## 1. NAME OF THE MEDICINAL PRODUCT

CARBAMAL-400 CR (CARBAMAZEPINE EXTENDED RELEASE TABLETS USP)

## 2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each Extended-Release Uncoated Tablet Contains:

| | |
|---|---|
| Carbamazepine USP | 400 mg |
| Excipients | Q.S |

## 3. PHARMACEUTICAL FORM

Oral Uncoated tablets

## 4. Clinical particulars

### 4.1 Therapeutic indications

Carbamazepine is indicated for:

- Epilepsy-generalised tonic-clonic and partial seizures.
- CARBAMAL-400 CR is indicated in newly diagnosed patients with epilepsy and in those patients who are uncontrolled or unable to tolerate their current anti-convulsant therapy.
- Note: Carbamazepine is not usually effective in absences (petit mal) and myoclonic seizures. Moreover, anecdotal evidence suggests that seizure exacerbation may occur in patients with atypical absences.
- The paroxysmal pain of trigeminal neuralgia.
- For the prophylaxis of manic-depressive psychoses in patients unresponsive to lithium therapy.

### 4.2 Posology and method of administration

Epilepsy:
Adults: It is advised that with all formulations of Carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. It may be helpful to monitor the plasma concentration of Carbamazepine to establish the optimum dose.
Elderly: Due to the potential for drug interactions, the dosage of Carbamazepine should be selected with caution in elderly patients.
Children: It is advised that with all formulations of Carbamazepine, a gradually increasing dosage scheme is used and this should be adjusted to suit the needs of the individual patient. It may be helpful to monitor the plasma concentration of Carbamazepine to establish the optimum dose.
Usual dosage 10-20mg/kg bodyweight daily in several divided doses.
Age up to 5 years:
5-10 years:
10-15 years: Carbamazepine Prolonged Release Tablets are not recommended
400-600mg daily
600-1000mg
Trigeminal neuralgia:
Slowly raise the initial dosage of 200-400mg daily (100mg twice daily in elderly patients) until freedom from pain is achieved (normally at 200mg 3-4 times daily). In the majority of patients a dosage of 200mg 3 or 4 times a day is sufficient to maintain a pain free state. In some instances, doses of 1600mg Carbamazepine daily may be needed. However, once the pain is in remission, the dosage should be gradually reduced to the lowest possible maintenance level.
For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy:
Initial starting dose of 400mg daily, in divided doses, increasing gradually until symptoms are controlled or a total of 1600mg given in divided doses is reached. The usual dosage range is 400-600mg daily, given in divided doses.

### 4.3 Contraindications

Known hypersensitivity to Carbamazepine or structurally related drugs (e.g. tricyclic antidepressants) or any other component of the formulation. Patients with atrioventricular block, a history of bone

marrow depression or a history of hepatic porphyrias (e.g. acute intermittent porphyria, variegate porphyria, porphyria cutaneatarda).The use of Carbamazepine is not recommended in combination with monoamine oxidase inhibitors (MAOIs)

## 4.4 Special warnings and precautions for use

Warning
Agranulocytosis and aplastic anaemia have been associated with CARBAMAL-400 CR. Decreased platelet or white blood cell counts occur occasionally to frequently in association with the use of CARBAMAL-400 CR. 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. Liver function tests should also be performed before commencing treatment. Severe hepatic reactions to Carbamazepine occur very rarely.

Precautions
CARBAMAL-400 CR 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 CARBAMAL-400 CR. Baseline and periodic complete urinalysis and BUN determinations are recommended.

## 4.5 Interaction with other medicinal products and other forms of interaction

Plasma levels of Carbamazepine increased by macrolide antibiotics, isoniazid, verapamil, danazol, fluvoxamine, grapefruit juice, azole antifungals, loratadine, ritonavir, diltiazem, fluoxetine, cimetidine. Carbamazepine may lower plasma levels of anticonvulsants, oral contraceptive, oral anticoagulants, digoxin, cyclosporine, levothyroxine, dehydropyridine calcium channel blockers, doxycycline, TCAs, estrogens/progestrogens, corticosteroids, benzodiazepines, haloperidol, protease inhibitors for HIV treatment, olanzapine, risperidone. Plasma levels of Carbamazepine may be reduced by phenytoin, Phenobarbital, rifampin, oxcarbazepine, St.John'sWort, valproic acid, phesuximide. Combined use of Carbamazepine with lithium or haloperidol may increase risk of neurotoxic side effects.

## 4.6 Pregnancy and Lactation

Pregnancy
In women of childbearing age CARBAMAL-400 CR 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 pregnancy, an effective antiepileptic treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the fetus. Folic acid deficiency is known to occur in pregnancy. Antiepileptic drugs have been reported to aggravate deficiency.

Lactation
Carbamazepine passes into the breast milk (about 25-60% of the plasma concentrations). The benefits of breast-feeding should be weighed against the remote possibility of adverse effects occurring in the infant. Mothers taking CARBAMAL-400 CR may breast-feed their infants, provided the infant is observed for possible adverse reactions (e.g. excessive somnolence, allergic skin reaction).

## 4.7 Effects on ability to drive and use machines

The patient's ability to react may be impaired by the medical condition resulting in seizures and adverse reactions including dizziness, drowsiness, ataxia, diplopia, impaired accommodation and blurred vision reported with Carbamazepine Extended Release tablets 400 mg, especially at the

start of treatment or in connection with dose adjustments. Patients should therefore exercise due caution when driving a vehicle or operating machinery.

## 4.8 Undesirable effects

Drowsiness, headache, ataxia, vertigo, fatigue, diplopia, dizziness, nausea, vomiting, allergic skin reactions, edema, fluid retention, dry mouth, leucopoenia, eosinophilia. Rarely, serious hematologic, hepatic, cardiovascular and dermatologic reactions (stop therapy).

## 4.9 Overdose

**Overdose**

CNS depression; disorientation, depressed level of consciousness, somnolence, agitation, Respiratory depression, pulmonary oedema, Tachycardia, hypotension and at times hypertension, Vomiting, delayed gastric emptying, reduced bowel motility, rhabdomyolysis, Retention of urine, oliguria or anuria; fluid retention, water intoxication, Hyponatraemia, possibly metabolic acidosis, possibly hyperglycemia, increased muscle creatine phosphokinase.

**Treatments**

There is no specific antidote. Management should initially be guided by the patient's clinical condition; admission to hospital. Measurement of the plasma level to confirm Carbamazepine poisoning and to ascertain the size of the overdose. Evacuation of the stomach, gastric lavage, and administration of activated charcoal.

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent; Dibenzazepine derivative.
ATC code: N03AF01.
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 from the tablets is slow and may vary amongst the various formulations and between patients. Peak concentrations of active substance in the plasma are attained within 24 hours of administration of single dose of Carbamal-400 CR. The prolonged release formulation shows about 15% lower bioavailability than standard preparations due mainly to the considerable reduction in peak plasma levels occasioned by prolonged release of the same dosage of carbamazepine. Plasma concentrations show less fluctuation but auto-induction of carbamazepine occurs as with standard carbamazepine preparations.
The bioavailability of Carbamal-400 CR in various oral formulations has been shown to lie between 85-100%.
Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of Carbamal-400 CR.
Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

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

**Distribution**
Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma (20-30%). Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels.
Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

**Biotransformation**
Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites.
Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.
Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

**Elimination**
The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours (auto-induction of the hepatic mono-oxygenase system), depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.
The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.
After administration of a single oral dose of 400mg 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.
Characteristics in patients
The steady-state plasma concentrations of carbamazepine considered as "therapeutic range" vary considerably inter-individually; for the majority of patients a range between 4-12µg/ml corresponding to 17-50µmol/l has been reported. Concentrations of carbamazepine 10, 11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.
Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.
There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.
No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

## 5.3 Preclinical safety data

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

Carcinogenicity
In rats treated with carbamazepine for two years, there was an increased incidence of hepatocellular tumours in females and benign testicular tumours in males. However, there is no

evidence to date that these observations are of any relevance to the therapeutic use of carbamazepine in humans.

Reproductive toxicity
In animals studies in mice, rats and rabbits oral administration of carbamazepine during organogenesis led to increased embryo-fetal mortality and fetal growth retardation at daily doses which were associated with maternal toxicity (above 200mg/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 reproduction study in rats, nursing offspring demonstrated a reduced weight gain at a maternal dosage level of 192 mg/kg/day.

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

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Hydroxy propyl methyl cellulose K4M,
Lactose,
Dibasic calcium phosphate,
Maize Starch,
Povidone K-30,
Isopropyl Alcohol,
Purified Talc,
Magnesium Stearate

### 6.2 Incompatibilities
Not applicable

### 6.3 Shelf life
24 months for the date of manufacturing.

### 6.4 Special precautions for storage
Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

### 6.5 Nature and contents of container<and special equipment for use, administration or implantation>

10 X 10 Tablets in Alu-Alu Blister pack

### 6.6 Special precautions for disposal <and other handling>
There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 <APPLICANT/MANUFACTURER>
**STALLION LABORATORIES PVT. LTD.**
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Dist: Ahmedabad-382220, Gujarat, India