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For the use only of a Registered medical practitioner or a Hospital or a Laboratory

OLEPTAL

(Oxcarbazepine Tablets, 300 mg & 600 mg)

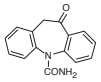
COMPOSITION

OLEPTAL 300: Each film coated tablet contains Oxcarbazepine……..300 mg

OLEPTAL 600: Each film coated tablet contains Oxcarbazepine……..600 mg

PROPERTIES

Oxcarbazepine is a white to faintly orange crystalline powder. It is slightly soluble in chloroform, dichloromethane, acetone and methanol and practically insoluble in ethanol, ether and water. Chemically it is 10,11-Dihydro-10-oxo-5H- dibenz [b,f]azepine-5-carboxamide,with the empirical formula $C_{15}H_{12}O_2N_2$ and molecular weight 252.27. Its structural formula is:



CLINICAL PHARMACOLOGY

MECHANISM OF ACTION

The pharmacological activity of oxcarbazepine is primarily exerted through the 10- monohydroxy metabolite (MHD) of oxcarbazepine. The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce blockade of voltage sensitive sodium channels, resulting in stabilization of hyper excited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high voltage activated calcium channels may contribute to the anticonvulsant effects of the drug.

PHARMACOKINETICS

Absorption

Following oral administration, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active metabolite MHD. The maximum plasma concentration (C_{max}) of oxcarbazepine of approximately 1mg/L is reached within the first hour and C_{max} for MHD is 4.6mg/L after a median T_{max} of 8 hours.

Steady state plasma concentrations of MHD are reached within 2-3 days in patients when oxcarbazepine is given twice a day. At steady state the pharmacokinetics of MHD is linear and shows dose proportionality over the dose range of 300 to 2400mg/day.

Distribution

Oxcarbazepine and its metabolite are widely distributed in the body. The apparent volume of distribution of MHD is 49L. About 40% of MHD are bound to serum proteins, predominantly to albumin.

Metabolism

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of oxcarbazepine. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD). In contrast to carbamazepine, MHD does not form neurotoxic epoxide metabolite.

Elimination

The half life of oxcarbazepine is about 2 hours, while the half life of MHD is about 9 hours, so that MHD is responsible for most anti-epileptic activity. Oxcarbazepine is cleared from the body mostly in the form of metabolites, which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

Special Populations

Hepatic impairment

Mild to moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment is recommended in these patients. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment.

Renal impairment

Mild to moderate renal impairment in adults has little effect on plasma MHD concentrations. However, in patients with renal failure (creatinine clearance <30ml/min), the elimination half-life of MHD is prolonged; with a two fold increase in AUC. Hence dosage of oxcarbazepine should be adjusted in patients with severe renal impairment.

Pediatric Use

After a single dose administration of 5 or 15mg/kg of oxcarbazepine, the dose adjusted AUC values of MHD is 30%-40% lower in children below the age of 8 years than in children above 8 years of age. The clearance in children greater than 8 years old approaches that of adults. Hence higher doses of oxcarbazepine may be required in children younger than 8 years.

Geriatric Use

Following administration of single (300mg) and multiple (600mg/day) doses of oxcarbazepine to elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD are 30%-60% higher than in younger volunteers (18-32 years of age).

INDICATIONS

OLEPTAL is indicated for use as a monotherapy and adjunctive therapy in the treatment of partial seizures in adult patients with epilepsy. It is also indicated as adjunctive therapy in the treatment of partial seizures in children in the age group of 4 – 16 years with epilepsy.

CONTRAINDICATIONS

OLEPTAL should not be used in patients with a known hypersensitivity to oxcarbazepine or to any of its components.

WARNINGS

Hyponatraemia

Clinically significant hyponatraemia generally occurred during the first three months of treatment with oxcarbazepine. Measurement of serum sodium levels should be considered for patients during maintenance treatment with oxcarbazepine, particularly if the patient is receiving other medications known to decrease serum sodium levels or if symptoms possibly indicating hyponatremia develop.

Patients with a past history of Hypersensitivity Reaction to Carbamazepine

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25-30% of them will experience hypersensitivity reactions with oxcarbazepine. If signs or symptoms of hypersensitivity develop, oxcarbazepine should be discontinued immediately.

Withdrawal of Antiepileptic drugs(AEDs)

As with all antiepileptic drugs, oxcarbazepine should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

Cognitive/Neuropsychiatric Adverse effects

Use of oxcarbazepine has been associated with central nervous system related adverse events. The most significant of these can be classified into three general categories:

1) Cognitive symptoms including psychomotor slowing, difficulty with concentration and speech or language problems
2) Somnolence or fatigue, and
3) Coordination abnormalities, including ataxia and gait disturbances.

Use In Pregnancy, Nursing Mothers And Children

Pregnancy

Safety of oxcarbazepine is not established during pregnancy. It should be used during pregnancy only if the potential benefit outweighs the potential risk of the fetus.

Nursing mothers

Oxcarbazepine and MHD are excreted in breast milk. Milk to plasma concentration ratio is about 0.5 for both. Because of the potential for serious reactions in nursing infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother.

Pediatric use

Oxcarbazepine is not recommended in children below 2 years of age.

Effect on ability to drive and operate machinery

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

ADVERSE EFFECTS

Oxcarbazepine is generally very well tolerated by majority of patients. As compared to carbamazepine, adverse effects are less frequent and less severe with oxcarbazepine therapy. The adverse effect profile of oxcarbazepine is similar in adults and children when used as monotherapy or adjunctive therapy.

The most commonly reported adverse effects of oxcarbazepine therapy are: Dizziness, somnolence, fatigue, nausea, vomiting, diplopia, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, gait disturbances, difficulties with coordination and marked hyponatraemia.

DRUG INTERACTIONS

Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. Several AED's that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

Antiepileptic drugs

Phenobarbital, phenytoin, carbamazepine, and valproate significantly decrease in MHD concentrations by 25%, 30%, 18% and 40% respectively.

Hormonal contraceptives

Concurrent use of oxcarbazepine with hormonal contraceptives has been shown to influence the plasma concentration of the two hormonal components, ethinylestradiol and levonorgestrel and may render these contraceptives less effective.

Calcium Antagonists

Calcium antagonists and oral contraceptives are resulting in a lower plasma concentration of these drugs. Oxcarbazepine may affect thyroid test.

Verapamil produces a 20% decrease of the plasma levels of MHD.

Alcohol and CNS depressants

CNS depression can be potentiated when alcohol or other CNS depressants are given with oxcarbazepine.

DOSAGE AND ADMINISTRATION

OLEPTAL is recommended as adjunctive and monotherapy in the treatment of partial seizures in adults and as adjunctive treatment for partial seizures in children 4 -16 years of age group. All dosing should be given in a twice a day (BID) regimen and can be given with or without food.

ADULTS

Adjunctive Therapy

Treatment with ***OLEPTAL*** should be initiated with a dose of 600mg/day, given in a BID regimen. If clinically indicated, the dose may be increased by a maximum of 600mg/day at approximately weekly intervals up to 1200mg/day in two divided doses.

Initiation of Monotherapy

Patients not currently being treated with AEDs may have monotherapy initiated with ***OLEPTAL***. In these patients, ***OLEPTAL*** should be initiated at a dose of 600mg/day (given in a BID regimen); the dose should be increased by 300mg/day every third day or 600mg/day at weekly intervals up to 1200mg/day in two divided doses. The dosage can be increased to a maximum of 2400mg/day.

A lower starting dose (150 BID) and slower titration may be considered for more sensitive patients.

Conversion to Monotherapy

Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with Oxcarbazepine at 600mg/day (given in a BID regimen) while simultaneously initiating the reduction of the dose of the concomitant AEDS. The concomitant AEDs should be completely withdrawn over 3-6 weeks, while the maximum dose of oxcarbazepine should be reached in about 2-4 weeks. Oxcarbazepine may be increased as clinically indicated by a maximum increment of 600mg/day at approximately weekly intervals to achieve the recommended daily dose of 2400mg/day.

When oxcarbazepine is substituted for carbamazepine, a suggested oxcarbazepine dose is 300 mg for each 200mg of carbamazepine.

PEDIATRIC PATIENTS

< 2 years: Not recommended

4-16 years:

Adjunctive therapy

Treatment should be initiated at a daily dose of 8-10 mg/kg generally not to exceed 600mg/day, given in a BID regimen. The target maintenance dose of oxcarbazepine should be achieved over 2 weeks, and is depend upon patient's weight, according to the following chart:

Weight (kg)	Maintenance Dose (mg/day)
20-29	900
29.1-39	1200
>39	1800

Younger children (age < 8 years) have an increased clearance (by about 30-40%) compared with older children and adults. Pediatric patients 8 years old and below received the highest maintenance doses.

PATIENTS WITH RENAL IMPAIRMENT

In patients with impaired renal function (creatinine clearance < 30ml/min) Oxcarbazepine therapy should be initiated at one-half the usual starting dose (300mg/day) and increased slowly to achieve the desired clinical response.

OVERDOSAGE

Overdose is rarely observed with Oxcarbazepine. There is no specific antidote. In case of overdose symptomatic and supportive treatment should be given. Removal of the drug by gastric lavage and/or inactivation by administering activated charcoal should be considered.

EXPIRY DATE

Do not use later than expiry date.

STORAGE

Store below 30^{0}C.

PRESENTATION

OLEPTAL 300: It is available as yellow coloured round biconvex, film coated tablets with break line on one side and plain on other side, in blister of 10 tablets.

OLEPTAL 600: It is available as yellow coloured, biconvex capsule shaped film coated tablets with break line on one side and plain on other side in blister of 10 tablets.

torrent PHARMA

Manufactured by :
TORRENT PHARMACEUTICALS LTD.
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