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Roxane Laboratories, Inc.
Columbus, Ohio 43216

OXCARBAZEPINE
Tablets

℞ only

DESCRIPTION

Oxcarbazepine Tablets are an antiepileptic drug available as 150 mg, 300 mg and 600 mg tablets for oral administration. Oxcarbazepine is 10,11-Dihydro-10-oxo-5*H*-dibenz[*b,f*] azepine-5-carboxamide, and its structural formula is

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. Its molecular weight is 252.27.

Oxcarbazepine Tablets contain the following inactive ingredients: crospovidone, hypromellose, iron oxide red 30, iron oxide yellow 10, magnesium stearate, microcrystalline cellulose, and silicon dioxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

The pharmacological activity of oxcarbazepine is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine (see **Metabolism and Excretion** subsection). 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 hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses. These actions are thought to be 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. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

Pharmacodynamics

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for 5 days and 4 weeks, respectively, with oxcarbazepine or MHD.

Pharmacokinetics

Following oral administration of oxcarbazepine tablets, oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). The half-life of the parent is about 2 hours, while the half-life of MHD is about 9 hours, so that MHD is responsible for most antiepileptic activity.

After single dose administration of oxcarbazepine tablets to healthy male volunteers under fasted conditions, the median t_{max} was 4.5 (range 3 to 13) hours.

In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, with approximately 70% present as MHD, and the remainder attributable to minor metabolites.

Effect of Food: Food has no effect on the rate and extent of absorption of oxcarbazepine from oxcarbazepine tablets. Therefore, oxcarbazepine tablets can be taken with or without food.

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

Distribution

The apparent volume of distribution of MHD is 49L.

Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.

Metabolism and Excretion

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).

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: The pharmacokinetics and metabolism of oxcarbazepine and MHD were evaluated in healthy volunteers and hepatically-impaired subjects after a single 900 mg oral dose. Mild-to-moderate hepatic impairment did not affect the pharmacokinetics of oxcarbazepine and MHD. No dose adjustment for oxcarbazepine is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment and, therefore, caution should be exercised when dosing severely impaired patients.

Renal Impairment: There is a linear correlation between creatinine clearance and the renal clearance of MHD. When oxcarbazepine is administered as a single 300 mg dose in renally-impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged to 19 hours, with a two-fold increase in AUC. Dose adjustment for oxcarbazepine is recommended in these patients (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections).

Pediatric Use: Weight-adjusted MHD clearance decreases as age and weight increases approaching that of adults. The mean weight-adjusted clearance in children 4 to 12 years of age is approximately 40% higher on average than that of adults. Therefore, MHD exposure in these children is expected to be about three-quarters that of adults when treated with a similar weight-adjusted dose. As weight increases, for patients 13 years of age and above, the weight-adjusted MHD clearance is expected to reach that of adults.

Additional pharmacokinetic information for pediatric patients ages 2 to 4 years of age is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

Geriatric Use: Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine to elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

Gender: No gender related pharmacokinetic differences have been observed in children, adults, or the elderly.

Race: No specific studies have been conducted to assess what effect, if any, race may have on the disposition of oxcarbazepine.

CLINICAL STUDIES

The effectiveness of oxcarbazepine as adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 2 to 16 years was established in 7 multicenter, randomized, controlled trials.

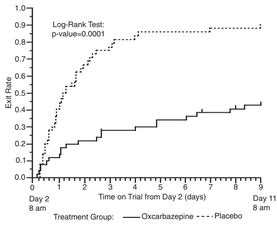
The effectiveness of oxcarbazepine as monotherapy for partial seizures in children aged 4 to 16 years was determined from data obtained in the studies described, as well as by pharmacokinetic/pharmacodynamic considerations.

Oxcarbazepine Monotherapy Trials

Four randomized, controlled, double-blind, multicenter trials, conducted in a predominately adult population, demonstrated the efficacy of oxcarbazepine as monotherapy. Two trials compared oxcarbazepine to placebo and two trials used a randomized withdrawal design to compare a high dose (2400 mg) with a low dose (300 mg) of oxcarbazepine, after substituting oxcarbazepine 2400 mg/day for one or more antiepileptic drugs (AEDs). All doses were administered on a BID schedule. A fifth randomized, controlled, rater-blind, multicenter study, conducted in a pediatric population, failed to demonstrate a statistically significant difference between low and high dose oxcarbazepine treatment groups.

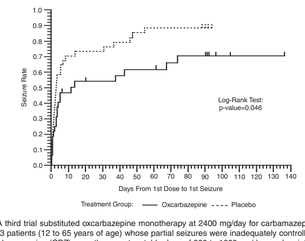
One placebo-controlled trial was conducted in 102 patients (11 to 62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all AEDs and were required to have 2 to 10 partial seizures within 48 hours prior to randomization. Patients were randomized to receive either placebo or oxcarbazepine given as 1500 mg/day on Day 1 and 2400 mg/day thereafter for an additional 8 days, or until one of the following three exit criteria occurred: 1) the occurrence of a fourth partial seizure, excluding Day 1, 2) two new-onset secondarily generalized seizures, where such seizures were not seen in the 1-year period prior to randomization, or 3) occurrence of serial seizures or status epilepticus. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria. There was a statistically significant difference in favor of oxcarbazepine (see Figure 1), p=0.0001.

Figure 1 Kaplan-Meier Estimates of Exit Rate by Treatment Group



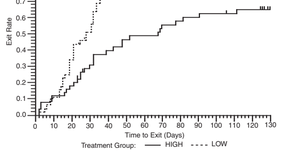
The second placebo-controlled trial was conducted in 677 untreated patients (8 to 69 years of age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or oxcarbazepine, initiated at 300 mg BID and titrated to 1200 mg/day (given as 600 mg BID) in 6 days, followed by maintenance treatment for 84 days. The primary measure of effectiveness was a between-group comparison of the time to first seizure. The difference between the two treatments was statistically significant in favor of oxcarbazepine (see Figure 2), p=0.046.

Figure 2 Kaplan-Meier Estimates of First Seizure Event Rate by Treatment Group



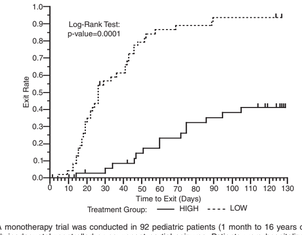
A third trial substituted oxcarbazepine monotherapy at 2400 mg/day for carbamazepine in 143 patients (12 to 65 years of age) whose partial seizures were inadequately controlled on carbamazepine (CBZ) monotherapy at a stable dose of 800 to 1600 mg/day, and maintained this oxcarbazepine dose for 56 days (baseline phase). Patients who were able to tolerate titration of oxcarbazepine to 2400 mg/day during simultaneous carbamazepine withdrawal were randomly assigned to either 300 mg/day of oxcarbazepine or 2400 mg/day oxcarbazepine. Patients were observed for 126 days or until one of the following 4 exit criteria occurred: 1) a doubling of the 28-day seizure frequency compared to baseline, 2) a two-fold increase in the highest consecutive 2-day seizure frequency during baseline, 3) a single generalized seizure if none had occurred during baseline, or 4) a prolonged generalized seizure. The primary measure of effectiveness was a between-group comparison of the time to meet exit criteria. The difference between the curves was statistically significant in favor of the oxcarbazepine 2400 mg/day group (see Figure 3), p=0.0001.

Figure 3 Kaplan-Meier Estimates of Exit Rate by Treatment Group



Another monotherapy substitution trial was conducted in 87 patients (11 to 66 years of age) whose seizures were inadequately controlled on 1 or 2 AEDs. Patients were randomized to either oxcarbazepine 2400 mg/day or 300 mg/day and their standard AED regimen(s) were eliminated over the first 6 weeks of double-blind therapy. Double-blind treatment continued for another 84 days (total double-blind treatment of 126 days) or until one of the 4 exit criteria described for the previous study occurred. The primary measure of effectiveness was a between-group comparison of the percentage of patients meeting exit criteria. The results were statistically significant in favor of the oxcarbazepine 2400 mg/day group (14/34; 41.2%) compared to the oxcarbazepine 300 mg/day group (42/45; 93.3%) (p<0.0001). The time to meeting one of the exit criteria was also statistically significant in favor of the oxcarbazepine 2400 mg/day group (see Figure 4), p=0.0001.

Figure 4 Kaplan-Meier Estimates of Exit Rate by Treatment Group



A monotherapy trial was conducted in 92 pediatric patients (1 month to 16 years of age) with inadequately-controlled or new-onset partial seizures. Patients were hospitalized and randomized to either oxcarbazepine 10 mg/kg/day or were titrated up to 40 to 60 mg/kg/day within three days while withdrawing the previous AED on the second day of oxcarbazepine therapy. Seizures were recorded through continuous video-EEG monitoring from Day 3 to Day 5. Patients either completed the 5-day treatment or met one of the two exit criteria: 1) three study specific seizures (i.e., electrographic partial seizures with a behavioral correlate), 2) a prolonged study specific seizure. The primary measure of effectiveness was a between group comparison of the time to meet exit criteria in which the difference between the curves was not statistically significant (p=0.2). The majority of patients from both dose groups completed the 5-day study without exiting.

Although this study failed to demonstrate an effect of oxcarbazepine as monotherapy in pediatric patients, several design elements, including the short treatment and assessment period, the absence of a true placebo, and the likely persistence of plasma levels of previously administered AEDs during the treatment period, make the results uninterpretable. For this reason, the results do not undermine the conclusion, based on pharmacokinetic/pharmacodynamic considerations, that oxcarbazepine is effective as monotherapy in pediatric patients 4 years old and older.

Oxcarbazepine Adjunctive Therapy Trials

The effectiveness of oxcarbazepine as an adjunctive therapy for partial seizures was established in two multicenter, randomized, double-blind, placebo-controlled trials, one in 692 patients (15 to 66 years of age) and one in 264 pediatric patients (3 to 17 years of age).

Patients in these trials were on 1 to 3 concomitant AEDs. In both of the trials, patients were stabilized on optimum dosages of their concomitant AEDs during an 8-week baseline phase. Patients who experienced at least 8 (minimum of 1 to 4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of oxcarbazepine in addition to their other AEDs.

In the studies, the dose was increased over a 2-week period until either the assigned dose was reached, or intolerance prevented increases. Patients then entered a 14 (pediatrics) or 24 week (adults) maintenance period.

In the adult trial, patients received fixed doses of 600, 1200 or 2400 mg/day. In the pediatric trial, patients received maintenance doses in the range of 30 to 46 mg/kg/day, depending on baseline weight. The primary measure of effectiveness in both trials was a between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase. This comparison was statistically significant in favor of oxcarbazepine at all doses tested in both trials (p=0.0001 for all doses for both trials). The number of patients randomized to each dose, the median baseline seizure rate, and the median percentage seizure rate reduction for each trial are shown in Table 1. It is important to note that in the high-dose group in the study in adults, over 65% of patients discontinued treatment because of adverse events; only 46 (27%) of the patients in this group completed the 28-week trial (see **ADVERSE REACTIONS** section), an outcome not seen in the monotherapy studies.

Table 1 Summary of Percentage Change in Partial Seizure Frequency From Baseline for Placebo-Controlled Adjunctive Therapy Trials

Trial	Treatment Group	N	Baseline Median Seizure Rate*	Median% Reduction
1 (pediatrics)	Oxcarbazepine	136	12.5	34.8[1]
	Placebo	128	13.1	9.4
2 (adults)	Oxcarbazepine 2400 mg/day	174	10	49.9[1]
	Oxcarbazepine 1200 mg/day	177	9.8	40.2[1]
	Oxcarbazepine 600 mg/day	168	9.6	26.4[1]
	Placebo	173	8.6	7.6

[1]p=0.0001; * = # per 28 days

Subset analyses of the antiepileptic efficacy of oxcarbazepine with regard to gender in these trials revealed no important differences in response between men and women. Because there were very few patients over the age of 65 in controlled trials, the effect of the drug in the elderly has not been adequately assessed.

Additional clinical trial information in pediatric patients ages 2 to 4 years of age is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

INDICATIONS AND USAGE

Oxcarbazepine Tablets are indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as monotherapy in the treatment of partial seizures in children aged 4 years and above with epilepsy, and as adjunctive therapy in children aged 4 years and above with epilepsy.

Additional pediatric use information in patients ages 2 to 4 years of age is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

CONTRAINDICATIONS

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

WARNINGS

Hyponatremia

Clinically significant hyponatremia (sodium <125 mmol/L) can develop during oxcarbazepine use. In the 14 controlled epilepsy studies 2.5% of oxcarbazepine-treated patients (38/1524) had a sodium of less than 125 mmol/L at some point during treatment, compared to no such patients assigned placebo or active control (carbamazepine and phenobarbital for adjunctive and monotherapy substitution studies, and phenytoin and valproate for the monotherapy initiation studies). Clinically significant hyponatremia generally occurred during the first 3 months of treatment with oxcarbazepine, although there were patients who first developed a serum sodium <125 mmol/L more than 1 year after initiation of therapy. Most patients who developed hyponatremia were asymptomatic but patients in the clinical trials were frequently monitored and some had their oxcarbazepine dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Whether or not these maneuvers prevented the occurrence of more severe events is unknown. Cases of symptomatic hyponatremia have been reported during post-marketing use. In clinical trials, patients whose treatment with oxcarbazepine was discontinued due to hyponatremia generally experienced normalization of serum sodium within a few days without additional treatment.

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 (for example, drugs associated with inappropriate ADH secretion) or if symptoms possibly indicating hyponatremia develop (e.g., nausea, malaise, headache, lethargy, confusion, obtundation, or increase in seizure frequency or severity).

Anaphylactic Reactions and Angioedema

Rare cases of anaphylaxis and angioedema involving the larynx, glottis, lips and eyelids have been reported in patients after taking the first or subsequent doses of oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with oxcarbazepine, the drug should be discontinued and an alternative treatment started.

These patients should not be rechallenged with the drug (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection).

Patients with a Past History of Hypersensitivity Reaction to Carbamazepine

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of them will experience hypersensitivity reactions with oxcarbazepine. For this reason patients should be specifically questioned about any prior experience with carbamazepine, and patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with oxcarbazepine only if the potential benefit justifies the potential risk. If signs or symptoms of hypersensitivity develop, oxcarbazepine should be discontinued immediately (see **WARNINGS**, **Anaphylactic Reactions and Angioedema** subsection; see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported in both children and adults in association with oxcarbazepine use. The median time of onset for reported cases was 19 days. Such serious skin reactions may be life threatening, and some patients have required hospitalization with very rare reports of fatal outcome. Recurrence of the serious skin reactions following rechallenge with oxcarbazepine has also been reported.

The reporting rate of TEN and SJS associated with oxcarbazepine use, which is generally accepted to be an underestimate due to underreporting, exceeds the background incidence rate estimates by a factor of 3- to 10-fold. Estimates of the background incidence rate for these serious skin reactions in the general population range between 0.5 to 6 cases per million-person years. Therefore, if a patient develops a skin reaction while taking oxcarbazepine, consideration should be given to discontinuing oxcarbazepine use and prescribing another antiepileptic medication.

Withdrawal of AEDs

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

PRECAUTIONS

Cognitive/Neuropsychiatric Adverse Events

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.

Adult Patients: In one large, fixed-dose study, oxcarbazepine was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as oxcarbazepine was added, reduction in oxcarbazepine dosage was not allowed if intolerance developed, and patients were discontinued if unable to tolerate their highest target maintenance doses. In this trial, 65% of patients were discontinued because they could not tolerate the 2400 mg/day dose of oxcarbazepine on top of existing AEDs. The adverse events seen in this study were primarily CNS related and the risk for discontinuation was dose related.

In this trial, 7.1% of oxcarbazepine-treated patients and 4% of placebo-treated patients experienced a cognitive adverse event. The risk of discontinuation for these events was about 6.5 times greater on oxcarbazepine than on placebo. In addition, 26% of oxcarbazepine-treated patients and 12% of placebo-treated patients experienced somnolence. The risk of discontinuation for somnolence was about 10 times greater on oxcarbazepine than on placebo. Finally, 28.7% of oxcarbazepine-treated patients and 6.4% of placebo-treated patients experienced ataxia or gait disturbances. The risk for discontinuation for these events was about 7 times greater on oxcarbazepine than on placebo.

In a single placebo-controlled monotherapy trial evaluating 2400 mg/day of oxcarbazepine, no patients in either treatment group discontinued double-blind treatment because of cognitive adverse events, somnolence, ataxia, or gait disturbance.

In the two dose-controlled conversion to monotherapy trials comparing 2400 mg/day and 300 mg/day oxcarbazepine, 1.1% of patients in the 2400 mg/day group discontinued double-blind treatment because of somnolence or cognitive adverse events compared to 0% in the 300 mg/day group. In these trials, no patients discontinued because of ataxia or gait disturbances in either treatment group.

Pediatric Patients: A study was conducted in pediatric patients (3 to 17 years old) with inadequately controlled partial seizures in which oxcarbazepine was added to existing AED therapy (up to two concomitant AEDs). By protocol, the dosage of concomitant AEDs could not be reduced as oxcarbazepine was added. Oxcarbazepine was titrated to reach a target dose ranging from 30 mg/kg to 46 mg/kg (based on a patient's body weight with fixed doses for pre-defined weight ranges).

Cognitive adverse events occurred in 5.8% of oxcarbazepine-treated patients (the single most common event being concentration impairment, 4 of 138 patients) and in 3.1% of patients treated with placebo. In addition, 34.8% of oxcarbazepine-treated patients and 14% of placebo-treated patients experienced somnolence. (No patient discontinued due to a cognitive adverse event or somnolence.). Finally, 23.2% of oxcarbazepine-treated patients and 7% of placebo-treated patients experienced ataxia or gait disturbances. Two (1.4%) oxcarbazepine-treated patients and 1 (0.8%) placebo-treated patient discontinued due to ataxia or gait disturbances.

Multi-Organ Hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4 to 60) to the initiation of oxcarbazepine therapy in adult and pediatric patients. Although there have been a limited number of reports, many of these cases resulted in hospitalization and some were considered life threatening. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, hepatitis, liver function test abnormalities, hematological abnormalities (e.g., eosinophilia, thrombocytopenia, neutropenia), pruritis, nephritis, oliguria, hepatorenal syndrome, arthralgia and asthenia. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, oxcarbazepine should be discontinued and an alternative treatment started. Although there are no case reports to indicate cross sensitivity with other drugs that produce this syndrome, the experience amongst drugs associated with multi-organ hypersensitivity would indicate this to be a possibility (see **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection).

Information for Patients

Anaphylactic reactions and angioedema may occur during treatment with oxcarbazepine. Patients should be advised to report immediately signs and symptoms suggesting angioedema (swelling of the face, eyes, lips, tongue or difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with their physician (see **WARNINGS, Anaphylactic Reactions and Angioedema** subsection).

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25% to 30% of these patients may experience hypersensitivity reactions with oxcarbazepine. Patients should be advised that if they experience a hypersensitivity reaction while taking oxcarbazepine they should consult with their physician immediately (See **WARNINGS, Patients with a Past History of Hypersensitivity Reaction to Carbamazepine** subsection.)

Patients should be advised that serious skin reactions have been reported in association with oxcarbazepine. In the event a skin reaction should occur while taking oxcarbazepine, patients should consult with their physician immediately (see **WARNINGS, Serious Dermatological Reactions** subsection).

Patients should be instructed that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) may be drug related and should be reported to the physician immediately (see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Female patients of childbearing age should be warned that the concurrent use of oxcarbazepine with hormonal contraceptives may render this method of contraception less effective (see **Drug Interactions** subsection). Additional non-hormonal forms of contraception are recommended when using oxcarbazepine.

Caution should be exercised if alcohol is taken in combination with oxcarbazepine therapy, due to a possible additive sedative effect.

Patients should be advised that oxcarbazepine may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery until they have gained sufficient experience on oxcarbazepine to gauge whether it adversely affects their ability to drive or operate machinery.

Laboratory Tests

Serum sodium levels below 125 mmol/L have been observed in patients treated with oxcarbazepine (see **WARNINGS** section). Experience from clinical trials indicates that serum sodium levels return toward normal when the oxcarbazepine dosage is reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction).

Laboratory data from clinical trials suggest that oxcarbazepine use was associated with decreases in T_4, without changes in T_3 or TSH.

Drug Interactions

Oxcarbazepine can inhibit CYP2C19 and induce CYP3A4/5 with potentially important effects on plasma concentrations of other drugs. In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

Oxcarbazepine was evaluated in human liver microsomes to determine its capacity to inhibit the major cytochrome P450 enzymes responsible for the metabolism of other drugs. Results demonstrate that oxcarbazepine and its pharmacologically active 10-monohydroxy metabolite (MHD) have little or no capacity to function as inhibitors for most of the human cytochrome P450 enzymes evaluated (CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, CYP4A9 and CYP4A11) with the exception of CYP2C19 and CYP3A4/5. Although inhibition of CYP3A4/5 by oxcarbazepine and MHD did occur at high concentrations, it is not likely to be of clinical significance. The inhibition of CYP2C19 by oxcarbazepine and MHD, however, is clinically relevant (see below).

In vitro, the UDP-glucuronyl transferase level was increased, indicating induction of this enzyme. Increases of 22% with MHD and 47% with oxcarbazepine were observed. As MHD, the predominant plasma substrate, is only a weak inducer of UDP-glucuronyl transferase, it is unlikely to have an effect on drugs that are mainly eliminated by conjugation through UDP-glucuronyl transferase (e.g., valproic acid, lamotrigine).

In addition, oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5) responsible for the metabolism of dihydropyridine calcium antagonists and oral contraceptives, resulting in a lower plasma concentration of these drugs.

As binding of MHD to plasma proteins is low (40%), clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Antiepileptic Drugs: Potential interactions between oxcarbazepine and other AEDs were assessed in clinical studies. The effect of these interactions on mean AUCs and C_{min} are summarized in Table 2.

Table 2 Summary of AED Interactions With Oxcarbazepine

AED Coadministered	Dose of AED (mg/day)	Oxcarbazepine Dose (mg/day)	Influence of Oxcarbazepine on AED Concentration (Mean Change, 90% Confidence Interval)	Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval)
Carbamazepine	400 to 2000	900	nc[1]	40% decrease [CI: 17% decrease, 57% decrease]
Phenobarbital	100 to 150	600 to 1800	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI: 12% decrease, 51% decrease]
Phenytoin	250 to 500	600 to 1800 >1200 to 2400	nc[1,2] up to 40% increase[3] [CI: 12% increase, 60% increase]	30% decrease [CI: 3% decrease, 48% decrease]
Valproic acid	400 to 2800	600 to 1800	nc[1]	18% decrease [CI: 13% decrease, 40% decrease]

[1]nc denotes a mean change of less than 10%
[2]Pediatrics
[3]Mean increase in adults at high oxcarbazepine doses

In vivo, the plasma levels of phenytoin increased by up to 40% when oxcarbazepine was given at doses above 1200 mg/day. Therefore, when using doses of oxcarbazepine greater than 1200 mg/day during adjunctive therapy, a decrease in the dose of phenytoin may be required. The increase of phenobarbital level, however, is small (15%) when given with oxcarbazepine.

Strong inducers of cytochrome P450 enzymes (i.e., carbamazepine, phenytoin and phenobarbital) have been shown to decrease the plasma levels of MHD (29% to 40%).

No autoinduction has been observed with oxcarbazepine.

Hormonal Contraceptives: Coadministration of oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of the two hormonal components, ethinylestradiol (EE) and levonorgestrel (LNG). The mean AUC values of EE were decreased by 48% [90% CI: 22 to 65] in one study and 52% [90% CI: 38 to 52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20 to 45] in one study and 52% [90% CI: 42 to 52] in another study. Therefore, concurrent use of oxcarbazepine with hormonal contraceptives may render these contraceptives less effective (see **Drug Interactions** subsection). Studies with other oral or implant contraceptives have not been conducted.

Calcium Antagonists: After repeated coadministration of oxcarbazepine, the AUC of felodipine was lowered by 28% [90% CI: 20 to 33].

Verapamil produced a decrease of 20% [90% CI: 18 to 27] of the plasma levels of MHD.

Other Drug Interactions: Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD. Results with warfarin show no evidence of interaction with either single or repeated doses of oxcarbazepine.

Drug/Laboratory Test Interactions: There are no known interactions of oxcarbazepine with commonly used laboratory tests.

Carcinogenesis/Mutagenesis/Impairment of Fertility

In 2-year carcinogenicity studies, oxcarbazepine was administered in the diet at doses of up to 100 mg/kg/day to mice and by gavage at doses of up to 250 mg/kg to rats, and the pharmacologically active 10-hydroxy metabolite (MHD) was administered orally at doses of up to 600 mg/kg/day to rats. In mice, a dose-related increase in the incidence of hepatocellular adenomas was observed at oxcarbazepine doses ≥70 mg/kg/day or approximately 0.1 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. In rats, the incidence of hepatocellular carcinomas was increased in females treated with oxcarbazepine at doses ≥25 mg/kg/day (0.1 times the MRHD on a mg/m^2 basis), and incidences of hepatocellular adenomas and/or carcinomas were increased in males and females treated with

Product + Component:	Oxcarbazepine Tablets, 150, 300, and 600 mg / Outsert
Identifier:	10003684/02
Country:	United States
Dimension:	20.25" x 12.50"
Circular for Correction:	**01**
Date:	12. September 2007
Colours:	Black
No. of films:	1
Manufacturer:	Boehringer Ingelheim Roxane, Inc.
No. of code:	Interleaved 2of5
Ref. drawing:	R-40
Sales/Samples/Hospital:	Sales
Front / Reverse:	Front
Software:	QuarkXPress 6.52

Additional Information:
- Barcode: FOR POSITION ONLY; barcode prints 100% Black: Interleaved 2of5; Magnification: 53.5%; Encodation: 10003684.
- Prints Head-to-Head.

Approvals

Signature(s):	Department:	Date: m/d/y
	Graphics	
	Graphics	
	Engineer	
	DRA	
	DRA	
	Other	

OXCARBAZEPINE
Tablets
10003684/02

MHD at doses of 600 mg/kg/day (2.4 times the MRHD on a mg/m^2 basis) and ≥250 mg/kg/day (equivalent to the MRHD on a mg/m^2 basis), respectively. There was an increase in the incidence of benign testicular interstitial cell tumors in rats at 250 mg oxcarbazepine/kg/day and at ≥250 mg MHD/kg/day, and an increase in the incidence of granular cell tumors in the cervix and vagina in rats at 600 mg MHD/kg/day.

Oxcarbazepine increased mutation frequencies in the Ames test *in vitro* in the absence of metabolic activation in one of five bacterial strains. Both oxcarbazepine and MHD produced increases in chromosomal aberrations and polyploidy in the Chinese hamster ovary assay *in vitro* in the absence of metabolic activation. MHD was negative in the Ames test, and no mutagenic or clastogenic activity was found with either oxcarbazepine or MHD in V79 Chinese hamster cells *in vitro*. Oxcarbazepine and MHD were both negative for clastogenic or aneugenic effects (micronucleus formation) in an *in vivo* rat bone marrow assay.

In a fertility study in which rats were administered MHD (50, 150, or 450 mg/kg) orally prior to and during mating and early gestation, estrous cyclicity was disrupted and numbers of corpora lutea, implantations, and live embryos were reduced in females receiving the highest dose (approximately 2 times the MRHD on a mg/m^2 basis).

Pregnancy Category C

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryolethality, growth retardation) were observed in the offspring of animals treated with either oxcarbazepine or its active 10-hydroxy metabolite (MHD) during pregnancy at doses similar to the maximum recommended human dose.

When pregnant rats were given oxcarbazepine (30, 300, or 1000 mg/kg) orally throughout the period of organogenesis, increased incidences of fetal malformations (craniofacial, cardiovascular, and skeletal) and variations were observed at the intermediate and high doses (approximately 1.2 and 4 times, respectively, the maximum recommended human dose [MRHD] on a mg/m^2 basis). Increased embryofetal death and decreased fetal body weights were seen at the high dose. Doses ≥300 mg/kg were also maternally toxic (decreased body weight gain, clinical signs), but there is no evidence to suggest that teratogenicity was secondary to maternal effects.

In a study in which pregnant rabbits were orally administered MHD (20, 100, or 200 mg/kg) during organogenesis, embryofetal mortality was increased at the highest dose (1.5 times the MRHD on a mg/m^2 basis). This dose produced only minimal maternal toxicity.

In a study in which female rats were dosed orally with oxcarbazepine (25, 50, or 150 mg/kg) during the latter part of gestation and throughout the lactation period, a persistent reduction in body weights and altered behavior (decreased activity) were observed in offspring exposed to the highest dose (0.6 times the MRHD on a mg/m^2 basis). Oral administration of MHD (25, 75, or 250 mg/kg) to rats during gestation and lactation resulted in a persistent reduction in offspring weights at the highest dose (equivalent to the MRHD on a mg/m^2 basis).

There are no adequate and well-controlled clinical studies of oxcarbazepine in pregnant women; however, oxcarbazepine is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. Given this fact, and the results of the animal studies described, it is likely that oxcarbazepine is a human teratogen. Oxcarbazepine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of oxcarbazepine on labor and delivery in humans has not been evaluated.

Nursing Mothers

Oxcarbazepine and its active metabolite (MHD) are excreted in human breast milk. A milk-to-plasma concentration ratio of 0.5 was 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 the mother.

Patients with Renal Impairment

In renally-impaired patients (creatinine clearance <30 mL/min), the elimination half-life of MHD is prolonged with a corresponding two-fold increase in AUC (see **CLINICAL PHARMACOLOGY, Pharmacokinetics** subsection). Oxcarbazepine therapy should be initiated at one-half the usual starting dose and increased, if necessary, at a slower than usual rate until the desired clinical response is achieved.

Pediatric Use

Oxcarbazepine is indicated for use as adjunctive therapy for partial seizures in patients aged 4 to 16 years. Oxcarbazepine is also indicated as monotherapy for partial seizures in patients aged 4 to 16 years. Oxcarbazepine has been given to 770 patients between the ages of 3 to 17 years in controlled clinical trials (332 treated as monotherapy) and about 615 patients between the ages of 3 to 17 years in other trials. (See **ADVERSE REACTIONS** section for a description of the adverse events associated with oxcarbazepine use in this population.)

Additional pediatric use information in patients ages 2 to 4 years of age is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this pediatric age group.

Geriatric Use

There were 52 patients over age 65 in controlled clinical trials and 565 patients over the age of 65 in other trials. Following administration of single (300 mg) and multiple (600 mg/day) doses of oxcarbazepine in elderly volunteers (60 to 82 years of age), the maximum plasma concentrations and AUC values of MHD were 30% to 60% higher than in younger volunteers (18 to 32 years of age). Comparisons of creatinine clearance in young and elderly volunteers indicate that the difference was due to age-related reductions in creatinine clearance.

ADVERSE REACTIONS

Most Common Adverse Events in All Clinical Studies

Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine and substantially more frequent than in placebo-treated patients were: dizziness, somnolence, diplopia, fatigue, nausea, vomiting, ataxia, abnormal vision, abdominal pain, tremor, dyspepsia, abnormal gait.

Approximately 23% of these 1537 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: dizziness (6.4%), diplopia (5.9%), ataxia (5.2%), vomiting (5.1%), nausea (4.9%), somnolence (3.8%), headache (2.9%), fatigue (2.1%), abnormal vision (2.1%), tremor (1.8%), abnormal gait (1.7%), rash (1.4%), hyponatremia (1%).

Monotherapy in Adults not Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in previously treated patients.

Approximately 9% of these 295 adult patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: dizziness (1.7%), nausea (1.7%), rash (1.7%), headache (1.4%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 4 Years Old and Above Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in adults.

Approximately 11% of these 456 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: somnolence (2.4%), vomiting (2%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), nystagmus (1.1%).

Monotherapy in Pediatric Patients 4 Years Old and Above not Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those in adults.

Approximately 9.2% of 152 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated (≥1%) with discontinuation were rash (5.3%) and maculopapular rash (1.3%).

Adjunctive Therapy/Monotherapy in Pediatric Patients 1 Month to <4 Years Old Previously Treated or Not Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with oxcarbazepine in these patients were similar to those seen in older children and adults except for infections and infestations which were more frequently seen in these younger children.

Approximately 11% of these 241 pediatric patients discontinued treatment because of an adverse experience. The adverse experiences most commonly associated with discontinuation were: convulsions (3.7%), status epilepticus (1.2%), and ataxia (1.2%).

Incidence in Controlled Clinical Studies: The prescriber should be aware that the figures in Tables 3, 4, 5 and 6 cannot be used to predict the frequency of adverse experiences in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and nondrug factors to the adverse event incidences in the population studied.

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs: Table 3 lists treatment-emergent signs and symptoms that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of oxcarbazepine. Table 4 lists treatment-emergent signs and symptoms in patients converted from other AEDs to either high dose oxcarbazepine or low dose (300 mg) oxcarbazepine. Note that in some of these monotherapy studies patients who dropped out during a preliminary tolerability phase are not included in the tables.

Table 3 Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Adjunctive Therapy in Adults (Events in at least 2% of Patients Treated With 2400 mg/day of Oxcarbazepine and Numerically More Frequent Than in the Placebo Group)

	Oxcarbazepine Dosage (mg/day)			
Body System/ Adverse Event	OXC 600 N=163 %	OXC 1200 N=171 %	OXC 2400 N=126 %	Placebo N=166 %
Body as a Whole				
Fatigue	15	12	15	7
Asthenia	6	3	6	5
Edema Legs	2	1	2	1
Weight Increase	1	2	2	1
Feeling Abnormal	0	1	2	0
Cardiovascular System				
Hypotension	0	1	2	0
Digestive System				
Nausea	15	25	29	10
Vomiting	13	25	36	5
Pain Abdominal	10	13	11	5
Diarrhea	5	6	7	6
Dyspepsia	5	5	6	2
Constipation	2	2	6	4
Gastritis	2	1	2	1
Metabolic and Nutritional Disorders				
Hyponatremia	3	1	2	1
Musculoskeletal System				
Muscle Weakness	1	2	2	0
Sprains and Strains	0	2	2	1
Nervous System				
Headache	32	28	26	23
Dizziness	26	32	49	13
Somnolence	20	28	36	12
Ataxia	9	17	31	5
Nystagmus	7	20	26	5
Gait Abnormal	5	10	17	1
Insomnia	4	2	3	1
Tremor	3	8	16	5
Nervousness	2	4	2	1
Agitation	1	1	2	1
Coordination Abnormal	1	3	2	1
EEG Abnormal	0	0	2	0
Speech Disorder	1	1	3	0
Confusion	1	1	2	1
Cranial Injury NOS	1	0	2	1
Dysmetria	1	2	3	0
Thinking Abnormal	0	2	4	0
Respiratory System				
Rhinitis	2	4	5	4
Skin and Appendages				
Acne	1	2	2	0
Special Senses				
Diplopia	14	30	40	5
Vertigo	6	12	15	2
Vision Abnormal	6	14	13	4
Accommodation Abnormal	0	0	2	0

Table 4 Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Monotherapy in Adults Previously Treated With Other AEDs (Events in at Least 2% of Patients Treated With 2400 mg/day of Oxcarbazepine and Numerically More Frequent than in the Low Dose Control Group)

	Oxcarbazepine Dosage (mg/day)	
Body System/ Adverse Event	2400 N=86 %	300 N=86 %
Body as a Whole		
Fatigue	21	5
Fever	3	0
Allergy	2	0
Edema Generalized	2	1
Pain Chest	2	0
Digestive System		
Nausea	22	7
Vomiting	15	5
Diarrhea	7	5
Dyspepsia	6	1
Anorexia	5	3
Pain Abdominal	5	3
Mouth Dry	3	0
Hemorrhage Rectum	2	0
Toothache	2	1
Hemic and Lymphatic System		
Lymphadenopathy	2	0
Infections and Infestations		
Infection Viral	7	5
Infection	2	0
Metabolic and Nutritional Disorders		
Hyponatremia	5	0
Thirst	2	0
Nervous System		
Headache	31	15
Dizziness	28	8
Somnolence	19	5
Anxiety	7	5
Ataxia	7	1
Confusion	7	0
Nervousness	7	0
Insomnia	6	3
Tremor	6	3
Amnesia	5	1
Convulsions Aggravated	5	2
Emotional Lability	3	2
Hypoesthesia	3	1
Coordination Abnormal	2	1
Nystagmus	2	0
Speech Disorder	2	0
Respiratory System		
Upper Respiratory Tract Infection	10	5
Coughing	5	0
Bronchitis	3	0
Pharyngitis	3	0
Skin and Appendages		
Hot Flushes	2	1
Purpura	2	0
Special Senses		
Vision Abnormal	14	2
Diplopia	12	1
Taste Perversion	5	0
Vertigo	3	0
Earache	2	1
Ear Infection NOS	2	0
Urogenital and Reproductive System		
Urinary Tract Infection	5	1
Micturition Frequency	2	1
Vaginitis	2	0

Controlled Clinical Study of Monotherapy in Adults not Previously Treated with other AEDs: Table 5 lists treatment-emergent signs and symptoms in a controlled clinical study of monotherapy in adults not previously treated with other AEDs that occurred in at least 2% of adult patients with epilepsy treated with oxcarbazepine or placebo and were numerically more common in the patients treated with oxcarbazepine.

Table 5 Treatment-Emergent Adverse Event Incidence in a Controlled Clinical Study of Monotherapy in Adults not Previously Treated With Other AEDs (Events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Oxcarbazepine N=55 %	Placebo N=49 %
Body as a Whole		
Falling Down NOS	4	0
Digestive System		
Nausea	16	12
Diarrhea	7	2
Vomiting	7	6
Constipation	5	0
Dyspepsia	5	4
Musculoskeletal System		
Pain Back	4	2
Nervous System		
Dizziness	22	6
Headache	13	10
Ataxia	5	0
Nervousness	5	2
Amnesia	4	2
Coordination Abnormal	4	2
Tremor	4	0
Respiratory System		
Upper Respiratory Tract Infection	7	0
Epistaxis	4	0
Infection Chest	4	0
Sinusitis	4	2
Skin and Appendages		
Rash	4	2
Special Senses		
Vision Abnormal	4	0

Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated with other AEDs: Table 6 lists treatment-emergent signs and symptoms that occurred in at least 2% of pediatric patients with epilepsy treated with oxcarbazepine or placebo as adjunctive treatment and were numerically more common in the patients treated with oxcarbazepine.

Table 6 Treatment-Emergent Adverse Event Incidence in Controlled Clinical Studies of Adjunctive Therapy/Monotherapy in Pediatric Patients Previously Treated With Other AEDs (Events in at least 2% of patients treated with oxcarbazepine and numerically more frequent than in the placebo group)

Body System/ Adverse Event	Oxcarbazepine N=171 %	Placebo N=139 %
Body as a Whole		
Fatigue	13	9
Allergy	2	0
Asthenia	2	1
Digestive System		
Vomiting	33	14
Nausea	19	5
Constipation	4	1
Dyspepsia	2	0
Nervous System		
Headache	31	19
Somnolence	31	13
Dizziness	28	8
Ataxia	13	4
Nystagmus	9	1
Emotional Lability	8	4
Gait Abnormal	8	3
Tremor	6	4
Speech Disorder	3	1
Concentration Impaired	2	1
Convulsions	2	1
Muscle Contractions Involuntary	2	1
Respiratory System		
Rhinitis	10	9
Pneumonia	2	1
Skin and Appendages		
Bruising	4	2
Sweating Increased	3	0
Special Senses		
Diplopia	17	1
Vision Abnormal	13	1
Vertigo	2	0

Other Events Observed in Association with the Administration of Oxcarbazepine

In the paragraphs that follow, the adverse events, other than those in the preceding tables or text, that occurred in a total of 565 children and 1574 adults exposed to oxcarbazepine and that are reasonably likely to be related to drug use are presented. Events common in the population, events reflecting chronic illness and events likely to reflect concomitant illness are omitted particularly if minor. They are listed in order of decreasing frequency. Because the reports cite events observed in open label and uncontrolled trials, the role of oxcarbazepine in their causation cannot be reliably determined.

Body as a Whole: Fever, malaise, pain chest precordial, rigors, weight decrease.

Cardiovascular System: Bradycardia, cardiac failure, cerebral hemorrhage, hypertension, hypotension postural, palpitation, syncope, tachycardia.

Digestive System: Appetite increased, blood in stool, cholelithiasis, colitis, duodenal ulcer, dysphagia, enteritis, eructation, esophagitis, flatulence, gastric ulcer, gingival bleeding, gum hyperplasia, hematemesis, hemorrhage rectum, hemorrhoids, hiccup, mouth dry, pain biliary, pain right hypochondrium, retching, sialoadenitis, stomatitis, stomatitis ulcerative.

Hemic and Lymphatic System: Leukopenia, thrombocytopenia.

Laboratory Abnormality: Gamma-GT increased, hyperglycemia, hypocalcemia, hypoglycemia, hypokalemia, liver enzymes elevated, serum transaminase increased.

Musculoskeletal System: Hypertonia muscle.

Nervous System: Aggressive reaction, amnesia, anguish, anxiety, apathy, aphasia, aura, convulsions aggravated, delirium, delusion, depressed level of consciousness, dysphonia, dystonia, emotional lability, euphoria, extrapyramidal disorder, feeling drunk, hemiplegia, hyperkinesia, hyperreflexia, hypoesthesia, hypokinesia, hyporeflexia, hypotonia, hysteria, libido decreased, libido increased, manic reaction, migraine, muscle contractions involuntary, nervousness, neuralgia, oculogyric crisis, panic disorder, paralysis, paroniria, personality disorder, psychosis, ptosis, stupor, tetany.

Respiratory System: Asthma, dyspnea, epistaxis, laryngismus, pleurisy.

Skin and Appendages: Acne, alopecia, angioedema, bruising, dermatitis contact, eczema, facial rash, flushing, folliculitis, heat rash, hot flushes, photosensitivity reaction, pruritus genital, psoriasis, purpura, rash erythematous, rash maculopapular, vitiligo, urticaria.

Special Senses: Accommodation abnormal, cataract, conjunctival hemorrhage, edema eye, hemianopia, mydriasis, otitis externa, photophobia, scotoma, taste perversion, tinnitus, xerophthalmia.

Surgical and Medical Procedures: Procedure dental oral, procedure female reproductive, procedure musculoskeletal, procedure skin.

Urogenital and Reproductive System: Dysuria, hematuria, intermenstrual bleeding, leukorrhea, menorrhagia, micturition frequency, pain renal, pain urinary tract, polyuria, priapism, renal calculus.

Other: Systemic lupus erythematosus.

Post-Marketing and Other Experience

The following adverse events not seen in controlled clinical trials have been observed in named patient programs or post-marketing experience:

Body as a Whole: Multi-organ hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia and arthralgia (see **PRECAUTIONS, Multi-Organ Hypersensitivity** subsection).

Anaphylaxis (see **WARNINGS**, **Anaphylactic Reactions and Angioedema** subsection).

Digestive System: Pancreatitis and/or lipase and/or amylase increase.

Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (see **WARNINGS, Serious Dermatological Reactions** subsection).

DRUG ABUSE AND DEPENDENCE

Abuse

The abuse potential of oxcarbazepine has not been evaluated in human studies.

Dependence

Intragastric injections of oxcarbazepine to four cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to self-administer oxcarbazepine by lever pressing activity.

OVERDOSAGE

Human Overdose Experience

Isolated cases of overdose with oxcarbazepine have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment.

Treatment and Management

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 administering activated charcoal should be considered.

DOSAGE AND ADMINISTRATION

Oxcarbazepine is recommended as adjunctive treatment in the treatment of partial seizures in adults and children aged 4 to 16 years. Oxcarbazepine is also recommended as monotherapy in the treatment of partial seizures in adults and children aged 4 to 16 years.

All dosing should be given in a twice-a-day (BID) regimen. Oxcarbazepine oral suspension and oxcarbazepine tablets may be interchanged at equal doses.

Oxcarbazepine should be kept out of the reach and sight of children.

Oxcarbazepine can be taken with or without food (see **CLINICAL PHARMACOLOGY, Pharmacokinetics** subsection).

Adults

Adjunctive Therapy: Treatment with oxcarbazepine should be initiated with a dose of 600 mg/day, given in a BID regimen. If clinically indicated, the dose may be increased by a maximum of 600 mg/day at approximately weekly intervals; the recommended daily dose is 1200 mg/day. Daily doses above 1200 mg/day show somewhat greater effectiveness in controlled trials, but most patients were not able to tolerate the 2400 mg/day dose, primarily because of CNS effects. It is recommended that the patient be observed closely and plasma levels of the concomitant AEDs be monitored during the period of oxcarbazepine titration, as these plasma levels may be altered, especially at oxcarbazepine doses greater than 1200 mg/day (see **PRECAUTIONS, Drug Interactions** subsection).

Conversion to Monotherapy: Patients receiving concomitant AEDs may be converted to monotherapy by initiating treatment with oxcarbazepine at 600 mg/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 to 6 weeks, while the maximum dose of oxcarbazepine should be reached in about 2 to 4 weeks. Oxcarbazepine may be increased as clinically indicated by a maximum increment of 600 mg/day at approximately weekly intervals to achieve the recommended daily dose of 2400 mg/day. A daily dose of 1200 mg/day has been shown in one study to be effective in patients in whom monotherapy has been initiated with oxcarbazepine. Patients should be observed closely during this transition phase.

Initiation of Monotherapy: Patients not currently being treated with AEDs may have monotherapy initiated with oxcarbazepine. In these patients, oxcarbazepine should be initiated at a dose of 600 mg/day (given in a BID regimen); the dose should be increased by 300 mg/day every third day to a dose of 1200 mg/day. Controlled trials in these patients examined the effectiveness of a 1200 mg/day dose; a dose of 2400 mg/day has been shown to be effective in patients converted from other AEDs to oxcarbazepine monotherapy (see above).

Pediatric Patients

Adjunctive Therapy (Aged 4 to 16 Years): In pediatric patients aged 4 to 16 years, treatment should be initiated at a daily dose of 8 to 10 mg/kg generally not to exceed 600 mg/day, given in a BID regimen. The target maintenance dose of oxcarbazepine should be achieved over 2 weeks, and is dependent upon patient weight, according to the following chart:

20 to 29 kg - 900 mg/day
29.1 to 39 kg - 1200 mg/day
>39 kg - 1800 mg/day

In the clinical trial, in which the intention was to reach these target doses, the median daily dose was 31 mg/kg with a range of 6 to 51 mg/kg.

Under adjunctive therapy (with and without enzyme-inducing AEDs), when normalized by body weight, apparent clearance (L/hr/kg) decreased when age increased such that children 4 to ≤12 years of age may require a 50% higher oxcarbazepine dose per body weight compared to adults.

Pediatric dosing and drug clearance information for pediatric patients ages 2 to <4 years is approved for Novartis Pharmaceuticals corporation's oxcarbazepine tablets. However due to Novartis' marketing exclusivity rights, this drug product is not labeled for this age group.

Conversion to Monotherapy (Aged 4 to 16 years): Patients receiving concomitant antiepileptic drugs may be converted to monotherapy by initiating treatment with oxcarbazepine at approximately 8 to 10 mg/kg/day given in a BID regimen, while simultaneously initiating the reduction of the dose of the concomitant antiepileptic drugs. The concomitant antiepileptic drugs can be completely withdrawn over 3 to 6 weeks while oxcarbazepine may be increased as clinically indicated by a maximum increment of 10 mg/kg/day at approximately weekly intervals to achieve the recommended daily dose. Patients should be observed closely during this transition phase.

The recommended total daily dose of oxcarbazepine is shown in the table below.

Initiation of Monotherapy (Aged 4 to 16 years): Patients not currently being treated with antiepileptic drugs may have monotherapy initiated with oxcarbazepine. In these patients, oxcarbazepine should be initiated at a dose of 8 to 10 mg/kg/day given in a BID regimen. The dose should be increased by 5 mg/kg/day every third day to the recommended daily dose shown in the table below.

Table 7 Range of Maintenance Doses of Oxcarbazepine for Children by Weight During Monotherapy

Weight in kg	From Dose (mg/day)	To Dose (mg/day)
20	600	900
25	900	1200
30	900	1200
35	900	1500
40	900	1500
45	900	1500
50	1200	1800
55	1200	1800
60	1200	2100
65	1200	2100
70	1500	2100

Patients with Hepatic Impairment

In general, dose adjustments are not required in patients with mild-to-moderate hepatic impairment (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** subsection).

Patients with Renal Impairment

In patients with impaired renal function (creatine clearance <30 mL/min) oxcarbazepine therapy should be initiated at one-half the usual starting dose (300 mg/day) and increased slowly to achieve the desired clinical response (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations** subsection).

HOW SUPPLIED

Oxcarbazepine Tablets are supplied as 150 mg, 300 mg, and 600 mg tablets. The 150 mg tablet is round, peach, speckled, debossed with product identification "54 331" on one side and a bisect on the other side. The 300 mg tablet is round, peach, speckled, debossed with product identification "54 515" on one side and a bisect on the other side. The 600 mg tablet is modified oval, peach, speckled, debossed with product identification "54 171" on one side and a bisect on the other side.

0054-0097-25	150 mg, peach speckled tablet, bottle of 100
0054-0097-20	150 mg, peach speckled tablet, 2x5x10 unit dose
0054-0098-25	300 mg, peach speckled tablet, bottle of 100
0054-0098-29	300 mg, peach speckled tablet, bottle of 500
0054-0098-20	300 mg, peach speckled tablet, 2x5x10 unit dose
0054-0099-25	600 mg, peach speckled tablet, bottle of 100
0054-0099-20	600 mg, peach speckled tablet, 2x5x10 unit dose

Storage

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature]. Dispense in tight container (USP).

10003684/02 **Revised September 2007**

Boehringer Ingelheim
Roxane Laboratories

Product + Component:	Oxcarbazepine Tablets, 150, 300, and 600 mg / Outsert
Identifier:	10003684/02
Country:	United States
Dimension:	20.25" x 12.50"
Circular for Correction:	**01**
Date:	12. September 2007
Colours:	Black
No. of films:	1
Manufacturer:	Boehringer Ingelheim Roxane, Inc.
No. of code:	Interleaved 2of5
Ref. drawing:	R-40
Sales/Samples/Hospital:	Sales
Front / Reverse:	Reverse
Software:	QuarkXPress 6.52

Additional Information:

- Barcode: FOR POSITION ONLY; barcode prints 100% Black: Interleaved 2of5; Magnification: 53.5%; Encodation: 10003684.
- Prints Head-to-Head.

Approvals

Signature(s):	Department:	Date: m/d/y
	Graphics	
	Graphics	
	Engineer	
	DRA	
	DRA	
	Other	

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

OXCARBAZEPINE
Tablet 150 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0097-20 9

NDC 0054-0098-20 10x10 Unit-Dose Tablets

OXCARBAZEPINE Tablets

300 mg

Each tablet contains 300 mg oxcarbazepine.

Dosage: See package insert.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Keep this and all drugs out of the reach of children.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

R_x only

Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0098-20 10x10 Unit-Dose Tablets

OXCARBAZEPINE Tablets

300 mg

LOT

EXP.

Boehringer Ingelheim
Roxane Laboratories

10003667/01

NDC 0054-0099-20 10x10 Unit-Dose Tablets

OXCARBAZEPINE
Tablets
600 mg

Each tablet contains 600 mg oxcarbazepine.

Dosage: See package insert.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Keep this and all drugs out of the reach of children.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

R_x only

Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0099-20 10x10 Unit-Dose Tablets

OXCARBAZEPINE
Tablets
600 mg

LOT

EXP.

Boehringer Ingelheim
Roxane Laboratories

10003668/01

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Keep this and all drugs out of the reach of children.

Dispense in tight container (USP).

NDC 0054-0099-25 100 Tablets

EXP. LOT

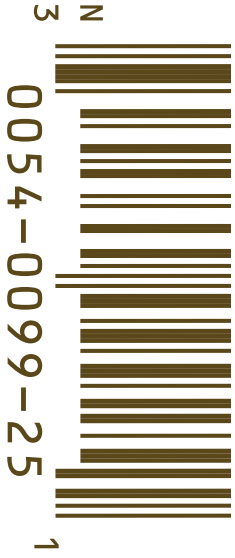
OXCARBAZEPINE
Tablets

600 mg

Each tablet contains
600 mg oxcarbazepine.

Dosage: See package insert.

℞ **only**



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Columbus, Ohio 43216

Boehringer Ingelheim
Roxane Laboratories

10003669/01

NDC 0054-0097-20 10x10 Unit-Dose Tablets

OXCARBAZEPINE
Tablets
150 mg

Each tablet contains 150 mg oxcarbazepine.

Dosage: See package insert.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Keep this and all drugs out of the reach of children.

This unit-dose package is not child-resistant. If dispensed for outpatient use, a child-resistant container should be utilized.

℞ only

Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0097-20 10x10 Unit-Dose Tablets

OXCARBAZEPINE
Tablets
150 mg

LOT

EXP.

Boehringer Ingelheim
Roxane Laboratories

10003683/01

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Keep this and all drugs out of the reach of children.

Dispense in tight container (USP).

Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0098-25 100 Tablets

OXCARBAZEPINE
Tablets

300 mg

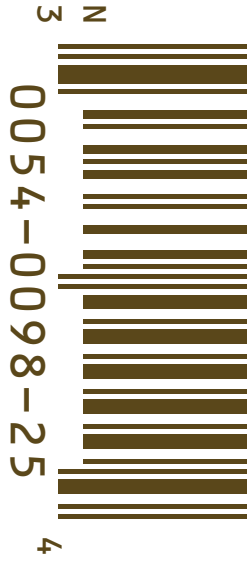
Each tablet contains 300 mg oxcarbazepine.

Dosage: See package insert.

℞ **only**

Boehringer Ingelheim
Roxane Laboratories

EXP. LOT



10003685/01

Store at 25°C (77°F); excursions permitted to 15° to 30° (59°F to 86°F). [See USP Controlled Room Temperature.]

Keep this and all drugs out of the reach of children.

Dispense in tight container (USP).

Roxane Laboratories, Inc.
Columbus, Ohio 43216

NDC 0054-0097-25 100 Tablets

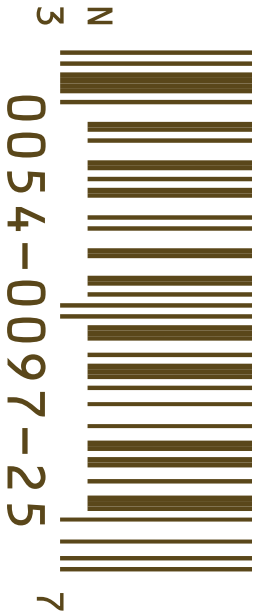
OXCARBAZEPINE
Tablets
150 mg

Each tablet contains 150 mg oxcarbazepine.

Dosage: See package insert.

R_x only

Boehringer Ingelheim
Roxane Laboratories



EXP. LOT

10003686/01

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE
Tablet 600 mg
Roxane • Columbus, Ohio 43216
LOT 000000X EXP. MMM YY
N (01) 1 03 0054-0099-20 3

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

OXCARBAZEPINE

Tablet 300 mg

Roxane • Columbus, Ohio 43216

LOT 000000X EXP. MMM YY

N (01) 1 03 0054-0098-20 6

NDC 0054-0098-29 500 Tablets

OXCARBAZEPINE
Tablets

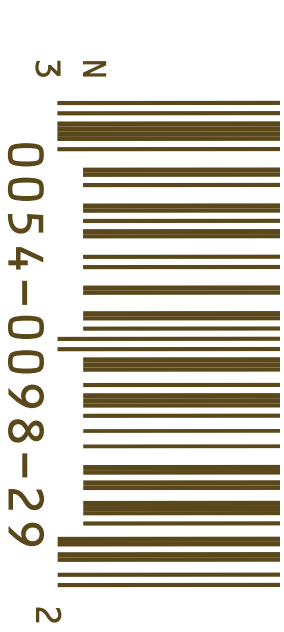
300 mg

Each tablet contains 300 mg oxcarbazepine.

Dosage: See package insert.

Keep this and all drugs out of the reach of children.

℞ **only**



Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

Dispense in tight container (USP).

Boehringer Ingelheim
Roxane Laboratories

10003680/01

Roxane Laboratories, Inc.
Columbus, Ohio 43216