileptics: clobazam, clonazepam, ethosuximide, felbamate, lamotrigine, oxcarbazepine, phenytoin, primidone, tiagabine, topiramate, valproic acid, zonisamide.

Antifungals: caspofungin, itraconazole, voriconazole. Alternative anitconvulsants may be recommended in patients treated with itraconazole or voriconazole

Anihelmintics: albendrazole, praziquantel

Antineoplastics: imatinib, cyclophosphamide, lapatinib, temsirolimus

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

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

Anxiolytics: alprazolam, midazolam, clobazam

Bronchodilatators or antiasthmatic drugs: theophylline

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

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

Corticosteroids: prednisolone, dexamethasone

Drugs used in erectile dysfunction: tadalafil

Immunosuppressants: ciclosporin, everolimus, tacrolimus, sirolimus

Thyroid agents: levothyroxine

Other drug interactions: quinidine, hydroquinidine, methylphenidate, propranolol, flunarizine, products containing oestrogens or progesterones (gestrinone, tibolone, toremifene)

Hormonal contraceptives

For products containing oestrogens and/or progestogens, including oral contraceptives and hormone replacement therapy (see section 4.4), reliable alternative contraceptive methods should be used. In patients taking the pill breakthrough bleeding or spotting may appear suddenly due to a decreased activity of the contraceptive. As a result, carbamazepine may cause a failure of the therapeutic effect of drugs containing oestrogens and/or progesterone containing drugs.

Carbamazepine may lower the plasma level of bupropion and may increase the level of its metabolite hydroxybupropion.

Other drug combinations to be taken into consideration

Concurrent use of carbamazepine and other psychotropic drugs, *e.g.* neuroleptics, antidepressants, sedatives, hypnotics, analgesics, sedative antihistaminics, may increase the occurrence of neurological side effects.

There is an indication of a higher risk of developing Stevens-Johnson syndrome with concomitant use of neuroleptics.

Co-administration of carbamazepine and paracetamol may reduce the bioavailability of paracetamol (acetaminophen) and long term co-administration may be associated with hepatotoxicity.

The concomitant use of carbamazepine and lithium or metoclopramide on the one hand and neuroleptics (haloperidol, thioridazine) on the other can favour the occurrence of neurological undesirable effects. In patients treated with neuroleptics, it must be noted that carbamazepine reduces the plasma levels of these medicinal products and can therefore cause worsening of the disease profile. Dosage adjustment of the neuroleptic may be necessary.

Risk of neurotoxic effects may be increased with concomitant use of carbamazepine

(ataxia) and lithium (cerebellar syndrome), despite the lithium plasma concentrations being in the normal range (see section 4.2). The following additional neurotoxic symptoms can be noted: unsteady gait, horizontal nystagmus, increased involuntary muscle reflexes, muscle twitching. These neurological effects are reversible after stopping the lithium.

The hepatic toxicity of isoniazid may be increased by carbamazepine.

The combination of carbamazepine with hypokalaemic diuretics (loop and thiazide diuretics) *e.g.* hydrochlorothiazide and furosemide, may cause hyponatraemia (see section 4.4).

Concomitant administration of carbamazepine and antiarrhythmics, cyclic antidepressants or erythromycin, increases the risk of cardiac conduction abnormalities.

The activity of muscle relaxants like pancuronium may be reduced by carbamazepine. A rapid recovery from neuromuscular blockade is therefore possible. Patients must be supervised accordingly and the dosage of the relaxant increased, if necessary.

Carbamazepine plasma levels must be checked during concurrent treatment with isotretinoin (acne treatment), as it has been reported to unpredictably alter the bioavailability of carbamazepine and its active metabolite.

Carbamazepine appears to increase the elimination of thyroid hormones and thus increase the hormone requirement of hypothyroid patients. A thyroid test should therefore be performed at the start and discontinuation of carbamazepine therapy in patients receiving thyroid hormone substitution. Dosage adjustment of thyroid hormone may be required.

A toxic serotonin-syndrome may be produced, if carbamazepine is taken together with drugs, which inhibit serotonin re-uptake (*e.g.* fluoxetine).

The severe haematological side effects of clozapine may be increased if used in combination with carbamazepine.

Concomitant use of carbamazepine and levetiracetam has been reported to increase carbamazepine-induced toxicity.

An increase in hypersensitivity (*e.g.* rash, hypereosinophilia) may occur when procarbazine is taken concurrently.

Carbamazepine, like other psychoactive drugs, may reduce alcohol tolerance. Therefore patients should abstain from alcohol during treatment.

Interference with serological examinations

Due to its interference with HPLC analysis, carbamazepine can lead to false positives for perphenazine concentrations. Carbamazepine and its 10,11-epoxide metabolite can lead to false positive concentrations of tricyclic antidepressants in fluorescence polarised immunoassay method.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk related to epilepsy and antiepileptic drugs in general:

It has been shown that in the offspring of epileptic women, the prevalence of malformations is two to three times greater than the rate of about 3% found in the general population. In the treated population an increase in malformed children has been noted with polytherapy, however the extent

to which the treatment and/or the illness are respectively responsible has not been elucidated as yet.

The most frequently encountered malformations are labial fusion defects and cardiovascular malformations.

Risk linked to carbamazepine:

Animal experiments have provided evidence of a teratogenic effect.

In humans, the number of women treated with carbamazepine in the first term trimester of pregnancy in the various prospective studies is still too limited for a firm conclusion to be drawn about whether this risk of malformation is real. However, some studies suggest that carbamazepine may cause an increase in neural tube closure anomalies, *e.g.* spina bifida, myelomeningocele (the risk reaches 1% which is 10-fold higher than the normal rate), malformations for which an antenatal diagnostic is possible and other congenital abnormalities *e.g.* craniofacial defects, cardiovascular malformations, hypospadias and anomalies involving various body systems.

Taking these data into consideration:

Carbamazepine may be used during pregnancy only after careful risk/benefit evaluation. Women of childbearing age should be advised of the necessity to plan and ensure supervision of pregnancy.

If a woman is pregnant or plans to become pregnant, the necessity of treatment should be reconsidered. In epilepsy, if possible, carbamazepine should be prescribed as a monotherapy, and minimum effective doses should be given, based on clinical response only. Monitoring of plasma concentrations of unbound carbamazepine may be useful (see section 4.2).

In women of childbearing age carbamazepine should, wherever possible, be prescribed as monotherapy, because the incidence of congenital abnormalities in the offspring of women treated with a combination of antiepileptic drugs is greater than in those of mothers receiving the individual drugs as monotherapy.

During the pregnancy, an effective antiepileptic carbamazepine treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Monitoring and prevention:

The prevention of neural tube anomalies by folic acid in pregnant women treated with carbamazepine is not fully demonstrated at present. However, taking into account that folic acid deficiency due to the enzyme induction caused by carbamazepine may be a contributory factor for foetal abnormality, it may therefore be beneficial to take folic acid before (2 months) and during pregnancy.

Patients should be informed of the increased risk of malformations and access to prenatal screening be made available. A specific antenatal diagnosis can be proposed even for women with a supplementary treatment of folic acid.

In the new-born child:

Enzymatic inducers have provoked:

Uncommon: bleeding disorders occurring in the first 24 hours of the life of a treated mother's child. Prevention by oral vitamin K1 to the mother, in the month prior to the birth, and an adapted dose to the new-born child at the moment of birth, seem appropriate.

Rarely: problems with the phosphocalcic metabolism and bone mineralisation.

A few cases of convulsions and/or respiratory depression in newborn babies have been reported, as well as some cases of vomiting, diarrhoea and/or reduced nutritional intake have been observed in connection with administration of antiepileptics. These could be signs of withdrawal syndrome in newborn babies.

Breast-feeding

Carbamazepine and its main metabolite, carbamazepine-epoxide, are both present in breast milk in concentrations of about 25 – 60 % of the total plasma concentration. Due to the possible onset of non-dose-dependent adverse effects in the neonate, breast-feeding is not recommended during treatment for safety reasons. Breast-feeding should be stopped if signs of sedation become apparent.

There are some reports of cholestatic hepatitis in newborn babies who were exposed to carbamazepine antenatally or during breast-feeding. As a result, breast-fed children whose mothers are being treated with carbamazepine should be carefully monitored for undesirable hepatobiliary effects.

Fertility

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

Women of child bearing age and contraception

Due to the adverse interactions of carbamazepine with oestrogen and/or progesterone containing drugs, an alternative method of contraception should be used (see section 4.5).

4.7 Effects on ability to drive and use machines

Carbamazapine has major influence on the ability to drive and use machines. It affects patients' reactions, causing dizziness, drowsiness, fatigue, ataxia, double vision, blurred vision, especially in the early stages of treatment. This may be further influenced by higher dose levels or the use of carbamazepine in combination with other centrally acting drugs or in conjunction with alcohol consumption. Patients should be warned of the possible hazards when driving or operating machinery.

4.8 Undesirable effects

The following undesirable effects appear dependent on the dose in particular at the start of therapy, too high initial dose or in older patients. These symptoms may abate spontaneously within a few days or if the dose is transiently reduced:

dizziness, headache, ataxia, drowsiness, fatigue, diplopia, 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 fractional doses.

Side effects listed according to organ system with the frequency estimate 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) and not known (cannot be estimated from the available data):

Infections and infestations

Not known: Reactivation of an infection with human herpes virus 6

Blood and lymphatic system disorders

Very common: Leucopenia

Common: eosinophilia, thrombocytopenia

Rare: Lymphadenopathy, leucocytosis

Very rare: Agranulocytosis, aplastic anaemia, pure red cell aplasia, anaemia, megaloblastic anaemia, reticulocytosis, haemolytic anaemia, enlarged spleen, pancytopenia

Not known: Bone marrow depression

According to literature sources the most frequent disorder is benign leucopenia, 10% of the cases being of a transient nature, 2% persistent.

Immune system disorders

Uncommon: Delayed multi-organ hypersensitivity disorder with fever, skin rashes, vasculitis, swollen lymph nodes, pseudolymphoma, painful joints (arthralgia), leucopenia, eosinophilia, hypogammaglobulinaemia, enlargement of liver and spleen or altered liver function tests and vanishing bile duct syndrome occurring in various combinations. Other organs such as lung, kidney, pancreas, colon and cardiac muscle may also be affected

Very rare: Generalised acute allergic reactions, anaphylactic reactions, angioedema, hypogammaglobulinaemia

Not known: Drug rash with eosinophilia and systemic symptoms (DRESS)

Endocrine disorders

Common: Weight gain, hyponatraemia

Metabolism and nutrition disorders

Common: Fluid retention

Rare: Folic acid deficiency, reduced appetite

Psychiatric disorders

Uncommon: Confusion and agitation in older patients, depressive disorders, aggressive behaviour, thinking difficulties, hallucinations (visual or auditory), activation of latent psychosis

Rare: Restlessness, mania

Very rare: Phobias

Nervous system disorders

Very common: Dizziness, somnolence, sedation, ataxia (atactic and cerebral disturbances)

Common: Headache

Uncommon: Lack of drive, involuntary movements like asterixis, tremor, dystonia or tics or nystagmus.

Rare: Dyskinetic disorders like orofacial dyskinesia, choreoathetosis, eye movement disturbances, speech disorders, paraesthesia, neuropathy peripheral, polyneuropathy, peripheral neuropathy, paresis

Very rare: Taste disturbances, neuroleptic malignant syndrome, aseptic meningitis with myoclonus and peripheral eosinophilia

Not known: Memory impairment

Eye disorders

Common: Accommodation disorders, diplopia

Rare: Lenticular opacities

Very rare: Conjunctivitis, retinotoxicity, cataracts

Ear and labyrinth disorders

Uncommon: Tinnitus

Very rare: Change in pitch perception, hypoacusis and hyperacusis

Cardiac disorders

Uncommon: Conduction disorders, AV-block, in isolated cases with syncope, bradycardia, cardiac arrhythmias, aggravation of coronary artery disease, congestive heart failure

Vascular disorders

Uncommon: Vasculitis

Rare: Hypertension, hypotension

Very rare: Thrombophlebitis, thrombo-embolism, circulatory collapse

Respiratory, thoracic and mediastinal disorders

Very rare: Pulmonary hypersensitivity reactions with fever, dyspnoea, pneumonitis or pneumonia (alveolitis), lung fibrosis

Gastrointestinal disorders

Very common: Nausea, vomiting

Common: Loss of appetite, dry mouth

Uncommon: Diarrhoea, constipation

Rare: Abdominal pain

Very rare: Stomatitis, gingivitis, glossitis, pancreatitis

Not known: Colitis

Hepatobiliary disorders

Rare: Jaundice, hepatitis (cholestatic, hepatocellular, granulomatous, mixed type), vanishing bile duct syndrome, liver failure

Skin and subcutaneous tissue disorders

Very common: Allergic skin reactions with or without fever like urticaria (which may be severe)

Uncommon: Pruritus, exfoliative dermatitis, erythroderma, alopecia, hyperhidrosis

Rare: Systemic lupus erythematosus

Very rare: Severe cutaneous adverse reactions (SCARS): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (see section 4.4), alterations in skin pigmentation, acne, hirsutism, photosensitivity, erythema exudativum, multiforme and nodosum, purpura, acute generalised exanthematous pustulosis (AGEP)

Not known: Lichenoid keratosis, onychomadesis

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).

Musculoskeletal and connective tissue disorders

Rare: Muscle weakness

Very rare: Arthralgia, muscle pain, muscle spasms, bone metabolism disorder

Not known: Fracture

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.

Carbamazepine may increase the metabolism of 25-OH-Cholecalciferol leading to a decreased calcium level, which rarely causes

osteomalacia, arthralgia, myalgia and muscle cramps.

Renal and urinary disorders

Uncommon: Renal impairment such as proteinuria, haematuria, oliguria, elevated BUN/azotaemia

Rare: Other micturition disorders like dysuria, pollakiuria, urinary frequency and urinary retention

Very rare: Renal failure, interstitial nephritis

Reproductive system and breast disorders

Rare: Gynaecomastia, galactorrhoea

Very rare: Sexual dysfunction like impotence, decreased libido and impaired male fertility and/or abnormal spermatogenesis (reduces sperm count and/or motility)

Congenital, familial and genetic disorders

Very rare: Porphyria acute (acute intermittent porphyria and variegate porphyria), porphyria non-acute (porphyria cutanea tarda)

General disorders and administration site conditions

Very common: Fatigue

Common: Oedema

Investigations

Very common: Elevated gamma-GT (due to hepatic enzyme induction), usually not clinically relevant

Common: Elevated alkaline phosphatase in the blood, reduced plasma osmolality due to an antidiuretic hormone (ADH)–like effect, leading in rare cases to water intoxication accompanied by lethargy, vomiting, headache, mental confusion, neurological abnormalities

Uncommon: Increased transaminases

Very rare: Elevated levels of cholesterol, including HDL cholesterol, and triglycerides, increased intraocular pressure, abnormal thyroid function tests: decreased L-Thyroxin (free thyroxine, thyroxine, tri-iodothyronine) and increased blood thyroid stimulating hormone, usually without clinical manifestations, blood prolactin increased, increase in serum cortisol

Carbamazepine may lower the plasma levels of folic acid and vitamin B12, and may increase the plasma level of homocysteine.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important.

4.9 Overdose

Carbamazepine overdose has been reported only with very high doses (4 - 20 g). Plasma levels were always above 20 µg/ml. A plasma level of 38 µg/ml was not lethal for the patient. Lethal cases of carbamazepine overdose have been reported in literature.

Symptoms

The presenting signs and symptoms of overdosage involve the central nervous, cardiovascular, gastrointestinal, musculoskeletal, renal or respiratory systems.

Central nervous system: CNS depression, disorientation, somnolence, agitation, hallucination, coma, stupor, vertigo, restlessness, confusion, blurred vision, slurred speech, dysarthria, nystagmus, ataxia, dyskinesia, initially hyperreflexia, later hyporeflexia; convulsions, psychomotor disturbances, myoclonus, opisthotonus,

involuntary movements, tremor, flushing, seizures, EEG dysrhythmia, hypothermia, mydriasis.

Respiratory system: Respiratory depression, pulmonary oedema, cyanosis, respiratory arrest.

Cardiovascular system: Tachycardia, changes in blood pressure (hypotension and at times hypertension), cardiac arrhythmias, AV block, cardiac arrest, flushing, conduction disturbance with widening of QRS complex; syncope in association with cardiac arrest.

Gastrointestinal system: Nausea, vomiting, delayed gastric emptying, reduced bowel motility.

Musculoskeletal system: Rhabdomyolysis

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, leucocytosis, leucopenia, neutropenia, glycosuria, acetonuria.

Management of symptoms

There is no specific antidote for carbamazepine overdose.

Management of symptoms due to overdosage will vary according to the patient's condition. This includes admission to hospital. Measurement of the plasma levels to confirm carbamazepine poisoning and to ascertain the size of the overdose. Evacuation of the stomach, gastric lavage, and administration of activated charcoal or laxative. Delayed evacuation of the stomach may lead to 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:

Hypotension: administer dopamine or dobutamine *i.v.*

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

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

Hyponatraemia (water intoxication): fluid restriction and slow careful NaCl 0.9 % infusion *i.v.*

These measures may be useful in preventing brain damage.

Charcoal haemoperfusion has been recommended. Haemodialysis is an effective option in the treatment of carbamazepine overdose. Forced diuresis, and peritoneal dialysis have been reported not to be effective.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptic

Mechanism of action

It is thought to block cyclic-AMP mediated calcium influx associated with transmitter release, and it is known to be an adenosine receptor antagonist: either of these actions might account for its antiepileptic action. Work in animals has shown that it has inhibitory effects on hippocampal discharges

and it also inhibits the reticulo-thalamic and thalamocortical projections which are involved in tonic-clonic seizures.

Antiepileptics have membrane-stabilising properties which have been found useful in the relief of neurogenic pain especially where there is a lancinating element, as in trigeminal neuralgia.

5.2 Pharmacokinetic properties

Absorption

Carbamazepine is almost completely absorbed but the rate of absorption is slow and may vary between patients.

Peak plasma concentrations of the unchanged active substance are attained within 24 hours. The bioavailability of carbamazepine has been shown to lie between 85 - 100 % and is unaffected by food.

Evaluation of literature allows the conclusion concerning therapeutic and toxic plasma levels that seizures are controlled at plasma levels between 4 and 12 µg/ml, levels above 20 µg/ml resulted in a deterioration of symptoms. Control of pain of trigeminal neuralgia was effective at plasma levels between 5 and 18 µg/ml. Side effects start appearing at plasma levels above 8–9 µg/ml.

Distribution

Carbamazepine is 70 - 80 % bound to plasma. The proportion of unbound carbamazepine is constant at a concentration of up to 50 µg/ml. The pharmacologically active metabolite carbamazepine-10,11-epoxide is bound to plasma protein at 48-53% (about 0.74 L/kg).

The concentration of carbamazepine in the cerebrospinal fluid is 33% of the current plasma concentration. The concentration of unchanged substance in the saliva represents the unbound portion in plasma, i.e. 20 - 30 % of total plasma concentration. In breast milk the concentration is 25 - 60% of total plasma concentration. Carbamazepine crosses the placental barrier. Apparent volume of distribution: 0.8 - 1.9 L/kg.

Biotransformation

Carbamazepine is extensively metabolised in the liver, mainly by oxidative pathways of which only the metabolite carbamazepine-epoxide is pharmacologically active. This may constitute up to 30 % of the circulating active material originality as carbamazepine. The inactive 10,11-diol represents the final stage of carbamazepine biotransformation. In children, the relatively high rate of metabolism of the drug may require higher dose (in mg/kg b.w.) of carbamazepine to maintain therapeutic concentrations.

Elimination

Only about 1 % of the administered dose is excreted in the urine in the unchanged form. A greater part is excreted in the urine almost entirely in the form of its metabolites; some is excreted in faeces.

Plasma clearance in healthy subjects is about 19.8 ± 2.7 ml/h/kg, in patients under monotherapy about 54.6 ± 6.7 ml/h/kg, in patients under combination therapy about 113.3 ± 33.4 ml/h/kg.

The elimination half-life of unchanged drug in the plasma averages approximately 36 hours following a single dose, whereas after repeated administration, it averages only 16 - 24 hours, depending on the duration of the medication. In patients receiving co-medication with other enzyme-inducing drugs such as phenytoin, phenobarbitone, half-life values averaging 9-10 hours have been observed.

Special population

Carbamazepine should be used with caution in patients with renal impairment.

In advanced hepatic disease, carbamazepine metabolism may be impaired.

The pharmacokinetics of carbamazepine are unaltered in older people but its metabolism may be affected by hepatic dysfunction. The controlled release formulation of carbamazepine produces a substantial reduction in intra-dose fluctuations in carbamazepine concentrations and tolerability and seizure control in patients with epilepsy may be improved.

The controlled release formulation should be considered in patients receiving high doses who suffer intermittent adverse effects such as diplopia, nausea, dizziness and tiredness and may offer the opportunity to reduce the dosage regimen.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, 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 2 years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no evidence that this observation is of importance for the therapeutic use of carbamazepine in humans.

Reproductive toxicity

In animal studies in mice, rats and rabbits oral administration of carbamazepine during organogenesis led to an increased embryo-foetal mortality and foetal growth retardation at daily doses which were associated with maternal toxicity (above 200mg/400mg/kg/day). Carbamazepine was teratogenic in a number of studies, particularly in mice, however showed no or only minor teratogenic potential at doses relevant to humans. In a reproductive study in rats, nursing offspring exhibited reduced weight gain at a maternal dosage level of 192 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

a) Each Controlled-release tablet contains:

Carbamazepine USP	200mg
Excipients	q.s.

b) Each Controlled-release tablet contains:

Carbamazepine USP	400mg
Excipients	q.s.

6.1 List of excipients
Ammonio methacrylate copolymer (type B) (contains: sorbic acid and sodium hydroxide), Methacrylic acid - ethyl acrylate copolymer (1:1) (contains: sodium laurilsulfate and polysorbate 80), Triacetin, Talc, Cellulose, microcrystalline, Crospovidone, Silica, colloidal anhydrous, Magnesium stearate

6.2 Incompatibilities
Not applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
No special precautions for storage

6.5 Nature and contents of container
Child-proof containers:

PVC/PVDC/Al blisters.

Pack sizes: Blisters: 7, 14, 28, 30, 50, 90, 100 and 500mg modified-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements

7. MANUFACTURED IN INDIA BY:

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