OXCARBAZEPINE (Systemic)

Introduction

INN: Oxcarbazepine
VA CLASSIFICATION (Primary)¾CN400

Commonly used brand name(s):Trileptal.
GP47680

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

Category

Anticonvulsant.

Indications

Accepted

Epilepsy, partial seizures (treatment)¾ Oxcarbazepine is indicated for monotherapeutic or adjunctive therapeutic use in the treatment of partial seizures in adults, and for adjunctive therapeutic treatment of partial seizures in children ages 4 to 16. 1

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight¾252.27 1

Solubility¾ Oxcarbazepine is slightly soluble in acetone, chloroform, dichloromethane, and methanol. It is practically insoluble in ethanol, ether, and water. 1

Mechanism of action/Effect:

The exact mechanism by which oxcarbazepine exerts its anticonvulsant effect is unknown. It is known that the pharmacological activity of oxcarbazepine occurs primarily through its 10-monohydroxy metabolite (MHD). In vitro studies indicate an MHD-induced blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neuronal membranes, inhibition of repetitive neuronal discharges, and diminution of propagation of synaptic impulses. 1

Absorption:

Oxcarbazepine is completely absorbed.
Food does not alter the rate and extent of absorption of oxcarbazepine 1

Distribution:

The apparent volume of distribution of the pharmacologically active 10- monohydroxy metabolite (MHD) is 49 liters. 1

Oxcarbazepine and MHD are distributed to breast milk 1

Protein binding:

Moderate (40%). Oxcarbazepine binds predominantly to serum albumin. Neither oxcarbazepine nor its 10-monohydroxy metabolite binds with alpha-1-acid blycoprotein. 1

Biotransformation:

Oxcarbazepine undergoes rapid and extensive hepatic metabolism to its 10-monohydroxy metabolite (MHD). MHD is further metabolized by conjugation with glucuronic acid. 1

Note:
Autoinduction has not been observed with oxcarbazepine. 1

Half-life:

Oxcarbazepine¾2 hours
10-monohydroxy metabolite¾9 hours 1

Note: In patients with renal function impairment with a creatinine clearance < 30 mL per minute, the half-life of MHD is prolonged to 19 hours, with a two-fold increase in the area under the concentration-time curve (AUC). 1

Time to peak concentration:

Median of 4.5 hours 1

Elimination:

Renal¾greater than 95%, with more than 99% of the dose excreted in the form of metabolites.
Fecal¾less than 4%. 1

Precautions to Consider

Cross-sensitivity and/or related problems

Approximately 25 to 30% of patients with hypersensitivity reactions to carbamazepine can be expected to react similarly to oxcarbazepine. Patients should be questioned particularly regarding any prior experience with carbamazepine before prescribing oxcarbazepine. 1

Carcinogenicity/Tumorigenicity

In several 2-year carcinogenicity studies, oxcarbazepine was administered orally at doses of up to 100 mg per kg of body weight (mg/kg) a day in mice and 250 mg/kg to rats, and the pharmacologically active 10-monohydroxy metabolite (MHD) was administered orally to rats at doses up to 600 mg/kg/day. A dose-related increased incidence of hepatocellular adenomas was observed in mice receiving oxcarbazepine doses ³ 70 mg/kg/day. The incidence of hepatocellular carcinomas was increased in female rats receiving oxcarbazepine at doses ³ 25 mg/kg/day (approximately 10% of the maximum recommended human dose[MRHD] on a mg per square meter of body surface area [mg/m2]basis), while the incidences of hepatocellular adenomas and/or carcinomas were increased in male and female rats receiving MHD 600 mg/kg/day (2.4 times the MRHD) and MHD 250 mg/kg/day or more (MRHD equivalent). An increase was seen in the incidence of benign testicular cell tumors in rats receiving oxcarbazepine ³ 250 mg/kg/day and in the incidence of granular cell tumors of the cervix and vagina in rats receiving MHD 600 mg/kg/day. 1

Mutagenicity

Oxcarbazepine increased mutation frequencies in 1 of 5 bacterial strains during in vitro Ames testing. Chromosomal aberrations and polyploidy were produced in the Chinese hamster ovary assay in vitro by both oxcarbazepine and its 10-monohydroxy metabolite, in the absence of metabolic activation. 1

Pregnancy/Reproduction

Fertility¾Rats administered MHD in doses of 50, 150, or 450 mg/kg prior to and during mating and the early stages of gestation experienced disruptions of estrous cyclicity, reductions in the numbers of corpus luteums and implantations, and produced fewer live embryos at the highest dose level (approximately 2 times the MRHD, on a mg/m2basis). 1

Pregnancy¾Adequate and well-controlled studies of oxcarbazepine in pregnant women have not been performed.
Reproduction studies in pregnant rats given oral oxcarbazepine (30, 300, or 1000 mg/kg) throughout the organogenesis stage of pregnancy revealed increased incidences of craniofacial, cardiovascular, and skeletal fetal malformations at intermediate and high doses (approximately 1.2 and 4 times the maximum recommended human dose, respectively). When female rats were dosed with oxcarbazepine (25, 50, or 150 mg/kg) during the latter stage of gestation and throughout lactation, a persistent reduction in body weights and behavior activity levels was observed in offspring exposed to the highest dose level. Similar reductions in offspring weights were observed at the highest dose in rats administered 25, 50, or 250 mg/kg of the 10-monohydroxy metabolite of oxcarbazepine during the latter stage of gestation and throughout lactation
Increased incidence in embryofetal mortality was observed in pregnant rats receiving 1000 mg/kg, and in pregnant rabbits receiving 200 mg/kg. 1

Note: Oxcarbazepine has a close structural relationship to carbamazepine, a known human teratogen. Although well-controlled clinical studies in pregnant women are lacking, it is likely that oxcarbazepine is teratogenic in humans, and should be used in pregnancy only if the potential benefits justify the potential associated fetal risk.
FDA Pregnancy Category CLabor and Delivery

The effect of oxcarbazepine on labor and delivery has not been studied.

Breast-feeding

Oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite are distributed into human breast milk. Both medications exhibited a milk-to-plasma concentration ratio of 0.5. 1

Pediatrics

Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of oxcarbazepine in children. Clearance of oxcarbazepine in children less than 8 years of age is 30 to 40 % greater than that in older children and adults; higher maintenance dosing may be required. 1

Geriatrics

Due to age-related changes in creatinine clearance, the maximum plasma concentration and area under the concentration-time curve (AUC) values of the 10-monohydroxy metabolite of oxcarbazepine were 30 to 60% higher in older volunteers (60 to 82 years of age) as compared with younger volunteers (18 to 32 years of age) 1

No information is available on the relationship of age to the effects of oxcarbazepine in geriatric patients. However, elderly patients are more likely to have age-related impairments in renal function , resulting in the need for dosing adjustments.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Other anticonvulsants that induce cytochrome P450 enzymes can decrease plasma concentrations of oxcarbazepine and its active 10-monohydroxy metabolite, MHD. Oxcarbazepine can inhibit CYP2C19, and induce CYP3A4/5; inhibition of CYP3A4/5 occurred at high concentrations, and is thought unlikely to be of clinical significance. Oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family, CYP3A4 and CYP3A5, resulting in increased metabolism and lower plasma concentrations of medications broken down via this route. Inhibition of CYP2C19 may increase concentrations of MHD by 22%, and oxcarbazepine by 47%. Oxcarbazepine and MHD have little or no capacity to inhibit CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9, and CYP4A11. 1

Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
>> Alcohol 1 or

>> CNS depression-producing medications, other (see Appendix II)

(additive sedative effects may occur)

Anticonvulsants , including

>> Carbamazepine

>> Phenobarbital

>> Phenytoin

>> Valproic acid

(Antiepileptic agents that are cytochrome P450 inducers have decreased plasma concentrations of oxcarbazepine and its 10-monohydroxy metabolite (MHD). 1)
(oxcarbazepine and MHD may increase the concentration of phenobarbital by about 14%; at oxcarbazepine doses above 1200 mg a day, phenytoin concentrations may be increased by about 40%)

>> Oral contraceptives

(Oxcarbazepine and MHD induce cytochrome enzymes CYP3A4 and CYP3A5, causing lower plasma concentrations of hormonal oral contraceptives and decreasing their effectiveness; use of additional non-hormonal forms of contraception is recommended 1)

>> >> Dihydropyridine calcium channel antagonists, including

>> Felodipine

>> Verapamil

(Oxcarbazepine and MHD induce cytochrome enzymes CYP3A4 and CYP3A5, causing lower plasma concentrations of dihydropyridine calcium channel blockers 1)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With physiology/laboratory test values

Serum electrolytes

(Serum sodium has declined to below 125 mmol/liter in patients treated with oxcarbazepine 1)

Thyroid function

((T4 levels were observed to decline during clinical trials of oxcarbazepine, without alteration of T3 or TSH levels 1))

Note: Abnormal liver function test results have been reported in postmarketing surveillance. 1

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problem exists

>> Previous allergic reaction to oxcarbazepine or to any of its metabolites 1

Risk-benefit should be considered when the following medical problems exist

>> Prior hypersensitivity reaction to carbamazepine 1

(Clinical trials have revealed that 25 to 30% of patients with previous allergic reactions to carbamazepine will experience hypersensitivity reactions to oxcarbazepine)

>> Hyponatremia

(condition may be exacerbated 1)

Renal function impairment 1

(excretion decreased in patients with a creatinine clearance < 30 mL per minute; dosage reductions may be needed)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
>> Serum sodium level

(Clinically significant hyponatremia has developed during oxcarbazepine use; this has generally occurred within the first 3 months of initiating therapy, although onset of serum sodium level decline below 125 mmol/liter has occurred more than a year after first dosing.)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Those indicating need for medical attention

Incidence more frequent

Ataxia or abnormal gait (change in walking and balance; clumsiness or unsteadiness); abnormal vision, diplopia, or nystagmus (change in vision; double vision ; uncontrolled back-and-forth and/or rolling eye movements); dizziness; emotional lability (crying ; false sense of well-being;

mental depression); upper respiratory tract infection (cough; fever; sneezing; or sore throat); vertigo (feeling of constant movement of self or surroundings; sensation of spinning) 1

Incidence less frequent

Abnormal accommodation (blurred vision; change in near or distance vision; difficulty in focusing); abnormal EEG (episodes of confusion ; unusual feelings); bronchitis (cough; shortness of breath; troubled breathing; tightness in chest; wheezing); bruising; fever; hyponatremia (agitation; loss of consciousness; confusion; convulsions; decreased urination; dizziness ; fast or irregular heartbeat; increased thirst; muscle cramps); hypotension (blurred vision; confusion; dizziness, faintness or light-headedness when getting up from a lying or sitting position ; unusual tiredness or weakness); neurotoxicity, especially abnormal coordination (awkwardness ; trembling or shaking of arms, legs, hands, or feet; trouble in walking); abnormal thinking (confusion ; disorientation); aggravated convulsions; amnesia (memory loss); dysmetria (poor control in body movements¾for example, when reaching or stepping); frequent falls; pharyngitis (congestion; cough; hoarseness; sore throat); sinusitis (fever; headache; pain or tenderness around eyes or cheekbones; stuffy or runny nose); skin rash; thirst, increased; urinary tract infection (bloody or cloudy urine; pain or burning while urinating; frequent urge to urinate); vaginitis (itching of the vagina, with or without white vaginal discharge); viral or other infections (fever; general feeling of illness) 1

Incidence rare

Agitation (anxiety; nervousness; irritability ; restlessness); confusion; edema in legs (swelling of the legs); erythema multiforme (sores, ulcers, or white spots in mouth or on lips; muscle pain, cramps, or weakness); gastritis (burning feeling in chest or stomach; stomach upset); hypoesthesia (decreased response to stimulation); lymphadenopathy (swollen glands); multiorgan hypersensitivity disorders, characterized by; skin rash ; fever; eosinophilia (fever); arthralgia (joint pain); purpura (purple spots on skin); rectal hemorrhage (rectal bleeding); Stevens-Johnson syndrome (redness, blistering, peeling, or loosening of skin; fever; hives or itching; bleeding or crusting sores on lips; sore throat ; chills; muscle or joint pain; unusual tiredness or weakness; chest pain); toxic epidermal necrolysis (fever; muscle pain; skin rash; sore throat) 1

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Abdominal pain; fatigue (unusual tiredness or weakness); headache; nausea; rhinitis (runny nose; stuffy nose; sneezing); somnolence (sleepiness or unusual drowsiness); tremor; vomiting 1

Incidence less frequent

Abnormal feeling (general feeling of illness); acne; back pain; chest pain; constipation; cough; diarrhea; dryness of mouth; dyspepsia (acid or sour stomach; belching; heartburn); epistaxis (bloody nose); hot flashes (feeling of warmth and redness of the face, neck, arms and occasionally chest); insomnia (trouble in sleeping); micturation disturbance (increased urination); muscle weakness; nervousness; speech disorder (difficulty in speaking); sweating, increased; taste perversion (change in your sense of taste)

Overdose

For more information on the management of overdose or unintentional ingestion, contact a poison control center (see Poison Control Center Listing).

Treatment of overdose

To decrease absorption¾
Absorption may be minimized by gastric lavage and/or administration of activated charcoal 1

Specific treatment¾
There is no specific antidote currently available for oxcarbazepine overdose. Symptomatic and supportive treatment has enabled the recovery from overdose by all cases reported to date 1

Supportive care¾
Patients in whom intentional overdose is confirmed or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Oxcarbazepine (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Patients with prior hypersensitivity reactions to carbamazepine, a structurally similar anticonvulsant.

Carcinogenicity/Tumorigenicity/Mutagenicity

Shown to be carcinogenic and mutagenic in animal studies
Pregnancy¾Oxcarbazepine has a close structural relationship to carbamazepine, a confirmed human teratogen. It is likely that oxcarbazepine is teratogenic in human, and should only be used in pregnancy if the potential benefits justify the associated risk to the fetus.

Breast-feeding¾Oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite are distributed into human breast milk.

Use in the elderly¾Elderly patients may require dosing adjustments due to age-related reductions in creatinine clearance.

Other medications, especially carbamazepine, felodipine, oral contraceptives, phenobarbital, phenytoin, valproic acid, or verapamil
Other medical problems, especially prior hypersensitivity response to carbamazepine, hyponatremia, or renal function impairment.

Proper use of this medication

>> Proper dosing
Taking as soon as possible; not taking if almost time for next scheduled dose; notifying physician if missing 2 or more doses; not doubling doses
Proper storage
Precautions while using this medication

>> Regular visits to physician to check progress of therapy

>> Caution when using alcoholic beverages or other drugs that could enhance the sedating effects of oxcarbazepine

>> Use of supplemental non-hormonal forms of contraception in addition to oral hormonal contraceptive agents

>> Checking with physician before discontinuing medication; gradual dose reduction is usually needed to maintain seizure control

>> Possible drowsiness, dizziness, blurred or double-vision, light-headedness, weakness, or muscular incoordination: Caution when driving, using machines, or performing other work that requires alertness

>> Caution when getting up suddenly from a lying or sitting position

Side/adverse effects

Signs of potential side effects, especially ataxia or abnormal gait, abnormal vision (including diplopia or nystagmus), dizziness, emotional lability, upper respiratory tract infection, vertigo, abnormal accomodation, abnormal EEG, bronchitis, bruising, fever, hyponatremia, hypotension, neurotoxicity (especially abnormal coordination, abnormal thinking, aggravated convulsions, amnesia, dysmetria, or frequent falls), pharyngitis, sinusitis, skin rash, increased thirst, urinary tract infection, vaginitis, viral or other infections, agitation, confusion, edema in legs, erythema multiforme, gastritis, hypoesthesia, lymphadenopathy, multiorgan hypersensitivity disorders, purpura, rectal hemorrhage, Stevens-Johnson syndrome, or toxic epidermal necrolysis

For oral dosing forms:

Patients receiving concomitant therapy with other antiepileptic drugs should have plasma levels of these drugs monitored during the period of oxcarbazepine introduction and titration. 1

Although older children (8 years of age and older) and adults share similarities in the pharmacokinetics of oxcarbazepine, younger children (less than 8 years of age) have 30 to 40% greater clearances compared with older children and adults, and may require higher maintenance dosing. 1

Anticonvulsant medications should be withdrawn gradually to minimize the potential for increased seizure frequency 1.

Diet/Nutrition

Oxcarbazepine may be taken with or without food. 1

Oral Dosage Forms

OXCARBAZEPINE TABLETS

Usual Adult Dose

Anticonvulsant¾
Adjunctive therapy¾
Oral, initially 300 mg two times a day. The dosage may be increased, as needed and tolerated, by a maximum of 600 mg a day at intervals of one week. The recommended daily dose is 1200 mg. 1

Note:
Doses above 1200 mg a day showed somewhat greater effectiveness in controlled trials, but most patients were unable to tolerate higher doses due to adverse effects. 1

Patients should be closely observed during the initiation of oxcarbazepine, and plasma concentrations of concomitant antiepileptic agents should be monitored.
Conversion to monotherapy¾
Oral, initially 300 mg two times a day. Dose reductions of concomitant anticonvulsants should be initiated simultaneously. The dosage of oxcarbazepine may be increased, as needed and tolerated, by a maximum of 600 mg a day at intervals of one week, to achieve the recommended daily dose of 2400 mg. The maximum dose of oxcarbazepine should be reached over 2 to 4 weeks, while the concomitant anticonvulsants should be completely withdrawn over 3 to 6 weeks. 1

Note:
Close observation of the patient is necessary during this transition period to monotherapy. 1

Initiation of monotherapy¾
Oral, initially 300 mg two times a day. The dosage may be increased, as needed and tolerated, by 300 mg a day at intervals of 3 days, until the total daily dose reaches 1200 mg.

Note: In patients with renal function impairments (creatinine clearance < 30 mL per minute), oxcarbazepine should be started at one-half the usual initiation dose, and increased slowly to reach the desired clinical response. 1

Usual adult prescribing limits

2400 mg a day. 1

Usual Pediatric Dose

Anticonvulsant (adjunctive therapy)¾Children 4 to 16 years of age 1

Initial¾Oral, 8 to 10 mg per kg of body weight per day, given in equally divided, two times a day doses. The total initial dose should not exceed 600 mg per day.
The target maintenance dose is dependent upon the patient's weight:
20 to 29 kg¾900 mg a day.
29.1 to 39 kg¾1200 mg a day.
Above 39 kg¾1800 mg a day.

Note: Achievement of the target maintenance dose of oxcarbazepine should occur over 2 weeks.Children up to 2 years of age

Safety and efficacy have not been established. 1

Usual pediatric prescribing limits

1800 mg per day 1.

Usual Geriatric Dose

See Usual adult dose.

Usual geriatric prescribing limits

See Usual adult prescribing limits".

Strength(s) usually available
U.S.¾150 mg (Rx)[Trileptal (double-scored) (film coated)]

300 mg (Rx)[Trileptal (double-scored) (film coated)]

600 mg (Rx)[Trileptal (double-scored) (film coated)]

Packaging and storage:

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F and 86 °F), in a tight container. 1

Auxiliary labeling:

· May cause drowsiness.
· Avoid alcoholic beverages.