

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202810Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OXTELLAR XR safely and effectively. See full prescribing information for OXTELLAR XR.

OXTELLAR XR (oxcarbazepine) extended-release tablets, for oral use
Initial US Approval: 2000

INDICATIONS AND USAGE

Oxtellar XR™ is an antiepileptic drug (AED) indicated for:

- Adults: Adjunctive therapy in the treatment of partial seizures
- Children: Adjunctive therapy in the treatment of partial seizures in children 6 to 17 years (1)

DOSAGE AND ADMINISTRATION

- Recommended daily dose is 1,200 mg to 2,400 mg once per day (2.2)
- Adults: Initiate with a dose of 600 mg once per day. Dose increases can be made at weekly intervals in 600 mg per day increments to achieve the recommended daily dose (2.2)
- Children: Target dose is based upon weight. Titrate to target dose over two to three weeks. Initiate with 8 mg/kg to 10 mg/kg once per day. Increase in weekly increments of 8 mg/kg to 10 mg/kg once daily, not to exceed 600 mg, to achieve target daily dose (2.3)
- Patients with creatinine clearance less than 30mL/minute: Start at 300 mg per day and increase slowly (2.4)
- Geriatric Patients: Start at lower dose (300 mg or 450 mg per day) and increase slowly (2.5)
- In conversion of oxcarbazepine immediate-release to Oxtellar XR™, higher doses of Oxtellar XR™ may be necessary (2.8, 12.3)

DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 150 mg, 300 mg and 600 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to oxcarbazepine or to any of its components (4)

WARNINGS AND PRECAUTIONS

- Hyponatremia:** Monitor sodium as recommended. (5.1)
- Anaphylactic Reactions and Angioedema.** Discontinue if occurs (5.2)
- Patients with a Past History of Hypersensitivity Reaction to Carbamazepine:** Only use based upon risk benefit (5.3)
- Serious Dermatological Reactions:** Discontinue if observed (5.4)
- Suicidal Behavior and Ideation:** Monitor for symptoms (5.5)
- Withdrawal of Oxtellar XR™:** Withdrawal gradually (5.6)
- Multi-Organ Hypersensitivity:** Discontinue if suspected (5.7)
- Hematologic Reactions:** Discontinue if suspected (5.8)

ADVERSE REACTIONS

Most commonly observed (≥5%) and more frequent than placebo adverse reactions were: dizziness, somnolence, headache, balance disorder, tremor, vomiting, diplopia, asthenia, and fatigue (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Supernus, Inc. at (1-866-398-0833) or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Phenytoin, Carbamazepine, and Phenobarbital:** Coadministration decreased blood levels of an active metabolite of Oxtellar XR™. Greater dose of Oxtellar XR™ may be required (2.6, 7.1).
- Oral Contraceptives:** Advise patients that Oxtellar XR™ may decrease the effectiveness of hormonal contraceptives. Additional non-hormonal forms of contraception are recommended. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy:** Plasma levels of active metabolite may be decreased. Monitor patients. Based on animal data, may cause fetal harm. (5.9, 8.1).
- Severe Hepatic Impairment:** Not recommended (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: October 2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Oxtellar XR™ is indicated as adjunctive therapy of partial seizures in adults and in children 6 years to 17 years of age.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Administer Oxtellar XR™ as a single daily dose taken on an empty stomach (at least 1 hour before or at least 2 hours after meals) [see *Clinical Pharmacology* (12.3)]. If Oxtellar XR™ is taken with food, adverse reactions are more likely to occur because of increased peak levels [see *Clinical Pharmacology* (12.3)].

Swallow Oxtellar XR™ tablets whole. Do not cut, crush, or chew the tablets. For ease of swallowing in pediatric patients or patients with difficulty swallowing, achieve daily dosages with multiples of appropriate lower strength tablets (e.g., 150 mg tablets).

2.2 Dosing for Adults in Adjunctive Therapy

The recommended daily dose of Oxtellar XR™ is 1,200 mg to 2,400 mg per day, given once daily. The dose of 2,400 mg per day showed slightly greater efficacy than 1,200 mg per day, but was associated with an increase in adverse reactions.

Initiate treatment at a dose of 600 mg per day given once daily for one week. Subsequent dose increases can be made at weekly intervals in 600 mg per day increments to achieve the recommended daily dose.

2.3 Dosing for Children (6 to 17 years of age) in Adjunctive Therapy

In pediatric patients 6 years to 17 years of age, initiate treatment at a daily dose of 8 mg/kg to 10 mg/kg once daily, not to exceed 600 mg per day in the first week.

Subsequent dose increases can be made at weekly intervals in 8 mg/kg to 10 mg/kg increments once daily, not to exceed 600 mg, to achieve the target daily dose. The target maintenance dose, achieved over two to three weeks, is displayed in Table 1.

Table 1: Target Daily Dose in Pediatric Patients Aged 6 to 17 Years Old

Weight	Target Daily Dose
20 kg to 29 kg	900 mg per day
29.1 kg to 39 kg	1200 mg per day
Greater than 39 kg	1800 mg per day

2.4 Dosage Modifications in Patients with Renal Impairment

In patients with severe renal impairment (creatinine clearance less than 30 mL/minute), initiate Oxtellar XR™ at one-half the usual starting dose (300 mg per day). Subsequent dose increases can be made at weekly intervals in increments of 300 mg to 450 mg per day to achieve the desired clinical response. [see *Use in Specific Populations (8.5)*].

2.5 Dosage Modifications in Geriatric Patients

In geriatric patients, consider starting at a lower dose (300 mg or 450 mg per day). Subsequent dose increases can be made at weekly intervals in increments of 300 mg to 450 mg per day to achieve the desired clinical effect [see *Use in Specific Populations (8.4)*].

2.6 Dosage Modification for use with Concomitant Antiepileptic Drugs

Enzyme inducing antiepileptic drugs such as carbamazepine, phenobarbital, and phenytoin decrease exposure to 10-monohydroxy derivative (MHD), the active metabolite. Dosage increases may be necessary. Consider initiating dose at 900 mg once per day [see *Drug Interactions (7.1)*].

2.7 Withdrawal of AEDs

As with all antiepileptic drugs, Oxtellar XR™ should be withdrawn gradually to minimize the potential of increased seizure frequency [see *Warnings and Precautions (5.6)*].

2.8 Conversion from Immediate-Release Oxcarbazepine to Oxtellar XR™

In conversion of oxcarbazepine immediate-release to Oxtellar XR™, higher doses of Oxtellar XR™ may be necessary [see *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Extended-release tablets:

150 mg: yellow modified-oval shaped with “150” printed on one side

300 mg: brown modified-oval shaped with “300” printed on one side

600 mg: brownish red modified-oval shaped with “600” printed on one side

4 CONTRAINDICATIONS

Oxtellar XR™ is contraindicated in patients with a known hypersensitivity to oxcarbazepine or to any of its components [see *Warnings and Precautions (5.2, 5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hyponatremia

Clinically significant hyponatremia (sodium <125 mmol/L) may develop during Oxtellar XR™ use. Serum sodium levels less than 125 mmol/L have occurred in immediate-release oxcarbazepine-treated patients generally in the first three months of treatment. However, clinically significant hyponatremia may develop more than a year after initiating therapy.

Most immediate-release oxcarbazepine-treated patients who developed hyponatremia were asymptomatic in clinical trials. However, some of these patients had their dose reduced, discontinued, or had their fluid intake restricted for hyponatremia. Serum sodium levels returned toward normal when the dosage was reduced or discontinued, or when the patient was treated conservatively (e.g., fluid restriction). Post-marketing cases of symptomatic hyponatremia have been reported during post-marketing use of immediate-release oxcarbazepine.

Among treated patients in a controlled trial of adjunctive therapy with Oxtellar XR™ in 366 adults with complex partial seizures, 1 patient receiving 2400 mg experienced a severe reduction in serum sodium (117 mEq/L) requiring discontinuation from treatment, while 2 other patients receiving 1200 mg experienced serum sodium concentrations low enough (125 and 126 mEq/L) to require discontinuation from treatment. The overall incidence of clinically significant hyponatremia in patients treated with Oxtellar XR™ was 1.2%, although slight shifts in serum sodium concentrations from Normal to Low (<135 mEq/L) were observed for the 2400 mg (6.5%) and 1200 mg (9.8%) groups compared to placebo (1.7%). Measure serum sodium concentrations if patients develop symptoms of hyponatremia (e.g., nausea, malaise, headache, lethargy, confusion, obtunded consciousness, or increase in seizure frequency or severity). Consider measurement of serum sodium concentrations during treatment with Oxtellar XR™,

particularly if the patient receives concomitant medications known to decrease serum sodium levels (for example, drugs associated with inappropriate ADH secretion).

5.2 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 immediate-release oxcarbazepine. Angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with Oxtellar XR™, discontinue the drug and initiate an alternative treatment. Do not rechallenge these patients with Oxtellar XR™.

5.3 Hypersensitivity Reactions in Patients with Hypersensitivity to Carbamazepine

Inform patients who have had hypersensitivity reactions to carbamazepine that approximately 25%-30% of them will experience hypersensitivity reactions with Oxtellar XR™. Question patients about any prior adverse reactions with carbamazepine. Patients with a history of hypersensitivity reactions to carbamazepine should ordinarily be treated with Oxtellar XR™ only if the potential benefit justifies the potential risk. Discontinue Oxtellar XR™ immediately if signs or symptoms of hypersensitivity develop [see *Warnings and Precautions (5.8)*].

5.4 Serious Dermatological Reactions

Serious dermatological reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have occurred in both children and adults in treated with immediate-release 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 immediate-release oxcarbazepine has also been reported.

The reporting rate of TEN and SJS associated with immediate-release 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 Oxtellar XR™, consider discontinuing Oxtellar XR™ use and prescribing another AED.

5.5 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Oxtellar XR™, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events per 1,000 Patients	Drug Patients with Events per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Oxtellar XR™ or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during Oxtellar XR™ treatment, the prescriber needs to

consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Withdrawal of AEDs

As with all AEDs, Oxtellar XR™ should be withdrawn gradually to minimize the potential of increased seizure frequency.

5.7 Multi-Organ Hypersensitivity

Multi-organ hypersensitivity reactions have occurred in close temporal association (median time to detection 13 days: range 4-60) to the initiation of immediate-release 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 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. These included the following: hematologic and lymphatic (e.g., eosinophilia, thrombocytopenia, lymphadenopathy, leukopenia, neutropenia, splenomegaly), hepatobiliary (e.g., hepatitis, liver function test abnormalities), renal (e.g., proteinuria, nephritis, oliguria, renal failure), muscles and joints (e.g., joint swelling, myalgia, arthralgia, asthenia), nervous system (e.g., hepatic encephalopathy), respiratory (e.g., dyspnea, pulmonary edema, asthma, bronchospasm, interstitial lung disease), hepatorenal syndrome, pruritus, and angioedema. Because the disorder is variable in its expression, other organ system symptoms and signs, not noted here, may occur. If this reaction is suspected, discontinue Oxtellar XR™ and initiate an alternative treatment.

5.8 Hematologic Reactions

Rare reports of pancytopenia, agranulocytosis, and leukopenia have been seen in patients treated with immediate-release oxcarbazepine during post-marketing experience. Discontinuation of Oxtellar XR™ should be considered if any evidence of these hematologic reactions develops.

5.9 Risk of Seizures in the Pregnant Patient

Due to physiological changes during pregnancy, plasma concentrations of the active metabolite of oxcarbazepine, the 10-monohydroxy derivative (MHD), may gradually decrease throughout pregnancy. Monitor patients carefully during pregnancy and through the postpartum period because MHD concentrations may increase after delivery.

5.10 Laboratory Tests

Laboratory data from clinical trials suggest that immediate-release oxcarbazepine may be associated with decreases in T4, without changes in T3 or TSH.

6 ADVERSE REACTIONS

The following adverse reactions are described in other sections of the labeling:

- Hyponatremia [see *Warnings and Precautions (5.1)*]
- Anaphylactic Reactions and Angioedema [see *Warnings and Precautions (5.2)*]
- Hypersensitivity Reactions in Patients with Hypersensitivity to Carbamazepine [see *Warnings and Precautions (5.3)*]
- Serious Dermatological Reactions [see *Warnings and Precautions (5.4)*]
- Suicidal Behavior and Ideation [see *Warnings and Precautions (5.5)*]
- Withdrawal of AEDs [see *Warnings and Precautions (5.6)*]
- Multi-Organ Hypersensitivity [see *Warnings and Precautions (5.7)*]
- Hematologic Reactions [see *Warnings and Precautions (5.8)*]
- Risk of Seizures in the Pregnant Patient [see *Warnings and Precautions (5.9)*]
- Laboratory Tests [see *Warnings and Precautions (5.10)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data presented below are from 384 patients with partial epilepsy who received Oxtellar XR™ (366 adults and 18 children) with concomitant AEDs.

In addition, safety data presented below are from a total of 2,288 patients with seizure disorders treated with immediate-release oxcarbazepine; 1,832 were adults and 456 were children.

Most Common Adverse Reactions Reported by Adult Patients Receiving Concomitant AEDs in Oxtellar XR™ Clinical Studies

Table 3 lists adverse reactions that occurred in at least 2% of adult patients with epilepsy treated with Oxtellar XR™ or placebo and concomitant AEDs and that were numerically more common in the patients treated with any dose of Oxtellar XR™ than in patients receiving placebo.

The overall incidence of adverse reactions appeared to be dose related, particularly during the Titration Period. The most commonly observed ($\geq 5\%$) adverse reactions seen in association with Oxtellar XR™ and more frequent than in placebo-treated patients were: dizziness, somnolence, headache, balance disorder, tremor, vomiting, diplopia, and asthenia.

Table 3: Adverse Reaction Incidence in a Controlled Clinical Study of Oxtellar XR™ with Concomitant AEDs in Adults*

	Oxtellar XR 2400 mg/day N=123 %	Oxtellar XR 1200 mg/day N=122 %	Placebo N=121 %
Any System / Any Term	69	57	55
Nervous System Disorders			
Dizziness	41	20	15
Somnolence	14	12	9
Headache	15	8	7
Balance Disorder	7	5	5
Tremor	1	5	2
Nystagmus	3	3	1
Ataxia	1	3	1
Gastrointestinal Disorders			
Vomiting	15	6	9
Abdominal Pain Upper	0	3	1
Dyspepsia	0	3	1
Gastritis	0	3	2
Eye Disorders			
Diplopia	13	10	4
Vision Blurred	1	4	3
Visual Impairment	1	3	0
General Disorders And Administration			
Site Conditions			
Asthenia	7	3	1
Fatigue	3	6	1
Gait Disturbance	0	3	1
Drug Intolerance	2	0	0
Infections And Infestations			
Nasopharyngitis	0	3	0
Sinusitis	0	3	2

* Reported by $\geq 2\%$ of Patients Treated with Oxtellar XR™ and Numerically More Frequent than in the Placebo Group

Adverse Reactions Associated with Discontinuation of Oxtellar XR™ Treatment: Approximately 23.3% of the 366 adult patients receiving Oxtellar XR™ in clinical studies discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation of Oxtellar XR™ (reported by $\geq 2\%$) were: dizziness (9.8%), vomiting (5.3%), nausea (3.7%), diplopia (3.2%), and somnolence (2.4%).

Adjunctive Therapy with Oxtellar XR™ in Pediatric Patients 4 to 16 Years Old Previously Treated with other AEDs

In a pharmacokinetic study in 18 children (age 4-16 years) with partial seizures treated with different doses of Oxtellar XR™, the observed adverse reactions seen in association with Oxtellar XR™ were similar to those seen in adults.

Most Common Adverse Reactions in Immediate-Release Oxcarbazepine Controlled Clinical Studies

Controlled Clinical Studies of Adjunctive Therapy with Immediate-Release Oxcarbazepine in Adults Previously Treated with other AEDs: Table 4 lists adverse reactions that occurred in at least 2% of adult patients with epilepsy treated with immediate-release oxcarbazepine or placebo with concomitant AEDs and that were numerically more common in the patients treated with any dose of immediate-release oxcarbazepine than in placebo. As immediate-release oxcarbazepine and Oxtellar XR™ were not examined in the same trial, adverse event frequencies cannot be directly compared between the two formulations.

Table 4: Adverse Reaction Incidence in a Controlled Clinical Study of Immediate Release Oxcarbazepine with Concomitant AEDs in Adults*

	Immediate-Release Oxcarbazepine Dosage (mg/day)			Placebo N = 166 %
	OXC 600 N = 163 %	OXC 1200 N = 171 %	OXC 2400 N = 126 %	
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	36	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

	Immediate-Release Oxcarbazepine Dosage (mg/day)			Placebo N = 166
	OXC 600	OXC 1200	OXC 2400	
	N = 163	N = 171	N = 126	
	%	%	%	%
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

* Events in at Least 2% of Patients Treated with 2400mg/day of Immediate-Release Oxcarbazepine and Numerically More Frequent than in the Placebo Group

Other Reactions Observed in Association with the Administration of Immediate-Release Oxcarbazepine

In the paragraphs that follow, the adverse reactions, other than those in the preceding tables or text, that occurred in a total of 565 children and 1,574 adults exposed to immediate-release 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 reactions observed in open label and uncontrolled trials, the role of immediate-release 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.

Hematologic and Lymphatic System: 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, bronchitis, coughing, 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.

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

Other: Systemic lupus erythematosus.

6.2 Postmarketing and Other Experience

The following adverse reactions have been identified during post-approval use of immediate-release oxcarbazepine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: multi-organ hypersensitivity disorders characterized by features such as rash, fever, lymphadenopathy, abnormal liver function tests, eosinophilia and arthralgia [see *Warnings and Precautions* (5.7)]

Anaphylaxis: [see *Warnings and Precautions* (5.2)]

Digestive System: pancreatitis and/or lipase and/or amylase increase

Hematologic and Lymphatic Systems: aplastic anemia [see *Warnings and Precautions* (5.8)]

Skin and Appendages: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis [see *Warnings and Precautions* (5.4)]

7 DRUG INTERACTIONS

Oxcarbazepine and MHD induce a subgroup of the cytochrome P450 3A family (CYP3A4 and CYP3A5).

In addition, several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD.

These interactions have implications when Oxtellar XR™ is used with other AEDs or hormonal contraceptives.

7.1 Other Antiepileptic Drugs

Potential interactions between immediate-release oxcarbazepine and other AEDs were assessed in clinical studies. Oxtellar XR™ would be expected to have the same effects on coadministered AEDs as immediate-release oxcarbazepine.

Table 5: AED Drug Interactions with Oxcarbazepine

AED Coadministered (daily dose)	IR-Oxcarbazepine (daily dose)	Influence of IR-Oxcarbazepine on AED Concentration Mean Change [90% Confidence Interval]	Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval)	Recommendation
Carbamazepine (400 – 2000 mg)	900 mg	nc ¹	40% decrease [CI: 17% decrease, 57% decrease]	Consider initiating Oxtellar XR™ at a higher dose. Monitor and titrate dose to desired clinical effect (see 2.6)
Phenobarbital (100 – 150 mg)	600 – 1800 mg	14% increase [CI: 2% increase, 24% increase]	25% decrease [CI: 12% decrease, 51% decrease]	
Phenytoin (250 – 500 mg)	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 mg)	600-1800	nc ¹	18% decrease [CI: 13% decrease, 40% decrease]	Monitor. Dose adjustment of Oxtellar XR™ may not be needed.

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

7.2 Hormonal Contraceptives

Coadministration of immediate-release oxcarbazepine with an oral contraceptive decreased the plasma concentrations of two components of hormonal contraceptives, ethinylestradiol and levonorgestrel. Therefore, concurrent use of Oxtellar XR™ with these hormonal contraceptives and other oral or implant contraceptives may render these contraceptives less effective [see *Clinical Pharmacology (12.3)*]. Additional non-hormonal forms of contraception are recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Oxtellar XR™ plasma concentrations may decrease during pregnancy [see *Warnings and Precautions* (5.9)]

Pregnancy Category C

There are no adequate and well-controlled clinical studies of Oxtellar XR™ in pregnant women; however, Oxtellar XR™ 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 Oxtellar XR™ is a human teratogen. Oxtellar XR™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity (embryo lethality, 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/m² 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/m² 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/m² 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/m² basis).

To provide information regarding the effects of in utero exposure to Oxtellar XR™, physicians are advised to recommend that pregnant patients taking Oxtellar XR™ enroll in the NAAED Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

8.2 Nursing Mothers

Oxcarbazepine and its active metabolite (MHD) are excreted in human milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to Oxtellar XR™ 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.

8.3 Pediatric Use

The short term safety and effectiveness of Oxtellar XR™ in pediatric patients ages 6 to 16 years with partial onset seizures is supported by:

- 1) An adequate and well-controlled short term safety and efficacy study of Oxtellar XR™ in adults that included pharmacokinetic sampling [see *Clinical Studies (14.1)*],
- 2) A pharmacokinetic study of Oxtellar XR™ in pediatric patients ages 4 to 16 years [see *Clinical Pharmacology (12.3)*], and
- 3) Safety and efficacy studies with the immediate-release formulation in adults and pediatric patients [see *Clinical Studies (14.2)* and *Adverse Reactions (6.1)*].

Oxtellar XR™ is not approved for pediatric patients less than 6 years of age because the size of the tablets are inappropriate for younger children, and has not been studied in patients younger than 4 years of age.

8.4 Geriatric Use

Following administration of single (300 mg) and multiple (600 mg/day) doses of immediate-release oxcarbazepine 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. Consider starting at a lower dose and lower titration [see *Dosage and Administration (2.5)*].

8.5 Renal Impairment

There is a linear correlation between creatinine clearance and the renal clearance of MHD. [see *Clinical Pharmacology (12.3)* and *Dosage and Administration (2.4)*].

The pharmacokinetics of Oxtellar XR™ has not been evaluated in patients with renal impairment. In patients with severe renal impairment (creatinine clearance <30 mL/min) given immediate release oxcarbazepine, the elimination half-life of MHD was prolonged with a corresponding two-fold increase in AUC [see *Clinical Pharmacology (12.3)*]. In these patients initiate Oxtellar XR™ at a lower starting dose and increase, if necessary, at a slower than usual rate until the desired clinical response is achieved [see *Dosage and Administration (2.4)*].

In patients with end-stage renal disease on dialysis, it is recommended that immediate release oxcarbazepine be used instead of Oxtellar XR™.

8.6 Hepatic Impairment

The pharmacokinetics of oxcarbazepine and MHD has not been evaluated in severe hepatic impairment, and therefore is not recommended in these patients. [see *Clinical Pharmacology* (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.2 Abuse

The abuse potential of Oxtellar XR™ has not been evaluated in human studies. Oxtellar XR™ is not habit forming, and is not expected to encourage abuse.

9.3 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.

10 OVERDOSAGE

Human Overdose Experience

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

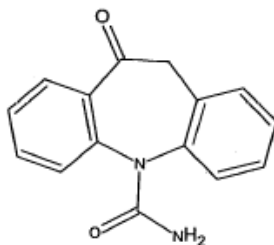
Treatment and Management

There is no specific antidote for Oxtellar XR™ overdose. Administer symptomatic and supportive treatment as appropriate. Options include removal of the drug by gastric lavage and/or inactivation by administering activated charcoal.

11 DESCRIPTION

Oxtellar XR™ is an antiepileptic drug (AED). Oxtellar XR™ extended-release tablets contain oxcarbazepine for once-a-day oral administration.

Oxcarbazepine is 10,11-Dihydro-10-oxo-5H-dibenz[b,f]-azepine-5-carboxamide, and its structural formula is



Oxcarbazepine is off-white to yellow crystalline powder.

Oxcarbazepine is sparingly soluble in chloroform (30-100 g/L). In aqueous media over pH range 1 to 8, oxcarbazepine is practically insoluble and its solubility is 40 mg/L (0.04 g/L) at pH 7.0, 25°C. The molecular formula is C₁₅H₁₂N₂O₂ and its molecular weight is 252.27.

Oxtellar XR™ tablets contain the following inactive ingredients: colloidal silicon dioxide, hypromellose, yellow iron oxide (150 mg, 300 mg tablets only), red iron oxide (300 mg, 600 mg tablets only), black iron oxide (300 mg tablet only), magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium lauryl sulfate, talc, and titanium dioxide. Each tablet is printed on one side with edible black ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The pharmacological activity of Oxtellar XR™ is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine [see *Clinical Pharmacology* (12.3)]. 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.

12.2 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 five days and four weeks, respectively, with oxcarbazepine or MHD.

12.3 Pharmacokinetics

Following oral administration, oxcarbazepine is absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD), which is responsible for most antiepileptic activity.

In clinical studies of Oxtellar XR™, the elimination half-life of oxcarbazepine was between 7 and 11 hours; the elimination half-life of MHD is between 9 and 11 hours.

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

Absorption

Oxtellar XR™ administered as a once daily dose is not bioequivalent to the same total dose of the immediate release formulation given twice daily at steady state. Steady state plasma concentrations of MHD are reached within 5 days when Oxtellar XR™ is given once daily. At steady state, when 1200 mg Oxtellar XR™ was given once daily, MHD C_{max} occurred 7 hours post-dose. At steady state, Oxtellar XR™ given once daily produced MHD exposures (AUC and C_{max}) about 19% lower and MHD minimum concentrations (C_{min}) about 16% lower than the immediate-release oxcarbazepine given twice daily when administered at the same 1200 mg total daily dose. When Oxtellar XR™ was administered at an equivalent 600 mg single dose (4 x 150 mg tablets, 2 x 300 mg tablets, or 1 x 600 mg tablet), equivalent MHD exposures (AUC) were observed.

Following a single dose of Oxtellar XR™ (1 x 150 mg tablets, 1 x 300 mg tablets, or 1 x 600 mg tablet), the pharmacokinetics of MHD are not linear and show greater than dose proportional increase in AUC and less than proportional increase in C_{max} : AUC increases 2.4-fold and C_{max} increases 1.9-fold with a 2-fold increase in dose.

Effect of Food: Single dose administration of 600 mg Oxtellar XR™ following a high fat meal (800 – 1000 calories) produced MHD exposure (AUC) equivalent to that produced under fasting conditions. Peak MHD concentration (C_{max}) was about 60% higher and occurred 2 hours earlier under fed conditions than under fasting conditions.

The increase in C_{max} , even without a significant change in the overall exposure, should be considered by the prescriber especially during the titration phase, when some adverse reactions are most likely to occur coincidentally with peak levels.

Distribution

The apparent volume of distribution of MHD is 49 L. 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

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to MHD, which is primarily responsible for the pharmacological effect of TRADENAME. 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).

Elimination

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of a dose of immediate-release oxcarbazepine appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of an 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.

The half-life of the parent was about two hours, while the half-life of MHD was about nine hours after the immediate release formulation. A population pharmacokinetic model for Oxtellar XR™ was developed in healthy normal adults and applied to pharmacokinetic data in patients with epilepsy. For oxcarbazepine, systemic parameters were scaled allometrically, suggesting that steady state oxcarbazepine exposure will vary inversely with weight.

Special Populations

Elderly

No studies with Oxtellar XR™ in elderly patients have been completed [see *Use in Specific Populations* (8.4)].

Following administration of single (300 mg) and multiple (600 mg/day) doses of immediate-release oxcarbazepine 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.

Pediatric

Oxtellar XR™ is not approved for pediatric patients less than 6 years of age because the size of the tablets are inappropriate for younger children, and has not been studied in patients younger than 4 years of age. A pharmacokinetic study of Oxtellar XR™ was performed in 18 pediatric patients with epilepsy, 4 to 16 years of age, after multiple doses. The population pharmacokinetic model suggested that dosing of pediatric patients with Oxtellar XR™ can be determined based on body weight. Weight-normalized doses in pediatric patients should produce MHD exposures (AUC) comparable to that in typical adults, with oxcarbazepine exposures ~40% higher in children than in adults [see *Use in Specific Populations* (8.3)].

Gender

The effects of gender have not been studied for Oxtellar XR™.

No gender-related pharmacokinetic differences have been observed in children, adults, or the elderly with immediate-release oxcarbazepine.

Race

The effects of race have not been studied for Oxtellar XR™.

Renal or Hepatic Impairment

The effects of renal or hepatic impairment have not been studied for Oxtellar XR™ [see *Use in Specific Populations (8.5, 8.6)*].

Based on investigations with immediate-release oxcarbazepine, there is a linear correlation between creatinine clearance and the renal clearance of MHD. When immediate-release 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 is recommended in these patients [see *Dosage and Administration (2.4)* and *Use in Special Populations (8.5)*].

The pharmacokinetics and metabolism of immediate-release 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 immediate-release oxcarbazepine and MHD. The pharmacokinetics of oxcarbazepine and MHD have not been evaluated in severe hepatic impairment, and therefore it is not recommended in these patients [see *Use in Specific Populations (8.6)*].

Pregnancy

Due to physiological changes during pregnancy, MHD plasma levels may gradually decrease throughout pregnancy [see *Use in Specific Populations (8.1)*]

Drug Interaction Studies

In Vitro: 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, is clinically relevant.

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 UDPglucuronyl 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, oral contraceptives and cyclosporine resulting in a lower plasma concentration of these drugs.

Several AEDs that are cytochrome P450 inducers can decrease plasma concentrations of oxcarbazepine and MHD. No autoinduction has been observed with immediate-release oxcarbazepine.

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

In Vivo:

Hormonal Contraceptives

Coadministration of immediate-release oxcarbazepine with an oral contraceptive has been shown to influence the plasma concentrations of two components of hormonal contraceptives, 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 oxcarbazepine with hormonal contraceptives may render these contraceptives less effective.

Calcium Channel Antagonists

After repeated coadministration of immediate-release oxcarbazepine, 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 after coadministration with immediate-release oxcarbazepine.

Other Interactions

Cimetidine, erythromycin and dextropropoxyphene had no effect on the pharmacokinetics of MHD after coadministration with immediate-release oxcarbazepine. Results with warfarin show no evidence of interaction with either single or repeated doses of immediate-release oxcarbazepine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In two-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/day 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/m² 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/m² 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/m² basis) and ≥ 250 mg/kg/day (equivalent to the MRHD on a mg/m² 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.

Mutagenesis

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.

Impairment of Fertility

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 two times the MRHD on a mg/m² basis).

14 CLINICAL STUDIES

Oxtellar XR™ has been evaluated as adjunctive therapy for partial seizures in adults. The use of Oxtellar XR™ for the treatment of partial seizures in children is based on adequate and well-controlled studies of Oxtellar XR™ in adults, along with clinical trials of immediate-release oxcarbazepine in children, and on pharmacokinetic evaluations of the use of Oxtellar XR™ in children.

14.1 Oxtellar XR™ Primary Trial

A multicenter, randomized, double-blind, placebo-controlled, three-arm, parallel-group study (Study 1) in male and female adults with refractory partial epilepsy (18 to 65 years of age, inclusive) was performed to examine the safety and efficacy of Oxtellar XR™.

Patients had at least three partial seizures per 28 days during an 8 week Baseline Period. Subjects were receiving treatment with at least one to three antiepileptic drugs and were on stable treatment for a minimum of 4 weeks. Subjects with a diagnosis other than partial epilepsy were excluded.

The study included an 8 week Baseline Period, followed by a Treatment Period, which included a 4 week Titration Phase followed by a 12 week Maintenance Phase. The primary endpoint of the study was median percentage change from baseline in seizure frequency per 28 days during the treatment period relative to the baseline period. The criterion for statistical significance was $p < 0.05$. A total of 366 patients were enrolled at 88 sites in North America and Eastern Europe. Subjects were randomized to one of three treatment groups and took Oxtellar XR™ (1200 or 2400 mg/day) or placebo.

Table 6 presents the primary efficacy results by treatment group.

Table 6: Primary Efficacy Results in Study 1: Percent Change from Baseline in Partial Seizure Frequency in the 16-week Treatment Period

	Median seizure frequency during 8-week baseline period (per 28 days)	Median seizure frequency during 16-week treatment period (per 28 days)	Median percent change in seizure frequency	Seizure frequency percent change effect size	P value vs placebo*
Placebo (N=121)	7.0	5.0	-28.7 %		
Oxtellar XR™ 1200mg/day (N=122)	6.0	4.3	-38.2 %	9.5%	0.078
Oxtellar XR™ 2400mg/day (N=123)	6.0	3.7	-42.9 %	14.2%	0.003

* Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 16-week Treatment Phase (Titration + Maintenance Periods) relative to the 8-week Baseline Phase.

Although the 1200 mg/day-placebo contrast did not reach statistical significance, concentration-response analyses reveal that the 1200 mg/day dose is an effective dose.

14.2 Immediate-Release Oxcarbazepine Adjunctive Therapy Trials

The effectiveness of immediate-release oxcarbazepine as an adjunctive therapy for partial seizures in adults was demonstrated at doses of 600mg per day, 1200mg per day and 2400mg per day (divided twice daily) in a randomized, double-blind, placebo-controlled trial. All doses resulted in a statistically significant reduction in seizure frequency when compared to placebo ($p < 0.05$).

The effectiveness of immediate-release oxcarbazepine in doses of 30-46 mg/kg/day, depending on baseline weight, as an adjunctive therapy for partial seizures in children 3 years to 17 years of age was studied in a randomized, double-blind, placebo-controlled trial. Oxcarbazepine in the single weight based dose group resulted in a statistically significant reduction in seizure frequency when compared to placebo ($p < 0.05$).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Dosage Form Supplied

150 mg (yellow modified-oval shaped tablet printed “150” on one side with edible black ink).

Bottles of 100 tablets.....NDC 17772-121-01

300 mg (brown modified-oval shaped tablet printed “300” on one side with edible black ink).

Bottles of 100 tablets.....NDC 17772-122-01

600 mg (brownish red modified-oval shaped tablet printed “600” on one side with edible black ink).

Bottles of 100 tablets..... NDC 17772-123-01

16.2 Storage and Handling

Store at 25°C (77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) [See USP controlled room temperature]. Protect from light and moisture. Dispense in a tight, light-resistant container.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved patient labeling (Medication Guide).

Inform patients and caregivers of the availability of a Medication Guide. Instruct patients and caregivers to read the Medication Guide prior to taking Oxtellar XR™.

- Advise patients to take the tablet whole with water or other liquid, and not to cut, chew or crush the tablet. Cutting, chewing or crushing Oxtellar XR™ tablet could affect its performance.
- Advise patients to take Oxtellar XR™ on an empty stomach. This means they should take Oxtellar XR™ at least one hour before food or at least two hours after food [see *Clinical Pharmacology (12.3)*].
- Advise patients that Oxtellar XR™ may reduce serum sodium concentrations especially if they are taking other medications that can lower sodium. Advise patients to report symptoms of low sodium like nausea, tiredness, lack of energy, confusion, and more frequent or more severe seizures [see *Warnings and Precautions (5.1)*].
- Anaphylactic reactions and angioedema may occur during treatment with Oxtellar XR™. Advise patients to immediately report 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 and Precautions (5.2)*].
- Inform patients who have exhibited hypersensitivity reactions to carbamazepine that approximately 25%-30% of these patients may also experience hypersensitivity reactions with Oxtellar XR™. If patients experience a hypersensitivity reaction while taking Oxtellar XR™, advise them to consult with their physician immediately [see *Warnings and Precautions (5.3)*].
- Advise patients that serious skin reactions have been reported in association with immediate-release oxcarbazepine. If patients experience a skin reaction while taking Oxtellar XR™, advise patients to consult with their physician immediately [see *Warnings and Precautions (5.4)*].
- Instruct patients that a fever associated with other organ system involvement (rash, lymphadenopathy, etc.) occurring during treatment with Oxtellar XR™ may be drug-related and advise them to consult their physician immediately [see *Warnings and Precautions (5.7)*].
- Advise patients that there have been rare reports of blood disorders reported in patients treated with immediate-release oxcarbazepine. Instruct patients to immediately consult with their physician if they experience symptoms suggestive of blood disorders during treatment with Oxtellar XR™ [see *Warnings and Precautions (5.8)*].
- Warn female patients of childbearing age that the concurrent use of Oxtellar XR™ with hormonal contraceptives may render this method of contraception less effective [see *Drug Interactions (7.2)*]. Additional non-hormonal forms of contraception are recommended when using Oxtellar XR™.
- Counsel patients, their caregivers, and families that AEDs, including Oxtellar XR™, may increase the risk of suicidal thoughts and behavior and that they need to

be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Advise them to immediately report behaviors of concern to healthcare providers.

- Advise patients to exercise caution if alcohol is taken in combination with Oxtellar XR™ therapy, due to a possible additive sedative effect.
- Advise patients that Oxtellar XR™ may cause dizziness and somnolence. Accordingly, advise patients not to drive or operate machinery until they have gained sufficient experience on Oxtellar XR™ to gauge whether it adversely affects their ability to drive or operate machinery.
- Encourage patients to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll free number 1-888-233-2334 [see *Use in Specific Populations (8.1)*].
- Advise patients that they should call their healthcare provider or poison control center (phone number 1-800-222-1222) if they take too much Oxtellar XR™.
- Discuss with your patient what they should do if they miss a dose.

Oxtellar XR™ is manufactured by:

Patheon Inc.

Whitby, Ontario L1N 5Z5 CANADA

Distributed by:

Supernus Pharmaceuticals, Inc.

Rockville, MD 20850 USA

Oxtellar XR™ is a trademark of Supernus Pharmaceuticals, Inc.

Revised: October 2012

MEDICATION GUIDE
Oxtellar XR™ ((ahks-TEH-lahr eks ahr))
(oxcarbazepine)
Extended-Release Tablets

Read this Medication Guide before you start taking Oxtellar XR™ and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about Oxtellar XR™?

Do not stop taking Oxtellar XR™ without first talking to your healthcare provider.

Stopping Oxtellar XR™ suddenly can cause serious problems.

Oxtellar XR™ can cause serious side effects, including:

1. Oxtellar XR™ may cause the level of sodium in your blood to be low.

Symptoms of low blood sodium include:

- nausea
- tiredness, lack of energy
- headache
- confusion
- more frequent or more severe seizures

Similar symptoms that are not related to low sodium may occur from taking Oxtellar XR™. You should tell your healthcare provider if you have any of these side effects and if they bother you or they do not go away.

Some other medicines can also cause low sodium in your blood. Be sure to tell your healthcare provider about all the other medicines that you are taking.

2. Oxtellar XR™ may also cause allergic reactions or serious problems which may affect organs and other parts of your body like the liver or blood cells. You may or may not have a rash with these types of reactions.

Call your healthcare provider right away if you have any of the following:

- swelling of your face, eyes, lips, or tongue
- trouble swallowing or breathing
- a skin rash
- hives
- fever, swollen glands, or sore throat that do not go away or come and go
- painful sores in the mouth or around your eyes

- yellowing of your skin or eyes
- unusual bruising or bleeding
- severe fatigue or weakness
- severe muscle pain
- frequent infections or infections that do not go away

Many people who are allergic to carbamazepine are also allergic to Oxtellar XR™. Tell your healthcare provider if you are allergic to carbamazepine.

3. Like other antiepileptic drugs, Oxtellar XR™ may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call your healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

Do not stop taking Oxtellar XR™ without first talking to a healthcare provider.

Stopping Oxtellar XR™ suddenly can cause serious problems. Stopping a seizure medicine suddenly in a patient who has epilepsy may cause seizures that will not stop (status epilepticus).

Suicidal thoughts or actions may be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

What is Oxtellar XR™?

Oxtellar XR™ is a prescription medicine used:

- with other medicines to treat partial seizures in adults
- with other medicines to treat partial seizures in children 6 to 17 years of age.

It is not known if Oxtellar XR™ is safe and effective in children under 6 years of age.

Who should not take Oxtellar XR™?

- Do not take Oxtellar XR™ if you are allergic to oxcarbazepine or any of the other ingredients in Oxtellar XR™. See the end of this leaflet for a complete list of ingredients in Oxtellar XR™.

What should I tell my healthcare provider before taking Oxtellar XR™?

Before taking Oxtellar XR™, tell your healthcare provider about all your medical conditions, including if you:

- have or have had suicidal thoughts or actions, depression or mood problems
- have liver problems
- have kidney problems
- use birth control medicine. Oxtellar XR™ may cause your birth control medicine to be less effective. Talk to your healthcare provider about the best birth control method to use.
- are pregnant or plan to become pregnant. Oxtellar XR™ may harm your unborn baby. Tell your healthcare provider right away if you become pregnant while taking Oxtellar XR™. You and your healthcare provider will decide if you should take Oxtellar XR™ while you are pregnant.
 - If you become pregnant while taking Oxtellar XR™, talk to your healthcare provider about registering with the North American Antiepileptic Drug (NAAED) Pregnancy Registry. The purpose of this registry is to collect information about the safety of antiepileptic medicine during pregnancy. You can enroll in this registry by calling 1-888-233-2334.
- are breastfeeding or plan to breastfeed. Oxtellar XR™ passes into breast milk. You and your healthcare provider should discuss whether you should take Oxtellar XR™ or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Taking Oxtellar XR™ with certain other medicines may cause side effects or affect how well they work. Do not start or stop other medicines without talking to your healthcare provider.

Especially tell your healthcare provider if you take: carbamazepine, phenobarbital, phenytoin, or birth control medicine.

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take Oxtellar XR™?

Do not stop taking Oxtellar XR™ without talking to your healthcare provider. Stopping Oxtellar XR™ suddenly can cause serious problems, including seizures that will not stop (status epilepticus). Take Oxtellar XR™ exactly as prescribed. Your healthcare provider may change your dose. Your healthcare provider will tell you how much Oxtellar XR™ to take.

Take Oxtellar XR™ 1 time each day.

Take Oxtellar XR™ on an empty stomach. This means you should take Oxtellar XR™ at least 1 hour before or at least 2 hours after a meal. Take Oxtellar XR™ tablets whole with water or other liquid.

Do not cut, crush, or chew the tablets before swallowing.

If you take too much Oxtellar XR™ call your healthcare provider or call the poison control center at 1-800-222-1222.

Take Oxtellar XR™ at the same time each day.

Talk with your healthcare provider about what you should do if you miss a dose.

What should I avoid while taking Oxtellar XR™?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how Oxtellar XR™ affects you. Oxtellar XR™ may slow your thinking and motor skills.
- Do not drink alcohol or take other drugs that make you sleepy or dizzy while taking Oxtellar XR™ until you talk to your healthcare provider. Oxtellar XR™ taken with alcohol or drugs that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

What are the possible side effects of Oxtellar XR™?

See **“What is the most important information I should know about Oxtellar XR™?”**

Oxtellar XR™ may cause other serious side effects including:

- your seizures can happen more often or become worse
- trouble concentrating
- problems with your speech and language
- feeling confused
- feeling sleepy and tired
- trouble walking and with coordination

Get medical help right away if you have any of the symptoms listed above or listed in “What is the most important information I should know about Oxtellar XR™?”

The most common side effects of Oxtellar XR™ include:

- dizziness
- sleepiness
- headache
- problems with walking and coordination (unsteadiness)
- shakiness
- nausea
- vomiting
- double vision
- weakness
- tiredness

These are not all the possible side effects of Oxtellar XR™. For more information, ask your healthcare provider or pharmacist.

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Oxtellar XR™?

- Store Oxtellar XR™ at room temperature 68°F to 77°F (20°C and 25°C)
- Keep Oxtellar XR™ in a tightly closed container, and keep Oxtellar XR™ out of the light.
- Keep Oxtellar XR™ tablets dry.

Keep Oxtellar XR™ and all medicines out of the reach of children.

General Information about the safe and effective use of Oxtellar XR™

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Oxtellar XR™ for a condition for which it was not prescribed. Do not give Oxtellar XR™ to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Oxtellar XR™. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for the full prescribing information about Oxtellar XR™ that is written for health professionals.

For more information, go to www.supernus.com or call 1-866-398-0833.

What are the ingredients in Oxtellar XR™?

Active ingredient: oxcarbazepine

Inactive ingredients:

150 mg tablets: colloidal silicon dioxide, hypromellose, yellow iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium lauryl sulfate, talc, and titanium dioxide.

300 mg tablets: colloidal silicon dioxide, hypromellose, yellow iron oxide, red iron oxide, black iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium lauryl sulfate, talc, and titanium dioxide.

600 mg tablets: red iron oxide, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, sodium lauryl sulfate, talc, and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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/s/

RUSSELL G KATZ
10/19/2012