NOVARTIS

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Trileptal®
(oxcarbazepine)

Tablets

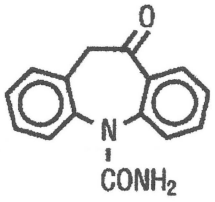
Oral Suspension

Rx only

Prescribing Information

DESCRIPTION

Trileptal® (oxcarbazepine) is an antiepileptic drug available as 150 mg, 300 mg and 600 mg film-coated tablets for oral administration. Trileptal is also available as a 300 mg/5mL (60 mg/mL) oral suspension. 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.

Trileptal film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc and titanium dioxide, yellow iron oxide.

Trileptal oral suspension contains the following inactive ingredients: ascorbic acid; dispersible cellulose; ethanol; macrogol stearate; methyl parahydroxybenzoate; propylene glycol; propyl parahydroxybenzoate; purified water; sodium saccharin; sorbic acid; sorbitol; yellow-plum-lemon aroma.

CLINICAL PHARMACOLOGY

Mechanism of Action

The pharmacological activity of Trileptal® (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 Trileptal 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.

Based on MHD concentrations, Trileptal tablets and suspension were shown to have similar bioavailability.

After single dose administration of Trileptal tablets to healthy male volunteers under fasted conditions, the median t_{max} was 4.5 (range 3 to 13) hours. After single dose administration of Trileptal oral suspension to healthy male volunteers under fasted conditions, the median t_{max} was 6 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 Trileptal tablets. Although not directly studied, the oral bioavailability of the Trileptal suspension is unlikely to be affected under fed conditions. Therefore, Trileptal tablets and suspension can be taken with or without food.

Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when Trileptal 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 Trileptal. 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 Trileptal is recommended in patients with mild-to-moderate hepatic impairment. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment.

Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. When Trileptal 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 Trileptal is recommended in these patients (see PRECAUTIONS and DOSAGE AND ADMINISTRATION sections).

Pediatric Use

After a single-dose administration of 5 or 15 mg/kg of Trileptal, the dose-adjusted AUC values of MHD were 30%-40% lower in children below the age of 8 years than in children above 8 years of age. The clearance in children greater than 8 years old approaches that of adults.

Geriatric Use

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

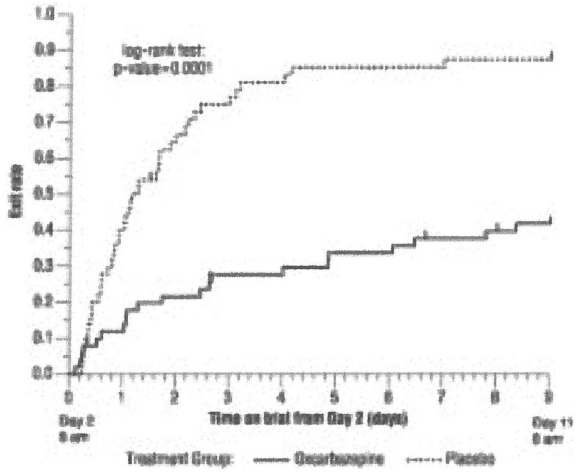
The effectiveness of Trileptal® (oxcarbazepine) as adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 4-16 was established in 6 multicenter randomized, double-blind controlled trials.

Trileptal Monotherapy Trials

Four randomized, double-blind, multicenter trials demonstrated the efficacy of Trileptal as monotherapy. Two trials compared Trileptal to placebo and two trials used a randomized withdrawal design to compare a high dose (2400 mg) with a low dose (300 mg) of Trileptal, after substituting Trileptal 2400 mg/day for one or more antiepileptic drugs (AEDs). All doses were administered on a BID schedule.

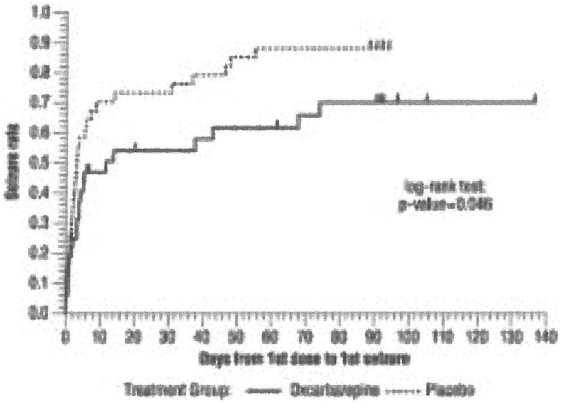
One placebo-controlled trial was conducted in 102 patients (11-62 years of age) with refractory partial seizures who had completed an inpatient evaluation for epilepsy surgery. Patients had been withdrawn from all AEDs and were required to have 2-10 partial seizures within 48 hours prior to randomization. Patients were randomized to receive either placebo or Trileptal given as 1500 mg/day on Day 1 and 2400 mg/day thereafter for an additional 9 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 Trileptal (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 67 untreated patients (8-69 years of age) with newly-diagnosed and recent-onset partial seizures. Patients were randomized to placebo or Trileptal, 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 Trileptal (see Figure 2), p=0.046.

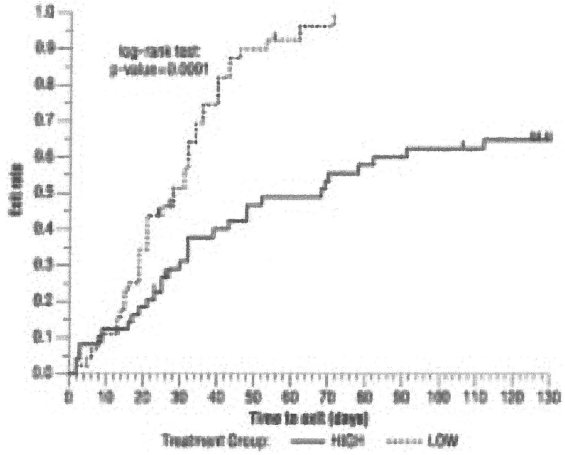
Figure 2: Kaplan-Meier estimates of first seizure event rate by treatment group



A third trial substituted Trileptal monotherapy at 2400 mg/day for carbamazepine in 143 patients (12-65 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 Trileptal dose for 56 days (baseline phase). Patients who were able to tolerate titration of Trileptal to 2400 mg/day during simultaneous carbamazepine withdrawal were randomly assigned to either 300 mg/day of Trileptal or 2400 mg/day Trileptal. 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

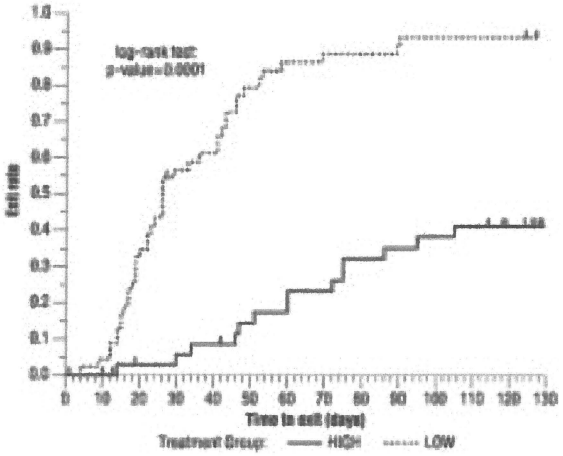
was a between group comparison of the time to meet exit criteria. The difference between the curves was statistically significant in favor of the Trileptal 2400 mg/day group (see Figure 3), p=0.0001.

Figure 3: Kaplan-Meier estimates of exit rate by treatment group



Another monotherapy substitution trial was conducted in 87 patients (11-66 years of age) whose seizures were inadequately controlled on 1 or 2 AEDs. Patients were randomized to either Trileptal 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 Trileptal 2400 mg/day group (14/34; 41.2%) compared to the Trileptal 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 Trileptal 2400 mg/day group (see Figure 4), p=0.0001.

Figure 4: Kaplan-Meier estimates of exit rate by treatment group



Trileptal Adjunctive Therapy Trials

The effectiveness of Trileptal as an adjunctive therapy for partial seizures was established in two multicenter, randomized, double-blind, placebo-controlled trials, one in 692 patients (15-66 years of age) and one in 264 pediatric patients (3-17 years of age). Patients in these trials were on 1-3 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 1-4 per month) partial seizures during the baseline phase were randomly assigned to placebo or to a specific dose of Trileptal in addition to their other AEDs.

In these 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 30-46 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 Trileptal 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 study (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	Median % Reduction
1 (pediatrics)	Trileptal	136	12.5	34.8 [1]
	Placebo	128	13.1	9.4
2 (adults)	Trileptal 2400 mg/day	174	10.0	49.9 [1]
	Trileptal 1200 mg/day	177	9.8	40.2 [1]
	Trileptal 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 Trileptal 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.

INDICATIONS AND USAGE

Trileptal® (oxcarbazepine) is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy.

CONTRAINDICATIONS

Trileptal® (oxcarbazepine) 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 Trileptal® (oxcarbazepine) use. In the 14 controlled epilepsy studies 2.5% of Trileptal 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 Trileptal, 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 Trileptal 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 Trileptal 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 Trileptal, 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).

Patients with a Past History of Hypersensitivity Reaction to Carbamazepine

Patients who have had hypersensitivity reactions to carbamazepine should be informed that approximately 25%-30% of them will experience hypersensitivity reactions with Trileptal. 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 Trileptal only if the potential benefit justifies the potential risk.

If signs or symptoms of hypersensitivity develop, Trileptal should be discontinued immediately.

Withdrawal of AEDs

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

PRECAUTIONS

Cognitive/Neuropsychiatric Adverse Events

Use of Trileptal® (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.

In one, large, fixed dose study, Trileptal was added to existing AED therapy (up to three concomitant AEDs). By protocol, the dosage of the concomitant AEDs could not be reduced as Trileptal was added, reduction in Trileptal 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 Trileptal 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 Trileptal, 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 Trileptal, 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.

Information for Patients

Patients who have exhibited hypersensitivity reactions to carbamazepine should be informed that approximately 25%-30% of these patients may experience hypersensitivity reactions with Trileptal. (See WARNINGS section.)

Female patients of childbearing age should be warned that the concurrent use of Trileptal 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 Trileptal.

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

Patients should be advised that Trileptal may cause dizziness and somnolence. Accordingly, patients should be advised not to drive or operate machinery until they have gained sufficient experience on Trileptal 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 Trileptal (see WARNINGS section). Experience from clinical trials indicates that serum sodium levels return toward normal when the Trileptal dosage is reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction).

Laboratory data from clinical trials suggest that Trileptal 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 cythochrome 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 Trileptal 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 Trileptal

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

In vivo, the plasma levels of phenytoin increased by up to 40% when Trileptal was given at doses above 1200 mg/day. Therefore, when using doses of Trileptal 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 Trileptal.

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

No autoinduction has been observed with Trileptal.

Hormonal Contraceptives

Co-administration of Trileptal 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: 22-65] in one study and 52% [90% CI: 38-52] in another study. The mean AUC values of LNG were decreased by 32% [90% CI: 20-45] in one study and 52% [90% CI: 42-52] in another study. Therefore, concurrent use of Trileptal 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 co-administration of Trileptal, the AUC of felodipine was lowered by 28% [90% CI: 20-33].

Verapamil produced a decrease of 20% [90% CI: 18-27] 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 Trileptal.

Drug/Laboratory Test Interactions

There are no known interactions of Trileptal 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 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 the 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 Trileptal in pregnant women; however, Trileptal 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 Trileptal is a human teratogen. Trileptal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of Trileptal 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 Trileptal 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). Trileptal 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

Trileptal has been shown to be effective as adjunctive therapy for partial seizures in patients aged 4-16 years old. Trileptal has been given to about 623 patients between the ages of 3-17 in controlled clinical trials (185 treated as monotherapy) and about 615 patients between the ages of 3-17 in other trials. (See ADVERSE REACTIONS for a description of the adverse events associated with Trileptal use in this population.)

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 Trileptal in elderly volunteers (60-82 years of age), the maximum plasma concentrations and AUC values of MHD were 30%-60% higher than in younger volunteers (18-32 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 Trileptal® (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 (1.0%).

Monotherapy in Adults not Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with Trileptal 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 Previously Treated with other AEDs: The most commonly observed (≥5%) adverse experiences seen in association with Trileptal 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 (2.0%), ataxia (1.8%), diplopia (1.3%), dizziness (1.3%), fatigue (1.1%), nystagmus (1.1%).

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 Trileptal or placebo as adjunctive treatment and were numerically more common in the patients treated with any dose of Trileptal. Table 4 lists treatment-emergent signs and symptoms in patients converted from other AEDs to either high dose Trileptal or low dose (300 mg) Trileptal. 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 Trileptal 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 Trileptal 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
Ear Ache	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 Trileptal or placebo and were numerically more common in the patients treated with Trileptal.

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 Trileptal 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 Trileptal or placebo

as adjunctive treatment and were numerically more common in the patients treated with Trileptal.

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 Trileptal 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 Involutary	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 Trileptal

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 Trileptal 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 Trileptal 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: Multiorgan hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia and arthralgia.

Skin and Appendages: Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

DRUG ABUSE AND DEPENDENCE

Abuse

The abuse potential of Trileptal® (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 Trileptal® (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

Trileptal® (oxcarbazepine) is recommended as adjunctive treatment and monotherapy in the treatment of partial seizures in adults and as adjunctive treatment for partial seizures in children ages 4-16. All dosing should be given in a twice a day (BID) regimen. Trileptal oral suspension and Trileptal film-coated tablets may be interchanged at equal doses.

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

Before using Trileptal oral suspension, shake the bottle well and prepare the dose immediately afterwards. The prescribed amount of oral suspension should be withdrawn from the bottle using the oral dosing syringe supplied. Trileptal oral suspension can be mixed in a small glass of water just prior to administration or, alternatively, may be swallowed directly from the syringe. After each use, close the bottle and rinse the syringe with warm water and allow it to dry thoroughly.

Trileptal can be taken with or without food (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Adults

Adjunctive Therapy

Treatment with Trileptal 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 Trileptal titration, as these plasma levels may be altered, especially at Trileptal 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 Trileptal 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 3-6 weeks, while the maximum dose of Trileptal should be reached in about 2-4 weeks. Trileptal 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 Trileptal. Patients should be observed closely during this transition phase.

Initiation of Monotherapy

Patients not currently being treated with AEDs may have monotherapy initiated with Trileptal. In these patients, Trileptal 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 Trileptal monotherapy (see above).

Pediatric Patients Age 4-16

Adjunctive Therapy

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

20-29 kg - 900 mg/day

29.1-39 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 6-51 mg/kg.

The pharmacokinetics of Trileptal are similar in older children (age >8 yrs) and adults. However, younger children (age <8 yrs) have an increased clearance (by about 30%-40%) compared with older children and adults. In the controlled trial, pediatric patients 8 years old and below received the highest maintenance doses.

Children below 2 years of age have not been studied in controlled clinical trials.

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) Trileptal 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

Tablets

150 mg Film-Coated Tablets: yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with T/D on one side and C/G on the other side.

Bottle of 100 ..... NDC 0078-0336-05
Bottle of 1000 ..... NDC 0078-0336-09
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0336-06

300 mg Film-Coated Tablets: yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with TE/TE on one side and CG/CG on the other side.

Bottle of 100 ..... NDC 0078-0337-05
Bottle of 1000 ..... NDC 0078-0337-09
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0337-06

600 mg Film-Coated Tablets: yellow, ovaloid, slightly biconvex, scored on both sides. Imprinted with TF/TF on one side and CG/CG on the other side.

Bottle of 100 ..... NDC 0078-0338-05
Bottle of 1000 ..... NDC 0078-0338-09
Unit Dose (blister pack)
Box of 100 (strips of 10) ..... NDC 0078-0338-06

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

Suspension

300 mg/5 mL (60 mg/mL) Oral Suspension: off-white to slightly brown or slightly red suspension. Available in amber glass bottles containing 250 mL of oral suspension. Supplied with a 10 mL dosing syringe and press-in bottle adapter.

Bottle containing 250 mL of oral suspension ..... NDC 0078-0357-52

Store Trileptal oral suspension in the original container. Shake well before using.

Use within 7 weeks of first opening the bottle.

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

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NOVARTIS

Tablets Manufactured by:
Novartis Pharma Stein AG
Schaffhauserstrasse 48
CH-4332 Stein, Switzerland

Oral Suspension Manufactured by:
Novartis Pharma S.A.
F-68330 Huningue, France

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

PRO:

Release Hearing, Judge Hayden:

p. 15:
Cocciola: "Would he pose a risk of danger to himself or others?"
Povinelli: "I believe if he got back to the marijuana again, he might certainly pose a risk."

And if not?

p. 57
Q ...what would you identify ... as risk factors that would make him dangerous to be in the community?
Povinelli: What would make Mr. Saunders dangerous would be a repeat performance of not taking medication, becoming manic, and adding marijuana into it. And drugs.

P. 75
Belsare: I was called by Cayuga County Medical Center by a nurse April 4th of this year, and she said that he had come into the hospital and that his presentation was one of him saying he had delusions.

Having myself taken in to the hospital when I realize I am delusional is a sign of cooperation rather than dangerousness.

Judge Rowley

Dr. Roberts

Insight

p. 29: "He says he does not have a mental illness":

By the legal definition, not the medical one. When the issue is raised, I ask which sense is meant (a medical illness presumably requires care and treatment, the legal definition posited in the MH law adds "rehabilitation" without any definition, either by example or elaboration). I don't think my current confinement promotes "rehabilitation." It appears the term is used loosely.

Dr. Roberts goes on to generalize this position as a rejection of all psychiatric diagnoses, which is not my position at all.

Etiology/Precipitants

p. 23: "And then he became paranoid by completely evading any conversation about himself when asked questions about his past history to try to enlighten him."

Huh? This was not the case.

p.23 "And we could never get him to discuss any precipitants until finally the social worker asked him why did you burn down the trailer, and he said I was angry."

Totally false, I've *never* made any statement to the effect that I was "angry" precisely because it's simply not the case: I was delusional and *scared spitless* over the prospect that "Hannibal Lecter" had somehow threatened to release biological warfare agents, e.g., anthrax. (This claim probably comes from Dr. Kennedy's baseless assertion that I was angry at the time of the arson. Dr. Povinelli describes my response a little more accurately in Hayden p. 14, except that I *don't* equate myself with Lecter!.)

P. 31: Convulsions in ambulance on trip to Elmira.

Dangerousness

p. 30:
Q: "Do you feel if he were discharged right now he would pose a risk of harm to himself or others?"
A: "Yes."
Q: "What do you base that on?"
A: "Past history of violence, arson, and assaultive behavior during prior episodes of decompensation."

NOTE I believe a higher standard of probability than mere "risk" applies (?)

p. 44: "His housemates took him to the hospital ... after he was trying to hurt himself."

False, I was not trying to hurt myself. I never did anything over the duration of the psychosis with the *intention of harming myself (claims from the CMC about "scalding himself" and "trying to hurt himself by* banging his hands" are misperceptions).

Medication:

p. 18:
A I prescribed Zyprexa or Zydis.
...
Q *And what prescription dosage or strength have you recommended?*
A I believe I started him at 15.
Q That's a low dosage? What kind of dosage is that?
A Well, studies have indicated that a patient receives maximum benefit and more rapid improvement if one starts at 15 or 20 milligrams. So I started where the studies are indicating.
Q Is that per day?
A Yes

From the monograph on olanzapine: "Olanzapine should be administered... beginning with 5 to 10 mg initially, with a target dose of 10 mg/day within several days." ... "Antipsychotic efficacy was demonstrated in a dose range of 10 to 15 mg/day in the clinical trials. However doses above 10 mg/day were not demonstrated to be more efficacious that the 10 mg/day dose. ... The safety of doses above 20 mg/day has not been evaluated in clinical trials."

p. 22: "... on a second occasion when I tried to – no, maybe a third. On another occasion when I tried to reinforce this idea by repeating a somewhat familiar statement in front of the team he became very angry and irritable and agitated during that interview."

It seems she can't really recall; presumably on 4/24 during the second real meeting with her (i.e., a meeting longer than 3 minutes), she made some effort to urge me to take Zyprexa, however once started along the "why did you commit the arson" trail I upon which I was launched early in the interview, I do indeed tend to become *upset!*

P. 24: "when I admitted Mr. Saunders... [medication/marijuana discussion] ... he refused to listen to that."

p. 47:
Q "Dr., how many times have you approached Mr. Saunders about taking medication?"
A: "At least four if not more." ... "Then we had a treatment plan meeting. That was another setting in which he was *given an opportunity to hear the medication recommendation.*"

Dr. Roberts may have engaged in a discussion of medications with me when I was still psychotic on 4/4 (as she

states herself, p. 16 passim!), but I certainly could not recall this conversation later. She did not discuss medications in other contexts. The Treatment Plan meeting was a repetition of the nightmare on 3/13, where a document listing various extreme allegations was presented, and I was supposed to sign the document: "He has a history of extreme violence against women," can't work successfully in a supervised setting, a recital of claims purportedly made by Susan Hamann in Dr. Kennedy's report, etc. This was hardly a context for "education," or an effort at persuasive engagement!)

Treatment Plan

p. 30:
Q: "And what would this medication do for him?"
A: "It would normalize his moods so he is neither manic, depressed, or irritable, lowering the threshold for circumstances which cause him to become agitated and angry, and also likely to treat his psychotic symptoms, paranoia, his preoccupation with being persecuted, and his violence."

NOTE that Dr. Roberts stated to me sometime after the hearing ended, around 5/20, that she thought I might be able to use Zyprexa only on an as-needed basis, and later that "whatever happens, we'll try to make sure that you don't wind up here. You don't belong in a place like this – you have too many strengths." This was after she asked to speak with me, and I started by complaining to her about the unfounded allegations of serial rape which appeared in her TOO application. I was upset, but we had a fairly reasonable (public) conversation on the issues, including discussing Susan's assault complaint, with me briefly noting that she had a prior history of abuse and suffered from PTSD after Dr. Roberts' asked whether she had suffered abuse in the past.

P. 45: "Well, this is his choice. These are the consequences which he is well aware of as being possible when he refuses to take medication and continues using marijuana. So I see this as his choice."

As Mr. Wenig noted later, this appears to advocate a punitive stance.

Judge Hayden

p. 15 Povinelli: "He has not been compliant with his conditions as a CPL patient for five years now."

This is false... I was compliant except for a couple of brief episodes of marijuana use for 3 whole years. Dr. Brink recommended Depakote once, I declined, she didn't encourage me to try medication in any of the 2 meetings I subsequently had with her.

PRO:

p. 15:
Cocciola: "Would he pose a risk of danger to himself or others?"
Povinelli: "I believe if he got back to the marijuana again, he might certainly pose a risk."

Recommitment Hearing Judge Rowley

Dr. Povinelli

p. 51-52:
Q: When you saw him in 1997 can you describe his behavior?
A: He was aware that he was acting psychotic himself. At that time he was showing signs of mania....
A: ... I felt that he showed the signs and symptoms of a bipolar disorder.
Q: What symptoms did you observe at that time?
A Pressured speech. He wasn't thinking clearly. He believed there was a conspiracy with regard to the police and

False, I no longer believed in this at that time. I was describing my beliefs at the time of the arson. Note the police conspiracy was a conspiracy of "good guys" (!).

P. 53: A: The diagnosis was bipolar disorder with psychotic features mood congruent.

False, it was "affective disorder with psychotic features": Depression.

P. 53
A: ... In 1997 he felt he was suffering from a drug disorder.

P. 55:
Q: Does he accept the diagnosis of bipolar? ... Did he back in 1997?
A No. In 1997 he felt that his illness was due to a drug reaction.

False, in 1997 at the time of my interview by Povinelli I believed I was suffering from a bizarre combination of neurological disorders (CIDP + TLE). Only 3 years later did I discover that Trazodone can cause peripheral numbness & that its byproduct mCPP is anxiogenic (and probably hallucinogenic).

Dangerousness

p. 57
Q ...*what would you identify ... as risk factors that would make him dangerous to be in the community*?

A What would make Mr. Saunders dangerous would be a repeat performance of not taking medication, becoming manic, and adding marijuana into it. And drugs.

Treatment Plan

p. 59 I recommend he be placed on medications as prescribed by Dr. Roberts, mood stabilizer, possibly an antipsychotic.

Belsare

Here she refers to the humbug about "may" means "must":

p. 64 A: I did mention to him that medications were ordered. On the Order of Conditions it was a legal requirement.
Q And what did he say?
A Well, he didn't believe that they were.

P. 68

re: Urine screen refusals, I had stated that I did not want to pay $50 for urine screens.

p. 69
Q Had you advised Mr. Saunders at any time that you thought he was in violation of his conditions?
A Yes

Only the first time I refused the Trileptal. Otherwise both Dr. Belsare and Janet Stevens claimed they were "trying to help me through my last year."

P.76
Q Do you feel if he were released he would pose a physical danger to himself or others?

A Yes, probably, yeah. ("probably"?)

Saunders

p. 230 MUST COPY!

Q You were upset about the fact ...
A These were never corrected. I discussed this at length with my therapist, and none of the problems were fixed.
Q And so that was distressing to you?
A Yes
Q And so you were unable to work as a result, really concentrate on your work?
A Not unable to work. I was unable to do –
Q Heavy lifting, right?
A – significant computer programming.

Belsare

MUST COPY: p. 63, amazing Belsare "borderline narcissistic features" comment: "injured ego ... compensates for by valuing their own performance as being extraordinary or greater, or themselves as being more important than they are in society."

P. 72
Q So last month it was schizophrenia. Now you are saying it's bipolar and possible schizo-affective disorder?
A There has been confusion about what his diagnosis is.

P. 73-74

Schizophrenia is manifested by: asserting I had 4 rather than 2 knives! (She misses the point I was trying to make completely. Repetition of this falsehood in the "Review" and elsewhere is very upsetting to me because it involves evidence suppression and perjury on the part of the State Troopers investigating the arson. I don't believe this error bearing on whether I should be under an order of conditions -- it bears on the question of whether these officers belong in uniform.)

Sanity is: "But, okay, ex-wife/girlfriend." !!!!!!!!

PINE 4.44 MESSAGE TEXT Folder: INBOX Message 2,253 of 2,288 ALL

Date: Sat, 8 Jun 2002 19:53:00 EDT
From: Cmrendei@aol.com
To: bonze@lightlink.com
Subject: Re: Houston to Keven, are you still alive
Parts/Attachments:

1.1	Shown	26 lines	Text
1.2	CK	21 lines	Text
2		245 KB	Image

If I did it right you now have a picture of me on a donkey in Big Bend last March..

Just a quick note--I'm busy rite now.....being a dad etc & I don't have my reading glasses--we are such old farts now!!!! I'm 3' from the computer

I actually saw Roberts today since I cut thru his subdivision. He has 2 kids. I see him about once a month since we work in differen't places. I am mostly downtown It sucks, but got me a promotion$$$$

I have 2 girls--14 & 16--soon to be Soph & Sr in HS

Scott Jepsen is in Alaska and getting a divorce. Has 2 kids
Jeff Gillespe (sp??) is a lawyer here in Houston. Jon sees him sometimes.
Dave Mancino is in St. Augustine FL

John McNeff is a dentist in Fort Worth--still with Libby--Just had another kid--the third is the last!!!
Absolutely won't happen again.

More later

Chris Rendeiro
3711 Sapling Trail Ct.
Spring TX 77388
281-288-6186

[Part 2, Image/GIF 327KB.]
[Cannot display this part. Press "V" then "S" to save in a file.]