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Tel. : 95250 - 2455801 / 2452714 / 2453525 • Fax : 95250 - 2452074 (0091 - 250 - 2452074) • Email : agog@vsnl.net & agogpharma@rediffmail.com

Brand Name : **ZEPIN-400 PR TABLETS** **Generic Name** : Prolonged-Release Carbamazepine Tablets BP 400 mg		2021
Module 1 **1.5**	Administrative Information and Product Information Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

ZEPIN-400 PR TABLETS (Prolonged Release Carbamazepine Tablets BP 400 mg)

2. Qualitative and Quantitative Composition:

Each prolonged-release film coated tablet contains: Carbamazepine Tablets BP 400 mg

3. Pharmaceutical form:

White, elongated, film coated tablet having a breakline on one side and other side plain of each tablet.

4. Clinical particulars:

4.1 Therapeutic Indications:

Epilepsy

Carbamazepine can be used either alone or in combination with other antiepileptic drugs. It is useful in the treatment of generalized tonic-clonic and partial (simple and complex) seizures and it is also effective in mixed seizure types of childhood. It is not effective in the treatment of absence seizures associated with $3s^{-1}$ spike and wave in the electroencephalogram or in myoclonic seizures of childhood or adolescence. Treatment with carbamazepine is usually begun with a small dose which is then gradually increased until the desired therapeutic effect is obtained. Monitoring of the plasma carbamazepine concentration may be used as a means of obtaining an optimum dose and this may be especially indicated when carbamazepine is used in combined therapy. The aim should be to achieve a plasma carbamazepine concentration of between 17-50 µmol.1-1. If treatment in a patient is changed to carbamazepine, the dosage of the antiepileptic drug to be withdrawn should be tailed off gradually.

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Trigeminal neuralgia

Carbamazepine is the treatment of choice in trigeminal neuralgia. In epilepsy, carbamazepine is presumed to suppress abnormal excitability in neurons and it is believed that the same mechanism may be responsible for the observed analgesia in trigeminal neuralgia. The initial dose is usually 200 mg daily and may be slowly increased until attacks of pain are prevented. In some instances a dose of 1600 mg daily is necessary. Its effects begin 24-48 h after the initial dose. Minor adverse effects (anorexia, nausea, vomiting, headache, dizziness, drowsiness and visual disturbances) usually disappear with continued treatment. After a pain free month, treatment should be gradually reduced and discontinued in the absence of recurrence. If carbamazepine alone is not effective, it may be combined with other drugs such as phenytoin.

Mood disorder

Since the early 1970s, a number of open and controlled trials have established that carbamazepine is effective in the acute treatment of mania and the prophylaxis of bipolar mood disorders. It is particularly effective in a group of rapid cycling bipolar patients (four or more episodes per year). Several predictors of poor response to lithium (severity of mania, anxiety and dysphoria, rapid cycling and a negative family history) may be associated with good antimanic response to carbamazepine. In patients unresponsive to lithium therapy, a starting dose of 400 mg daily in divided doses is given, increasing gradually to a maximum dose of 1600 mg daily in divided doses. The usual effective dose range is 400-600 mg daily. It can used as an adjunct to lithium but the potential for enhanced neurotoxicity must be considered.

Aggression

Carbamazepine has been advocated for the control of aggression in both epileptic and non epileptic patients. Several uncontrolled studies have indicated that carbamazepine may be effective in decreasing aggressive behavior associated with dementia, developmental disabilities, schizophrenia and a variety of other organic brain disorders.

Diabetes insipidus

Since carbamazepine was found to have a beneficial effect on neurohypophysial diabetes insipidus, several studies have been carried out to investigate its efficacy and mechanism of action in this condition. In 1969 it was demonstrated that carbamazepine increased the concentration of antidiuretic hormone in the serum of diabetes insipidus patients.

The average dose for adult patients is 200 mg carbamazepine given two to three times daily. In children the dose should be determined according to body weight (10-20 $mg.kg^{-1}$). The antidiuretic effect appears within 24-36 h after start of therapy. Prolonged treatment has not reduced its effectiveness and the antidiuretic effect has continued for up to 2 months after withdrawal of carbamazepine therapy.

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4.2 Posology and Method of Administration:

Dosage in adults

The initial dose of carbamazepine is 100-200 mg once or twice daily and this is then gradually increased by 200 mg daily every week until seizure control or therapeutic plasma concentrations (20-40 $\mu mol.l^{-1}$) are achieved. The best response is often obtained with doses of 800-1200 mg daily. Higher doses may be necessary when it is combined with other enzyme inducing antiepileptic drugs. In some instances 1600 mg or even 2000 mg daily may be necessary.

Dosage in children

The dose in children is determined on the basis of body weight (10-20 $mg.kg^{-1}$) and age. Children 0 to 1 year old, 100-200 mg daily; 1 to 5 years, 200-400 mg daily; 6 to 10 years old, 400–600 mg daily; 11 to 15 years old, 600-1000 mg daily. The total dose should be given in two to four divided doses during the day.

Method of administration : Oral.

4.3 Contraindications:

1. Previous sensitivity to carbamazepine or structurally related drugs.
2. Atrioventricular conduction abnormalities
3. History of previous bone marrow depression or of intermittent porphyria.

4.4 Special Warnings and Precautions for Use :

Before initiating therapy, a detailed history and physical examination should be made.

Carbamazepin should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Carbamazepin has been associated with increased frequency of generalized convulsions.

Therapy should be prescribed only after critical benefit to risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic or hypersensitivity reaction to other drugs, including reactions to other anticonvulsants; or interrupted courses of therapy with Carbamazepin.

Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported. In some cases, hepatic effects may progress despite discontinuation of the drug.

Multi-organ hypersensitivity reactions occurring days to weeks or months after initiating treatment have been reported in rare cases.

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Discontinuation of carbamazepine should be considered if any evidence of hypersensitivity develops.

Hypersensitivity reactions to carbamazepine have been reported in patients who previously experienced this reaction to anticonvulsants including phenytoin and Phenobarbital. A history of hypersensitivity reactions should be obtained for a patient and the immediate family members. If positive, caution should be used in prescribing carbamazepine.

Since a given dose of Carbamazepin suspension will produce higher peak levels than the same dose given as the tablet, it is recommended that patients given the suspension be started on lower doses and increased slowly to avoid unwanted side effects.

Information for patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, as well as dermatologic, hypersensitivity or hepatic reactions. These symptoms may include, but are not limited to, fever, sore throat, rash, ulcers in the mouth, easy bruising, lymphadenopathy and petechial or purpuric hemorrhage, and in the case of liver reactions, anorexia, nausea/vomiting, or jaundice. The patient should be advised that, because these signs and symptoms may signal a serious reaction, that they must report any occurrence immediately to a physician. In addition, the patient should be advised that these signs and symptoms should be reported even if mild or when occurring after extended use.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

4.5 Interaction with other medicinal products, and other forms of interaction:

Potentially hazardous interactions

Oral anticoagulants

A patient who has been well stabilized on anticoagulant therapy while on carbamazepine may suffer a serious bleeding disorder if carbamazepine is suddenly withdrawn. The dose of the anticoagulant should be appropriately reduced when carbamazepine is withdrawn and the induction of microsomal drug metabolizing enzymes declines.

Oral contraceptives

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Women using oral contraceptive pills may become pregnant during therapy with carbamazepine. There is increased metabolism of the components of the pill due to induction of cytochrome P450 dependent enzymes in the liver. Midcycle spotting may be a warning sign that the effect of the pill is being interfered with. Women receiving carbamazepine should be given a contraceptive pill containing 50 µg of estrogen together with a high dose of progestogen or consider alternative non hormonal contraceptive methods.

Propoxyphene

Toxic effects of carbamazepine such as headaches, dizziness, ataxia and nausea have been observed in patients who were given propoxyphene as well. Propoxyphene interferes with the metabolism and clearance of carbamazepine.

Fluvoxamine

Addition of the hepatic enzyme inhibitor fluvoxamine to the treatment of patients taking carbamazepine has provoked symptomatic carbamazepine toxicity.

Monoamine oxidase inhibitors

Increased incidence of cardiac arrhythmias has been observed in patients treated with carbamazepine and monoamine oxidase inhibitors at the same time. The manufacturers recommend that carbamazepine should not be administered with, or within 2 weeks of cessation of, monoamine oxidase inhibitors.

Anticonvulsants

Several anticonvulsants cause induction of hepatic microsomal enzymes resulting in increased metabolism of other drugs. Phenytoin, Phenobarbital, primidone, methsuximide, ethosuximide and ethylphenacemide with decrease carbamazepine plasma concentrations while carbamazepine will induce the metabolism of phenytoin, valproic acid and lamotrigine.

Alcohol

Carbamazepine, like any other psychoactive drug, may reduce the patient's tolerance to alcohol. Patients should be advised to be extremely moderate with alcohol during treatment with the drug.

<u>Other significant interactions</u>

Carbamazepine has been observed to shorten the half life of doxycycline. Triacetyloleandomycin may increase the plasma carbamazepine concentration probably through enzymatic interaction. Salicylic acid can increase free carbamazepine concentration in plasma. The mechanism involved appears to be displacement from binding sites. Some anticonvulsant drugs have been shown to

affect calcium metabolism but there is only scanty evidence that carbamazepine affects the metabolism of vitamin D or calcium resulting in osteomalacia.

When lamotrigine is added to carbamazepine therapy, CNS adverse effects such as dizziness and diplopia become more common. It is thought that this is caused by pharmacodynamic interaction because no change in the metabolism of carbamazepine occurs.

Neurotoxic reactions have occurred when carbamazepinehas been used together with lithium in spite of the lithium being within the therapeutic range; the mechanism involved is yet to be elucidated.

4.6 Pregnancy and Lactation:

Pregnancy

If a woman taking carbamazepine becomes pregnant, the use of the drug should be very carefully reviewed to balance the need to control seizures in the mother with the risk to the fetus, especially in the first trimester. Minimum effective doses should be given in pregnancy and plasma levels monitored. Pregnancy decreases the plasma concentration of carbamazepine. This is largely the result of an increase in the rate of metabolism. It may therefore be necessary to increase the dose of carbamazepine during pregnancy in order to maintain a satisfactory clinical response. There are reports of possible teratogenic effects associated with maternal carbamazepine therapy. These include small head circumference, finger and toe nail hypoplasia and craniofacial defects. Folic acid supplementation is recommended before and during pregnancy. In addition, bleeding disorders in the newborn caused by antiepileptic agents have been reported. As a precaution, vitamin K should be administered in the last week of pregnancy and to the newborn.

Lactation

Carbamazepine and its main metabolite, carbamazepine epoxide, are both present in breast milk of nursing mothers in concentrations of between 30-60% of those in plasma. Breast feedings in not contraindicated, however, because the amount of drug ingested by the breast fed infant is too small to cause adverse pharmacological effects.

4.7 Effects on ability to drive and use machines:

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Carbamazepine Tablets refrain from driving or using machines.

4.8 Undesirable effects:

Most of the adverse effects commonly encountered in practice are dose related and transient and will disappear despite continuation of therapy.
Potentially life threatening effects

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Aplastic anemia has been associated with carbamazepine therapy but a definite cause effect relationship has not been established. In isolated cases, agranulocytosis has also been associated with carbamazepine. Fatal hepatitis resulting from carbamazepine therapy has been reported although the total number of reports is small. Severe exfoliative dermatitis, toxic epidermal necrolysis and Stevens Johnson syndrome, sometimes fatal, have also been reported in patients on carbamazepine therapy. A few cases of lupus erythematosus have occurred.

Severe or irreversible adverse effects

Generalized erythematous skin rashes occur commonly with carbamazepine, between 3 and 10% of patients receiving the drug for the first time are affected. Usually rashes are minor, involving particularly the hands, and pruritus may be prominent; sometimes a fixed drug eruption may be seen which disappears on reduction of the dose. Occasionally the rash may be widespread and associated with other manifestations of allergy such as fever, lymphadenopathy, disturbed hepatic function and jaundice. Transient leucopenia is observed commonly with carbamazepine but sometimes a low grade leucopenia with persist during treatment. This does not require withdrawal of treatment but should be monitored with regular hematological tests. Thrombocytopenia has also been reported. Intrahepatic cholestasis has also been reported.

Oliguria, hematuria, proteinuria and renal failure have been observed and are thought to be related to the antidiuretic effects of the drug. Bradycardia and heart failure may also result from therapy with carbamazepine. Water intoxication and hyponatremia caused by an increased circulating antidiuretic hormone level may be caused by carbamazepine, particularly with serum concentrations above the therapeutic range but this risk is less likely in patients on combined therapy with phenytoin because the latter drug induces carbamazepine metabolism and lowers the steady state serum concentration. There have been a few reports of acute interstitial pneumonitis in association with carbamazepine.

Symptomatic adverse effects

Carbamazepine is associated with a large number of symptomatic adverse effects and treatment need not be stopped when they appear. The most common symptoms include dizziness, ataxia, headaches, diplopia, drowsiness, nausea, vomiting and asthenia. These symptoms are usually dose related and will disappear with a reduction in dose.

4.9 Overdose:

Doses of up to 20 g are known to have been taken but no deaths have been reported. The symptoms of overdosage include erythema of the face, tremor, ataxia, psychomotor restlessness, changes in blood pressure muscle hypotonia, dilatation of the pupils, unconsciousness and convulsions. A prolonged P wave in the

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electrocardiogram may persist for 3 days. An electroencephalogram may show dysrhythmias in the occipital regions.

There is no specific antidose to carbamazepine toxicity. Measures to ensure adequate cardiorespiratory function should be taken first. Prevention of further absorption of the drug from the gastrointestinal tract may be achieved by gastric lavage and administration of activated charcoal. Cardiac monitoring should be carried out as well as careful correction of any electrolyte imbalance. Diazepam is indicated when convulsions occur. Delayed absorption can cause a relapse on the second or third day.

5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Carbamazepine is used in the treatment of generalized tonic-clonic as well as simple and complex partial seizures. It is not effective against absence seizures. Used as a sole agent in the treatment of partial seizures, carbamazepine has been shown to be as effective as phenytoin and valproate. Encouraging clinical improvement has also been observed in mood disorders and aggression. Carbamazepine has antidiuretic and antineuralgic effects.

5.2 Pharmacokinetic Properties:

There are several methods available for the determination of carbamazepine concentrations in biological fluids but those that are commonly used include the immunoassay techniques, gas liquid chromatography (GLC) with flame ionization detection and high pressure liquid chromatography (HPLC) with ultraviolet detection. The GLC and HPLC methods can be used to determine the concentration of both carbamazepine and its epoxide metabolite in biological fluids. The latter method has a limit of sensitivity for the parent compound of 20 $\mu g.1^{-1}$ and for the epoxide of 120 $\mu g.1^{-1}$.

There is no parenteral preparation of carbamazepine suitable for pharmacokinetic studies in humans but in animal experiments where oral and intravenous preparations of carbamazepine have been used the drug was found to be 58-80% biovailable and only 1% of the oral dose was recovered in feces suggesting a first pass effect. The gastrointestinal absorption of carbamazepine in humans has been estimated at between 72% and 96% with peak plasma concentrations occurring between 6 and 24 h. Solutions of carbamazepine are absorbed more completely and produce earlier and higher peaks than commercial tablets. Carbamazepine is lipophilic and once in the circulation it rapidly penetrates through cell membranes to gain access to various body tissues and fluids with an apparent volume of distribution of about $11.kg^{-1}$.

The concentration of Carbamazepine in brain is similar to that found in plasma, while in cerebrospinal and amniotic fluids it has been estimated at 17-31%, in brest milk

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about 60% and in saliva 20-30% of the concentrations found in plasma. The concentration of Carbamazepine epoxide in saliva was similar to that of the parent drug while in the cerebrospinal fluid it was 45-55% of that in plasma. Carbamazepine is about 75% bound to plasma proteins. Albumin as well as other plasma proteins are implicated in the binding of carbamazepine. Carbamazepine is eliminated in the urine mainly as metabolites and its elimination is faster in patients receiving other antiepileptic drugs in addition. Carbamazepine epoxide is about 90% absorbed and about 50% bound to plasma proteins. Its apparent volume of distribution is about 0.71 kg^{-1} with a plasma clearance of about 1.4 $ml.min^{-1}$ kg^{-1} and a half life of about 6 h.

In multiple dose studies plasma carbamazepine concentrations have been found to be 40-50% below the expected values. The low values are thought to be caused by increased carbamazepine metabolism resulting from autoinduction. The half life following a single dose is 30-40 h whereas on multiple dosing it is 11.7 h. Autoinduction has also been observed in babies born to mothers who were on carbamazepine during pregnancy. Hemodialysis increases plasma carbamazepine clearance from the usual 27.5 $ml.min^{-1}$ to 53.6 $ml.min^{-1}$.

Oral absorption	72-96%
Presystemic metabolism	----------
Plasma half life	
Range	30-40 h
Mean (epoxide)	35 h (6 H)
Volume of distribution	0.8-2 $l.kg^{-1}$
Plasma protein binding (epoxide)	54-80% (50%)

Concentration – effect relationship

Seizure control was observed in patients when carbamazepine concentrations were within 20-40 $\mu mol.l^{-1}$ (4.7-9.5 $mg.l^{-1}$). Plasma carbamazepine concentrations above 100 $\mu mol.l^{-1}$ (24.0 $mg.l^{-1}$) have produced unconsciousness in some patients. In patients with trigeminal neuralgia the optimum therapeutic effect has been observed at plasma carbamazepine concentrations between 24-42 $\mu mol.l^{-1}$ (5.7-10.0 $mg.l^{-1}$). The effective and toxic plasma concentrations of carbamazepine epoxide are similar to those of the parent compound.

Metabolism

Carbamazepine is extensively metabolized in the liver may only about 1% of the administered dose excreted in urine in the unchanged form. There are four main metabolic pathways involved and these have been described as follows.

Epoxidation of the 10,11-double bond of the azepine ring, hydroxylation of the six membered aromatic rings, direct N-glucuronidation at the carbamoyl side chain and substitution of the six membered rings with sulfur containing groups. The most important oxidative pathway involves the formation of a stable epoxide

(carbamazepine-10,11-epoxide) which possesses anticonvulsant activity similar to that of the parent compound.

5.3 Pre-clinical safety data:

Toxicity studies lasting up to 12 months in mice have shown no evidence of teratogenicity or mutagenicity. However, longer toxicity studies (up to 2 years) in female rats have indicated that Carbamazepine may be carcinogenic to the liver. There is evidence of teratogenicity, particularly when combined with sodium valproate. This may be caused by the 10, 11-epoxide metabolite.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Lactose	BP
Elegance EL-SR Base-II	BP
Polyvinyl pyrrolidone K-30 (Povidone)	BP
Iso Propyl Alcohol	BP
Magnesium stearate	BP
Colloidal Silicon Dioxide	BP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:
100 tablets packed in one Jar. Such jar packed in export worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:

AGOG PHARMA LTD.
Plot No. 33, Sector II,
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Co-Op. Estate Ltd., Gauraipada,
Vasai (E), Dist. Thane, India.

8. Manufacturer:

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Plot No. 33, Sector II,
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India.

9. Date of revision of the text :