PRESCRIBING INFORMATION : For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

ZENOXA OD-300

(Oxcarbazepine sustained release tablets 300 mg)

COMPOSITION

ZENOXA OD-300

Each film coated sustained release tablet contains:
Oxcarbazepine 300 mg
Colour : Ferric Oxide Yellow & Titanium Dioxide
Excipients : Q.S.

DESCRIPTION

Oxcarbazepine is an orally administered antiepileptic drug (AED). Oxcarbazepine is a keto analogue of carbamazepine and has a more favorable pharmacokinetic profile. Its chemical name is 10,11-Dihydro-10-oxo-5H-dibenz[b,*f*]azepine-5-carboxamide.
Its molecular formula is $C_{15}H_{12}N_2O_2$ and molecular weight is 252.27.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

The antiseizure activity of oxcarbazepine is primarily exerted through its 10-monohydroxy metabolite (MHD). In the rodents, oxcarbazepine and MHD abolish the tonic hind limb extension component of the maximal electroshock-induced seizure. To a lesser degree they also protect these animals against chemoconvulsant-induced clonic seizures. In addition, chronically recurring focal seizures in the Rhesus monkeys with aluminium implants are abolished or their frequency is reduced. Clinically, oxcarbazepine is as effective as carbamazepine, phenytoin, and valproate in controlling simple and complex partial seizures with or without secondary generalisation.
The mechanism of action of oxcarbazepine and MHD appears to be mainly based on blockade of voltage-sensitive sodium channels, thus resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminishment of propagation of synaptic impulses. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may also contribute to the anticonvulsant effects of the drug.

PHARMACOKINETICS

Absorption

After ingestion, oxcarbazepine from ZENOXA OD-300 is absorbed in a slow and sustained manner. As such, oxcarbazepine is completely absorbed and extensively converted to its active metabolite MHD (10,11-dihydro-10-hydroxy-carbamazepine). This metabolite is present in the plasma at much higher concentrations than the parent drug. Food has no effect on the rate or extent of absorption of oxcarbazepine.

Distribution

Oxcarbazepine exhibits first-order linear kinetics during long-term administration. The reported apparent volume of distribution of MHD is 49L. About 40% of MHD is bound to plasma proteins, mainly 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 are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

Elimination

Elimination half-lives are about 2 hours for oxcarbazepine and 9 hours for racemic MHD. Approximately 96% of the dose of oxcarbazepine is excreted via the kidneys either as glucuronides of MHD or as unchanged MHD; but <1% appears in the urine as unchanged drug and also very little amount of drug excreted via fecal route.

SPECIAL POPULATIONS

In hepatic impairment

Mild to moderate hepatic impairment does not affect the pharmacokinetic of oxcarbazepine and MHD. No dose adjustment for oxcarbazepine is recommended in patients with mild to moderate hepatic impairment. The Pharmacokinetic of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment.

In renal impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. The elimination half-life of MHD is prolonged by 60-90 % (16 to 19 hours), with two-fold increase in AUC in renally impaired patients (creatinine clearance <30 mL/min). Dose adjustment for oxcarbazepine is recommended in these patients.

Pediatric use

ZENOXA OD-300 has not been evaluated in pediatric patients, hence, not recommended for use in them.

Geriatric use

In elderly patients the maximum plasma concentrations and AUC values of MHD are 30%-60% higher than younger volunteers and this difference is due to age-related reduction in creatinine clearance. The dosage of oxcarbazepine is individually titrated to achieve the desired therapeutic end-point, so these age-related differences probably have minimum clinical implications.

INDICATIONS

ZENOXA OD-300 is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

CONTRAINDICATIONS

ZENOXA OD-300 should not be used in patients with a known hypersensitivity to oxcarbazepine or to any other ingredients present in the formulation.

DOSAGE AND ADMINISTRATION

Adults

Monotherapy and Adjunctive therapy

In mono- and adjunctive therapy, treatment with ZENOXA OD-300 is initiated with 2 tablets given once a day. For monotherapy the dose should be increased by every 3 day by an increment of 1 tablet of ZENOXA OD-300 once a day to a dose of 1200 mg/day. If clinically indicated for adjunctive therapy the daily dose may be increased progressively through addition of 150–600 mg/day as required at weekly intervals, until the desired response is achieved. The maximum dose of ZENOXA OD-300 is 2400 mg/day.
It is recommended that the patient be observed closely and plasma levels of the concomitant anti-epileptic drugs (AEDs) be monitored during the period of ZENOXA OD-300 dose titration, as these plasma levels may be altered, especially at ZENOXA OD-300 doses greater than 1200 mg/day.

Patients who are on oxcarbazepine immediate-release formulation with/without other AEDs

Conventional oxcarbazepine preparation should be replaced by ZENOXA OD-300 (switched over) in equal doses. If clinically indicated (as per the discretion of the physician) the dose may be suitably modified. The maximum dose of ZENOXA OD-300 is 2400 mg/day.

Elderly

Adjustment of the dose is recommended in the elderly with compromised renal function.

Patients with Hepatic Impairment

No dosage adjustment is required for patients with mild to moderate hepatic impairment. Oxcarbazepine has not been studied in patients with severe hepatic impairment.

Patients with Renal Impairment

In patients with impaired renal function ZENOXA OD-300 therapy should be initiated at half the usual starting dose (300 mg/day) and increased, in at least weekly intervals, to achieve the desired clinical response. Dose escalation in renally impaired patients may require more careful observation.

Administration and Compliance

ZENOXA OD-300 can be taken with or without food. Tablets are to be swallowed whole and not to be crushed or chewed.

WARNINGS

Hypersensitivity reactions

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25 - 30% of these patients may experience hypersensitivity reactions (e.g. severe skin reactions) with oxcarbazepine. Hypersensitivity reactions may also occur in patients without history of hypersensitivity to carbamazepine. In general, if signs and symptoms suggestive of hypersensitivity reactions occur, ZENOXA OD-300 should be discontinued immediately.

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Department	PMQC	R.A.	Packing Dev.	Q.A.	Head Q.A.
Signature					
Date					

Product Name : Zenoxa OD
Size : 140 x 210 (mm)
Folding Size : 140 x 30 (mm)
No. of Col. : 1
Date : 08/12/15

File name : 85 820 0 8805232-Zenoxa OD-PIL
Col. Shade No. : Pantone Black

Hyponatremia
Clinically significant hyponatremia (sodium <125 mmol/L) can develop during oxcarbazepine use. There is a higher chance of development of hyponatremia in pre-existing renal conditions associated with low sodium or in patients treated concomitantly with sodium-lowering drugs (e.g. diuretics, desmopressin) as well as non-steroidal anti-inflammatory drugs (e.g. diclofenac), and elderly patients. Therefore serum sodium levels should be measured prior to initiating therapy, after approximately two weeks and then at monthly intervals for the first three months during therapy.

Withdrawal of antiepileptic drug
As with all antiepileptic drugs, ZENOXA OD-300 should be withdrawn gradually to minimize the possibility of increased seizure frequency.

PRECAUTIONS

Very rare cases of hepatitis have been reported, which in most of the cases resolved favorably. When a hepatic event is suspected, liver function should be evaluated and discontinuation of oxcarbazepine should be considered.
Female patients of childbearing age should be warned that the concurrent use of ZENOXA OD-300 with hormonal contraceptives might render this type of contraceptive less effective due to drug interaction. Therefore, additional non-hormonal forms of contraception are recommended when using oxcarbazepine.
Caution should be exercised if alcohol is taken in combination with ZENOXA OD-300 therapy, due to a possible additive sedative effect.

Carcinogenesis / mutagenesis / impairment of fertility
Animal toxicity studies carried out in the rats and mice indicated that both oxcarbazepine and MHD have some carcinogenic and mutagenic potential in these species when administered in amounts several times higher than the maximum recommended dosage in humans. Similarly, very high amounts of MHD were found to adversely affect fertility in female rats.

Pregnancy
There are no adequate and well-controlled clinical studies of oxcarbazepine in pregnant women. However, structurally oxcarbazepine is closely related to carbamazepine, which is considered to be teratogenic in humans. Data on a limited number of pregnancies indicate that oxcarbazepine may cause serious birth defects (e.g. cleft palate) when administered during pregnancy. If women receiving oxcarbazepine become pregnant, or if the need to initiate treatment with oxcarbazepine arises during pregnancy, the drug's potential benefits must be carefully weighted against the potential risk of foetal malformations. This is particularly important during the first three months of pregnancy. Minimum effective doses should be given.

Nursing mothers
Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 is found for both. Because of the potential for serious adverse reactions to oxcarbazepine 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 mother.

Laboratory tests
Serum sodium levels <125 mmol/L has been observed in patients treated with oxcarbazepine. Laboratory data from clinical trials suggest that oxcarbazepine use was associated with decreases in T_4, and without changes in T_3 or TSH.

DRUG INTERACTIONS

Enzyme inhibition
Oxcarbazepine and its active metabolite MHD inhibit the CYP2C19. Therefore, the plasma concentration of drugs which metabolized by CYP2C19 (e.g. phenobarbitone, phenytoin) are increasing when concomitantly administered with oxcarbazepine. A reduction of dose of co-administered drugs might be necessary.

Enzyme induction
Oxcarbazepine and MHD induce *in vitro* and *in vivo*, the cytochromes CYP3A4 and CYP3A5 responsible for the metabolism of dihydropyridine calcium antagonists, oral contraceptives(e.g. ethinylestradiol and levonorgestrel) and AEDs (e.g. carbamazepine) resulting in a lower plasma concentration of these medicinal products.

In vitro, MHD is a weak inducer of UDP-glucuronyl transferase and, therefore, *in vivo* it is unlikely to have an effect on drugs, which are mainly eliminated by conjugation through the UDP-glucuronyl transferases (e.g. valproic acid, lamotrigine). Even in view of the weak induction potential of oxcarbazepine and MHD, a higher dose of concomitantly used drugs that are metabolized via CYP3A4 or via conjugation (UDPGT) may be necessary. In the case of discontinuation of oxcarbazepine therapy, a dose reduction of the concomitant medication may be necessary.

No autoinduction has been observed with oxcarbazepine.

Calcium antagonists
After repeated co-administration of oxcarbazepine, the AUC values of felodipine are lowered. However, the plasma levels remain in the recommended therapeutic range. On the other hand, verapamil produces a decrease of the plasma levels of MHD. This decrease in plasma levels of MHD is not considered to be of clinical relevance.

Other drug interactions
Results with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.
On theoretical grounds (structural relationship to tricyclic antidepressants) the use of oxcarbazepine is not recommended in combination with monoamine-oxidase inhibitors (MAOIs). The combination of lithium and oxcarbazepine might cause enhanced neurotoxicity.

ADVERSE REACTIONS
The following are most common adverse reactions in oxcarbazepine treated patients: Dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

In addition, the following adverse events have been reported uncommonly with oxcarbazepine:
Body as a whole: asthenia
Central nervous system (CNS): headache, agitation, amnesia, apathy, impaired concentration, confusion, depression, emotional liability (e.g. nervousness), nystagmus
Cardiovascular system: arrhythmia (e.g. AV-block)
Digestive system: constipation, diarrhoea
Liver: increase in transaminases and alkaline phosphatase
Metabolic and nutritional disorders*:* hyponatremia,
Skin and appendages: acne, alopecia, rash
Special senses*:* vertigo

OVERDOSAGE
Isolated cases of overdose with oxcarbazepine have been reported. The maximum dose taken is approximately 2400 mg. All patients recovered with symptomatic treatment.

There is no specific antidote. Symptomatic and supportive treatment should be administered as appropriate. Removal of the drug by gastric lavage and/or inactivation by administrating activated charcoal should be considered.

STORAGE
Store in a cool dry place, protected from light.

PRESENTATION
ZENOXA OD-300 is available in blister of 10's tablets.

Manufactured by:

INTAS

INTAS PHARMACEUTICALS LTD.
Bhagey Khola, Rangpo,
East Sikkim-737 132, INDIA

85 820 0 8805232

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